Professor Timothy David Noakes

Submission for the degree of
DSc in Medicine (Exercise Science)

University of Cape Town

A detailed synopsis of the contents of the work
including a statement on the nature and
the value of the contribution.

Cape Town, South Africa
August 8th 2002
(with revisions added prior to this publication in May 2004
and after the awarding of the degree in December 2002)

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Dedication

For Marilyn Anne, my lifetime companion and to our shared treasures, Travis Miles and Candice Amelia.

Your contributions have been beyond measure.

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Director: Professor T D Noakes

Dear Professor Padayachee,

Submission of materials for consideration for registration as a candidate for the DSc (Medicine) degree: Professor Timothy Noakes.

I have pleasure enclosing the appropriate documents including a copy of the fourth edition of *Lore of Running*, for consideration for registration as a candidate for the DSc (Med) degree in the Faculty of Health Sciences of the University of Cape Town. I believe that these document summarise my intellectual contributions to the field of sports science and sports medicine both nationally and internationally and that this work, in its totality, should be of a sufficient standard to warrant consideration for candidature for this degree.

In making this submission I am aware that this award is given only occasionally to persons of exceptional academic merit and then only for work of international standing that is regarded as seminal. I appreciate that the criteria for the award are appropriately strict and that it is only work of a unique nature that is considered for this award. Accordingly I have included a detailed motivation that explains why I feel this work matches that very high standard and why it fulfils the extremely exacting requirement that would be expected for a submission for this prestigious degree.

I would like it understood that whilst the book might in and of itself be considered a seminal contribution since it internationally accepted as the only book of its kind in current circulation internationally, it is not principally the book that has been submitted as evidence for this award. Rather, what is being submitted, is a body of scientific work that has led to the publication of the book. The book details the international and historical context of that work and which cannot really be fully understood other than through reference to the book. Hence the book is only a part, albeit the most important part, of the submission.

I thank you for your attention to this matter and await the outcome with interest.

Yours Sincerely,

Professor Tim Noakes

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Discovery Health

SPORTS SCIENCE INSTITUTE OF SOUTH AFRICA

University of Cape Town

"The farther backwards you can look, the further forwards you can see."

Sir Winston Churchill

About the artwork on the cover

Front Cover

Top Panel: The original A.V. Hill Cardiovascular/Anaerobic Model of Exercise Physiology.

Centre Panel: Front-runners in the 56km Two Oceans Marathon held annually since 1970, in Cape Town, South Africa.

Bottom Panel: Original concept drawing of the Central Governor Model of Exercise Physiology.

Spine

A.V. Hill and F.G. Hopkins. Two British scientists of the early 1900s both of whom won the Nobel Prize and both of whose ideas were central to the development of Hill's Cardiovascular/Anaerobic Model of Exercise Physiology.

Back Cover

Top Panel: Chest X-rays, taken 5 days apart, of the first reported case of the hyponatraemia (low blood sodium concentration) of exercise. The X-ray taken on June 1st 1981 shows the presence of fluid in the lungs (pulmonary oedema) associated with an enlarged heart. The X-ray on June 5th 1981 shows resolution of those changes.

Middle Panel: An unconscious athlete is carried across the finish line of the 56km Argus Two Oceans Marathon. This picture appeared the same day on the front page of the *Argus* newspaper under the headline: "Another dehydrated athlete collapses in the Two Oceans Marathon." In fact, this athlete was suffering from the opposite – water intoxication causing the hyponatraemia of exercise. For as he admitted in an interview the following day when he had recovered consciousness, this athlete had entered the race in an under-trained state. To compensate for his lack of training, he thought that only by drinking "as much as tolerable" would he be able to complete the race. He duly drank ~1.5ℓ/hr for 5 hours. He recovered consciousness only 7 hours after this picture was taken. Since the medical team at that race were fully aware that this condition is due to water intoxication, this athlete did not receive intravenous or oral fluids during his recovery. Photo courtesy of the *Argus* newspaper.

Lower Panel: The definitive graph from the article by Irving et al (*Journal of Applied Physiology* 1991) proving the mechanism causing the hyponatraemia of exercise. The graph shows that runners who developed the hyponatraemia of exercise during the 89km Comrades Marathon were fluid overloaded by an average of 2.5ℓ. But they did not have a greater sodium (salt) deficit than did control runners completing the race with normal blood sodium concentrations. This study disproves the incorrect theory that a sodium deficit, preventable by drinking sports drinks, causes the hyponatraemia of exercise.

Text Inserts

Two opposing guidelines for fluid ingestion during exercise. Note that this condition – the hyponatraemia of exercise – became a significant problem in the United States (US) Army and amongst female marathon runners/walkers in the US, only after the adoption of the 1996 Fluid Replacement guidelines of the American College of Sports Medicine. The more conservative guidelines, based on the research described in this thesis, were published in the Clinical Journal of Sports Medicine in 2003, and have been accepted by US Track and Field for implementation in all US road running race after April 2003.

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b.	A detailed synopsis of the contents of the work including a statement on the nature and value of the contribution	pages B-1 to B-16
c.	One set of copies of work submitted for the degree. This includes a copy of the 4th Edition of *Lore of Running* plus a set of scientific papers.	pages C-1 to C-403
d.	A statement affirming that the work is the original work of the applicant. Where the work is of a joint nature, this has been indicated.	page D-1
e.	A statement that the work has not been submitted for consideration for an equivalent degree at this or any other university.	page E-1

In addition, documents related to the examination and awarding of the degree are also included. These are:

f.	Copies of the reports of 3 examiners.	pages F-1 to F-10
g.	Reproduction of copy for the awarding of the Degree of Doctor of Science in Medicine as it appeared in the Faculty of Health Sciences Graduation Ceremony 2002 programme.	pages G-1 to G-3
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a. Curriculum Vitae (abbreviated)

University of Cape Town

PROFESSOR TIMOTHY DAVID NOAKES, MB ChB, MD DSc, FACSM
Updated – April 2004.

Personal Information

Born	:	Harare, Zimbabwe
Resident	:	Cape Town, South Africa
Citizenship	:	South African
Wife	:	Marilyn Anne
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Education

* 1st Class Matriculation - Diocesan College, Rondebosch, Cape Town, South Africa (1966)
* American Field Student Exchange Scholarship to Los Angeles, California (1967/68)
* MB ChB, University of Cape Town, South Africa (1974)
* MD for thesis "Exercise and the Heart", University of Cape Town, South Africa (1981)
* DSc (Med) in Exercise Science (2002)

Professional Functions

* Professor in the Liberty Life Chair of Exercise and Sports Science, Department of Physiology at the University of Cape Town (1989 – 1999)

* Professor in the Discovery Health Chair of Exercise and Sports Science, Department of Human Biology (formerly Physiology) at the University of Cape Town (2000 – date)

* Director of Medical Research Council/University of Cape Town Research Unit for Exercise Science and Sports Medicine in the Sports Science Institute of South Africa, Newlands, South Africa (1989 – date)

* Executive Co-Director, Sports Science of Institute of South Africa (December 2003 – date)

Research Activities

The current research focus of the MRC/UCT Research Unit is to develop a novel neurobiological model of integrated human function during exercise and to use this model to optimise human exercise performance, the treatment and prevention of sports injuries, and the treatment and prevention of chronic diseases. Professor Noakes's research has led to more than 350 scientific publications in many leading scientific publications and to 5 books including the self-authored *Lore of Running* which is in its 4th Edition and, with a series of co-authors, *Running Injuries*, *Running your Best*, *Lore of Cycling*, *Rugby Without Risk* and, in preparation, *The Art and Science of Cricket and Coaching*, and, *Waterlogged.*

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Major Appointments

1990 –2004	Editorial Board of thirteen international publications and one local scientific publication.

Awards

1973	Medical Association of South Africa. Best student paper published in the South African Medical Journal in 1973
1983	Andries Blignaut Award. Best multi-authored paper published in the South African Medical Journal in 1983
1983	One of Jaycees Four Outstanding Young South Africans
1989	Fellow of the American College of Sports Medicine
1989	Endowed (Liberty Life) Chair in Exercise and Sports Science at the University of Cape Town

1991	Andries Blignaut Award. Best multi-authored paper published in the South African Medical Journal in 1991
1992	Elected Fellow of the University of Cape Town for sustained excellence in original scientific work
1992 and 1993	One of the three finalists of the Burroughs Wellcome Gold Medical award for medical research in South Africa
1993	Medical Research Council Publication Award for the best publication record by a South African medical scientist during the previous 3 years
1995	Selection Committee - International Olympic Committee (IOC) Olympic Science Prize (sub-committee of the IOC Medical Committee)
1996	Citation Award of the American College of Sports Medicine
1996	J B Wolffe Memorial Lecture, American College of Sports Medicine
1998	John Cutter Memorial Lecture, School of Public Health, Harvard University, USA
1999	Honour Award of the South African Sports Medicine Association (First such award)
1999	Elected Founding Member of the IOC Olympic Academy of Sports Sciences, (IOC Medical Commission)
2000	Endowed (Discovery Healthy) Chair in Exercise and Sports Science at the University of Cape Town
2001	Ministerial Commission into High Performance Sport in South Africa
2001	International Cannes Grand Prix Award for Research in Medicine and Water
2002	Best Congress presentation - Annual Congress of the Canadian Sports Medicine Association
2003	Book Award of the University of Cape Town (*Lore of Running*)
2003	National Research Foundation, Technology and Human Resources for Industry Programme (THRIP) Excellence Award

Timothy Noakes is Professor in the Discovery Health Chair of Exercise and Sports Science at the University of Cape Town. He is also Director of the UCT/MRC Research Unit for Exercise Science and Sports Medicine and co-founder with Morné du Plessis of the Sports Science Institute of South Africa, of which he is presently the Executive Co-Director with Mr du Plessis. Whilst a student at UCT, he rowed for the South African Universities on two consecutive seasons and was awarded University full Blue colours. He began long distance running in 1972 and, at the time of his last marathon in 1990, had run more than 70 marathon and ultra-marathon races including 7 Comrades Marathons (best

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time 6 hours 49 minutes) and 15 Two Oceans Marathons (best time 3 hours 59 minutes). Thereafter he was active in cycling and triathlon events and completed the Argus 105km Cycle race on 8 occasions.

Noakes is the author or co-author of more than 350 scientific publications and is on the Editorial Boards of 13 international scientific publications. He is a Fellow of the American College of Sports Medicine. In 1992, he was elected a Fellow of the University of Cape Town for sustained excellence in original scientific work. In 1992 and 1993 he was also one of the three finalists for the Burroughs Wellcome Gold Medal award for Medical Research. In 1993 he received the Medical Research Council Publications award for the best publication record in the previous three years by a South African medical scientist. In 1996 he was awarded the Citation Award of the American College of Sports Medicine and was the first African and one of very few non-North Americans to present the prestigious J B Wolffe Memorial Lecture at the American College of Sports Medicine. In 1999 he was elected as one of 22 founding members of the International Olympic Committee (IOC) Olympic Science Academy. In 2001 he received the International Cannes Grand Prix Award for Research in Medicine and Water, for his studies of water intoxication in athletes, especially marathon and ultra-marathon runners. In 2002 he received the Doctor of Science degree from the University of Cape Town.

His book *Lore of Running* is in its fourth edition in South Africa and the United States and has been translated into Japanese and currently into French. It is widely praised as the most complete such book yet written – the "Bible" of running. In 2003, *Lore of Running* was awarded the University of Cape Town Book Award. Noakes is also co-author of *Running Injuries* (with Steve Granger), *Lore of Cycling*, *Running Your Best* (with Steve Granger) and *Rugby Without Risk* (with Morné du Plessis). Currently he is working on *The Art and Science of Cricket and Coaching* (with Bob Woolmer and Helen Moffett) and *Waterlogged*, the latter detailing the evolution of the condition of water intoxication in marathon and other endurance athletes.

Noakes is married to Marilyn Anne. They have two children, Travis (born 1973) and Candice (born 1975), both of whom are resident in Cape Town, South Africa.

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(b) A detailed synopsis of the contents of the work including a statement on the nature and value of the contribution.

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I was appointed as a lecturer at the University of Cape Town in January 1981 in order to initiate the BSc Med. Honours Course in Sports Science as it was then known. The teaching and research opportunities provided by that appointment has produced a body of work over the past 20 years that has, in my view, made a seminal contribution to the development of knowledge in the exercise sciences. It is this body of work that I wish to be considered for the award of this degree. In the following sections of this submission I have detailed the nature of that work and the reasons why it might be sufficiently seminal to be considered for the award of this degree. This part of the submission includes a series of papers grouped according to 4 separate research foci.

During this period I have also written four editions of the book, *Lore of Running*. The book has been extremely well received internationally. The *British Journal of Sports Medicine* has called the book the "Runner's Bible" whilst the Editor of *Runner's World* in the United States, the running magazine with the largest international circulation, has ranked the third edition, as the top book ever written on running. The fourth (South African) edition has recently been reviewed in both *Science* and *Nature*.

That book tracks the development of the knowledge that has derived from my research and teaching efforts, placing that work in an international and historical context more effectively than I would be able to do without also including another very long manuscript with this submission. Only in the book has it been possible to place the contributions of my academic career in an historical perspective and to develop certain contentious themes in their entirety. Thus I have taken the opportunity also to submit copies of that book so that the reviewers are fully conversant with what I consider to be the full scope of my work submitted for consideration for this degree.

I thank the reviewers for the time they spend in the review of this submission.

(i) The marathoners's heart immunity theory of Bassler

Perhaps my first significant contribution was to show that marathon runners are not immune from heart disease as had been proposed by a Californian pathologist in the early 1970s. This work was published in the New England Journal of Medicine (*Paper 1*) and in the Annals of the New York Academy of Sciences (NYAS) (*Paper 2*) after I had presented the work at the NYAS Conference on the Marathon in New York in November 1976. This work comprised a portion of my MD thesis. The novelty of this work was such that it was afforded the honour of an accompanying editorial in the New England Journal of Medicine under the title Cardiomythology and Marathons (*Paper 3* – not my work). This was my first encounter with some of the mythologies of the sports sciences.

The historical background to this debate was unfortunately removed from this edition of Lore of Running due to limitations in the size of the final book that could be published (no more than 1280 pages can be bound by current methods at the Cape Town publishing house). However the details of the debate are probably adequately covered in *Papers 1–3* of this submission.

Related work also completed for my MD thesis, was amongst the first to show that hearts from trained rats were better able to resist the development of ventricular fibrillation during experimental heart attack (acute myocardial infarction) (*Paper 4*) produced by abrupt ligation of the anterior descending coronary artery. This protective effect may have resulted from an altered myocardial cyclic AMP metabolism induced by exercise training.

A subsequent study undertaken to extend those findings and completed with my guidance, showed that rats that were exercise trained after they had undergone an initial experimental myocardial infarction also showed an increased resistance to ventricular fibrillation during a subsequent acute myocardial infarction (*Paper 5*). This provided experimental evidence that training that commenced even after a first heart attack might beneficially reduce the risk of sudden death during a subsequent myocardial infarction.

Large-scale epidemiological studies have since shown that those who are physically active are at about one-third the risk of dying suddenly from primary cardiac arrest, compared to those who are inactive. The strongest evidence for this conclusion is detailed on *pages 1111* and *1112 of Lore of Running*. Other relevant material can be found between *pages 1113* and *1125*.

Hence the laboratory studies that I initiated anticipated the findings from large-scale epidemiological studies. They also provide a potential biological basis for the protective effect of exercise training against the development of sudden cardiac death. A more detailed discussion of the biological changes in the heart that are brought about by exercise training was also removed in the final editing process for this edition of *Lore of Running*.

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(ii) The "dehydration myth" including the first report of water intoxication during prolonged exercise and the first confirmation of the physiological mechanism causing that condition.

A paper published in 1969 by researchers at the Chamber of Mines in Johannesburg gave rise to the theory that dehydration is the most dangerous affliction to strike endurance athletes, marathon runners in particular. It was concluded that more severe levels of dehydration would cause heatstroke and impair performance. This theory represented a fundamental intellectual indeed paradigm shift since, until then, the popular practice of marathon runners was to avoid all fluid ingestion during exercise since it was believed that such ingestion would impair their racing performances, not least by causing gastrointestinal symptoms (*Paper 6*). The full context of these historical ideas and our novel contributions are detailed between *pages 239–248* and *251–265 of Lore of Running*. More recently I have re-discovered British work from the 1950s which develops a theory, clearly also lost after 1969, that humans are unique in that they probably exist in a mildly-overhydrated state (compared to most other mammals) and have a fluid reservoir of about 2.5 litres that does not need to be replaced during exercise. There is much in our own findings that could be explained by this old theory.

Two events happened that made me uncertain that this new paradigm was correct. The first was our first description of cases of hyponatraemia during prolonged exercise. Since it is usually taught that hyponatraemia in healthy persons results from fluid overload and since the runners who developed this condition either recalled that they had drunk substantial volumes of fluid over many hours during very prolonged exercise or else they showed high rates of urine production during recovery (suggesting that they had finished such races in a state of positive fluid balance), we concluded that this condition likely occurred in athletes who simply drank too much during exercise (*Paper 7*). Indeed we concluded that athletes should be warned that:

> "The etiology of this condition appears to be voluntary overhydration with hypotonic solutions combined with moderate sweat sodium chloride losses ... Advice (on fluid replacement) should be tempered with the proviso that the intake of hypotonic solutions in excess of that required to balance sweat and urine losses may be hazardous in some individuals."

My second moment of insight occurred during a study in which I measured the rectal temperature of the winner of an ocean paddling (kayaking) race and discovered that despite not drinking at all during a 4 hour stage in which he finished first (he had lost his bottles when paddling out through large surf at the start of the stage), his rectal temperature was barely elevated (*Paper 8*). It was clear that marked dehydration could be present without the inevitable increase in rectal temperature predicted by the Wyndham and Strydom hypothesis (*Figure 4.9 on page 253 of Lore of Running*). Hence there had to be some other confounding variable that produced what I suspected must be a spurious relationship that Wyndham and Strydom had detected and had assumed to be a causal relationship. Establishing that variable would clearly be important especially if this single finding was being used (i) as the scientific basis for a radical change in the way running races were to be conducted in the future so that future athletes would be encouraged to

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drink "as much fluid as tolerable" during exercise in order to prevent even the slightest dehydration, and (ii) as the basis for the therapeutic protocols that were being developed for the treatment of athletes who collapsed during or after exercise.

A series of experiments then followed in which we were unable to reproduce the classical Wyndham/Strydom linear relationship between the post-race rectal temperature and the level of dehydration that developed in competitive athletes during *out-of-doors* competition. Since there also seemed to be no evidence that dehydration had a significant effect on athletic performance in out-of-doors competition (since the most dehydrated runners were usually the winners of these events as also reported by Wyndham and Strydom), I coined the term the "dehydration myth" to identify what I believed to be an unproven theory that dehydration is necessarily harmful for performance or dangerous for health during exercise (*Paper 9*). I was particularly concerned that the propagation of this mythical hypothesis would have undesirable practical consequences since it would encourage athletes to drink "as much as tolerable" during exercise and this might have fatal consequences for some who followed the advice to the letter, since they would develop water intoxication (hyponatraemia) (*Paper 7*). This new paradigm would also likely encourage clinicians to assume that all the problems that develop during prolonged exercise are the result solely of "dehydration" (next section). The full extent of this debate can be found in *Box 4.4 on pages 254–258 in Lore of Running.*

At the same time, our further studies of hyponatraemia established that the condition was not as uncommon as expected; it exists in symptomatic and asymptomatic forms and that, without exception (since confirmed), the symptomatic form is due to fluid overload (*Paper 10*) to which any associated sodium deficit can play no part since the condition cannot occur but with fluid overload, most especially an absolute expansion of both the extracellular (ECF) and intracellular fluid spaces. Whilst any sodium deficit will exacerbate the degree of hyponatremia at any level of fluid overload, the sodium deficit is not the primary cause of the condition. Hence if sodium-containing drinks are ingested in excess of rates of fluid loss from the body during exercise, they will still cause hyponatremia to develop. (This is because the average sodium concentration of sports drinks is only about 20mmol per litre whereas the ECF sodium concentration is 140 mmol per litre. Thus for each litre of ECF stored from an ingested sports drink, the ECF sodium content will be 120mmoles (140–20 mmoles) less than it should be. If the ECF volume is 12 litres, this will cause the ECF sodium concentration to fall by 10mmoles per litre).

It is important to point out that at the very time that our research had established beyond doubt that the hyponatraemia of exercise results from fluid overload, the opponents of this view were promoting the concept that drinking "as much as tolerable" is the only safe technique to reduce the risk of heat injury and to optimise performance during exercise. Note that, from that time, water and sports drinks were being prescribed as a medicine (to prevent a medical illness – heat injury) but had not been exposed to the usual practice of other therapeutic interventions in which the safe dosage range of the product must first be determined before the product is released for public use. The explanation is perhaps obvious: How could water or a sports drink be dangerous to health? Especially when these new guidelines enjoyed the absolute scientific credibility provided by the endorsement of the American College of Sports Medicine and its leading scientists.

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As a result of these new theories, in 1989 the United States (US) Military introduced new guidelines for drinking during military activities out-of-doors. These new guidelines seem to have been occasioned by the Gulf War in which much was made of the role of water as a tactical weapon in desert warfare. Similarly at about the same time, the American College of Sports Medicine (ACSM) produced guidelines that promoted this same philosophy that the optimum strategy for fluid ingestion is to drink "as much as tolerable" both before and during exercise.

As foreseen by our findings, these new guidelines had a sequence of predictable consequences. First, the incidence of hyponatraemia rose alarmingly in the US Military after 1989 with 19 hospitalisations for severe symptomatic hyponatraemia reported annually between 1989 and 1999. Thereafter the guidelines were revised with a return to the more conservative drinking policy of previous years. Revision of these guidelines occurred shortly after the first (avoidable and preventable) deaths from this condition were reported in the US Military. Fortunately the US Military came immediately to the correct conclusions about what was causing this condition; other influential organisations were not as expeditious in their capacity to accept the obvious. By 1998 it was also clear that this condition, which in other countries had been restricted largely to athletes participating in ultra endurance events lasting 8 or more hours, had suddenly begun to occur in much greater numbers in marathon runners in the United States, particularly in those who took 5 or more hours to complete standard 42km marathon races. The first (avoidable) death from this condition in this group of athletes was reported in a married (with children) female US marathon runner in 1998 although it seems certain that at least one other death had occurred as early as 1993 in another female runner in the Valley of the Giants Marathon in California, USA.

As such deaths occurred in persons who were likely in the peak of their physical condition, and since the deaths were self-inflicted, these cases were particularly disturbing, especially since I believed that we had already published the definitive study establishing why these deaths would occur (*Paper 10*) and how they could very easily be prevented (*Papers 6 and 10*).

The commercial sports drinks industry which became increasingly more powerful after its development in the mid-1970s, especially in the United States but also in Europe and the rest of the world about a decade later, is one possible external factor that may have contributed both to the evolution of this disease and to the scientific disinformation necessary to delay the acceptance of its solution. Included in this erroneous scientific information are the revised guidelines for fluid replacement during exercise produced by the American College of Sports Medicine (ACSM) in 1996. The gist of these guidelines is that athletes should drink "as much as can be tolerated" during exercise, specifically to prevent any degree of dehydration, since any dehydration will impair athletic performance and increase the risk of serious heat illness including death.

Some very recent examples of the "scientifically endorsed" promotional hype that encourages this drinking approach are provided in *Figures 11* to *15* and *Paper 13*. Interestingly, *Figure 11* comes from the January/February 2002 *New York Runner* magazine. This despite the fact that a special medical meeting was held the day before the

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(November) 2001 New York City Marathon, specifically to address the problem of overdrinking during modern US marathon races. *Figure 12* is from newspaper interviews published before the (January) 2002 Houston Marathon and collected for me by a young scientist involved in that race whose research I have assisted and which has helped to establish that this information is totally incorrect. Not surprisingly, the Houston Marathon has the highest incidence of hyponatremia in any marathon race in the world. Only after research undertaken in the 2002 race showed the stupidity of this advice, did the "penny finally drop" so that from 2003, there will be fewer aid stations in the Houston Marathon and runners will no longer be encouraged to "drink as much as possible" during that race (*Paper 13* – not my own work). *Figure 14* appeared in the June 2002 issue of *Runner's World* (US edition) whereas *Figure 15* appeared one month later, in July 2002.

This is an historical sequence since it establishes that between June and July 2002, there was a fundamental change in the advertising material produced by the Gatorade Sports Science Institute so that the July advertisement finally warns about the dangers of overdrinking anything (either water or sports drinks) since this practice could be fatal, in line with our conclusion drawn in 1985 (*Paper 7 quoted earlier*).

Since (i) some of the scientists involved in the development of the ACSM guidelines also received support including research grants, from the sports drinks industry (as does our work in South Africa but only from a South African company that does not promote this "drink as much as tolerable" philosophy) and (ii) the sports drinks industry is one of the title sponsors of the programmes of the ACSM, there must clearly be some possible concerns that subtle, long term commercial interests might have interfered with the scientific process in this issue. Note for example the statement in the commercial advert in *Figure 11* to the effect that this information is the result of "thousands of tests" conducted by scientists in the Gatorade Sports Science Institute. This statement is not evidence-based.

The debate finally reached flash point with the publication in the past two years of a series of papers which finally link the rising incidence of hyponatraemia in the US Military and US marathon runners with this "drink as much as tolerable" philosophy. During this time, one of my own publications (*Paper 16*) was subject to bitter attack with the following comments being typical of the emotive nature of this debate:

> "We have spent months correcting damage among physicians, athletic trainers, coaches and athletes done by the article published last year by Dr Noakes on hyponatremia and similar comments by him in the October 2000 *Runner's World*."
>
> "I am incensed by the article on hyponatremia by Flinn and Sherer and the commentary by Dr Noakes, both of which fail to address the consensus opinions of hyperthermia as relating to dehydration ...".

These statements are typical of the comments to which I have been subjected at times during the past 15 years, especially by US scientists involved in research of fluid balance during exercise. I have reason to believe that these were not the only ways in which these ideas were targeted by some members of the scientific community. But an editorial (*Paper 17* – not my work) that appeared with these articles and my rebuttal (*Paper 18*) lead me to conclude that this is a case of "abnormal" science in that what seems clearly to be the truth

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was being subverted for reasons that exist beyond the confines of science. An editorial in the South African Medical Journal (*Paper 19*) emphasized the frustrations that I felt at the time and again brought the issue to the attention of South African clinicians.

Subsequent research from the San Diego and Houston Marathons in the United States has produced the first papers from that country finally to acknowledge that excessive fluid consumption is the sole cause of the hyponatremia that has become an unfortunate feature, especially of those two marathon races in the past 5 years. Together with other studies from the United States Military which draw an identical conclusion, these papers have finally forced an acceptance of our tentative conclusions first drawn in 1985. Thus I foresee that there will be a complete revision of the advice given to marathon runners and that our ideas will finally be embraced as scientifically credible and well ahead of their time.

[**Note added in preparation of this publication in November 2003**: As reported subsequently, this revision occurred in April 2003, much earlier than expected.]

The full details of all this work are described in chapter 4 of Lore of Running. One result is that the ACSM has been forced to review the scientific basis for their guidelines and that review process is now in progress. Part of that process is a paper I have recently completed for a new ACSM journal, Current Sports Medicine Reviews (Paper 20). In that paper I concluded that the death of even one athlete or military person from hyponatraemia is an indictment of the exercise sciences and the period of "pathological science" that has been allowed to divert the debate away from the truth. Not unexpectedly, that comment did not make it to the final published version of the paper! Furthermore, the editors of three important sports medicine journals, The British Journal of Sports Medicine, the Clinical Journal of Sports Medicine and the Physician and Sports Medicine have agreed to organise a consensus conference on hyponatremia in April 2003 under the auspices of the International Olympic Committee, finally to close this sad chapter in the exercise sciences.

[**Note added in preparation of this document in November 2003**: Events overtook even this optimistic prediction. As discussed subsequently, in April 2003 United States of America Track and Field (USATF) announced that as from that time the guidelines developed through the research programme described here would be adopted for all running races in the United States. These guidelines include the specific advice to avoid overdrinking in order to prevent hyponatraemia.]

Included in *chapter 4* is reference to another innovative contribution, which was to predict that the volume of fluid in the stomach is the most important determinant of the rate of gastric emptying (*Paper 21*). This has important implications for the optimum drinking procedure that athletes should adopt during exercise (*Figures 4.12* and *4.13* on *pages 282* and *284* of *Lore of Running*). But somewhat paradoxically, if athletes do not need to drink "as much as tolerable" during exercise, then they have little need for this method. But it does explain why it is indeed possible for humans to drink at rates of up to 2 litres per hour and to empty that fluid into the intestine from where it is rapidly absorbed, setting up the necessary conditions for the development of hyponatraemia, as described in *Paper 22*. This paper appeared together with an editorial that also addressed the "dehydration myth" (*Paper 19*).

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It may be of some interest that, on the basis of this work on fluid balance during exercise, I was awarded the Cannes International Grand Prix Award for Research in Medicine and Water for the year 2002. I receive that award at the Annual Congress of that organisation held in Cannes, France in June, 2002.

Perhaps the relevant point is that my contribution was that I remained faithful to what I believed to be the truth despite what may yet prove to be an orchestrated programme to promote commercial interests despite the scientific evidence. In the end, it seems that scientific truth did eventually prevail.

[**Note added in preparation of this publication in November 2003**: In April 2002, a 28-year-old female collapsed during the Boston (USA) Marathon and subsequently died from hyponatraemic encephalopathy despite receiving medical care. Subsequently it was reported in the New York Times that she died because she had drunk a large volume of the sports drink, Gatorade. This death encouraged me to revise and re-submit an editorial on the dangers of overdrinking during exercise that I had first submitted unsuccessfully to a North American medical journal in 2000. Two further submissions to North American medical Journals in 2002 were equally unsuccessful. However in June 2003, the editorial was finally published in the British Medical Journal on July 19th 2003 (*Paper 23*). The editorial was widely reported in the media around the world. This finding that overdrinking during exercise can be dangerous was also selected as one of the top 100 scientific findings of 2003 by *Discover* magazine for their annual (January 2004) publication – accessible at www.discover.com.]

(iii) Development of a novel approach to the management of exercise-associated collapse in marathon and ultra marathon runners including the re-definition of the so-called "heat illnesses" of exercise.

Since Wyndham and Strydom's publication established the belief that dehydration is the essential cause of heatstroke and the other forms of so called "heat illnesses" in athletes, it was natural to assume that athletes who collapsed in marathon and longer distance races were suffering from a condition, the optimum treatment of which would simply be to correct their associated fluid deficit. Hence the "dehydration myth" (*Paper 9*) spurned a specific approach to the treatment of athletes who collapsed in marathon and longer distance races. The standard practice became one in which the diagnosis was obvious ("dehydration") so that there was no need to perform even a basic clinical examination before beginning the incontestably ideal treatment which was the correction, with intravenous fluids, of the sole aetiological factor which was always dehydration (*Paper 24*).

During my early years as a doctor following my graduation in 1974, I was frequently asked to provide medical cover at the finish of those marathon or other races in which I was competing. Our approach was completely lackadaisical by modern standards, simply because we essentially never saw any athletes who required medical care at the end of those races. This despite the fact that the amounts of fluid ingested by runners in those races was very much less than has subsequently become the practice and was essentially negligible

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as detailed on *pages 251–254* of *Lore of Running*. For example, in my first 88km Comrades Marathon in 1973, I did not drink at all for the first 27km (2 hours) and probably drank a maximum of about 350ml per hour for the remaining 61km of the race for a total of about 1700ml.

However with the boom in marathon running that began after 1976 (*Figure 10.1* on *page 780* of *Lore of Running*), there was a sudden and very dramatic increase in the number of athletes who required medical care after those marathon and ultra marathon races. It was also at about this time that seconding (aid) stations, positioned at regular intervals of 2–3 kilometres along the course, became a common feature of these races. At each of these aid stations, runners were implored not to pass up the opportunity to feast on the oceans of fluid and other culinary accoutrements that were on offer. It was also at this time that I became puzzled by the obvious discrepancy between a theory that predicted that this approach would reduce the number of athletes requiring medical care after these races and the opposite reality. I therefore initiated a series of studies to determine the likely aetiology of this novel running pandemic.

There were 3 crucial findings from these studies. First, the vast majority (>99%) of athletes requiring medical care after these races could *not* be classified as suffering from heat illnesses (the popular international diagnosis) since (a) their rectal temperatures were no higher than were those of control runners who completed the same races without requiring medical care (*Paper 25*); (b) they did not require actively to be cooled (by being placed in an ice bath, for example) to insure their recovery. This contrasts with the outcome in the single true heat illness in athletes, heatstroke, for which death is the only probable outcome if active cooling is not initiated as a matter of some considerable urgency; (c) the vast majority (~75%) of athletes who collapse during marathon and ultra marathon races do so only after they cross the finishing line (*Paper 25*). This immediately suggested that dehydration cannot be the important aetiological factor since, if dehydration altered cardiovascular function such that the regulation of blood pressure was impaired, then this collapse should occur during the race when the cardiovascular demands are greatest and not after the athlete finishes the race, after which the cardiovascular demands are falling; and (d) postural hypotension develops after prolonged exercise in a majority of athletes (*Paper 26*).

On the basis of these findings, we developed the concept that athletes collapse after completing exercise, not because they are dehydrated, but because they develop a postural hypotension that begins the moment they stop exercising (*Papers 25* and *26*). The proposed physiological basis for this hypotension is described on *pages 313–315* of *Lore of Running*. Only more recently have I become aware of what I have termed the Barcroft/Edholm reflex, first described in 1944 and subsequently forgotten, it seems, in which a falling right atrial pressure causes a reflex vasodilatation in skeletal muscle, inducing fainting (*Paper 27*) and which is likely to be a major component of this condition.

Using these ideas we have developed (*Paper 28*) and field tested a novel management approach for post exercise collapse (*Papers 29* and *30*; see also *pages 318–323* of *Lore of Running*) and have used it successfully for the past four years in the management of athletes requiring medical care after the 56km Two Oceans ultra marathon foot race and

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the 226km Cape Town Ironman Triathlon. During that time we have successfully treated a few hundred athletes without once reverting to the "standard" treatment, which is the use of intravenous fluids. This confirms that the ideas first proposed in 1988 (*Paper 24*) are likely to be correct.

The result is that in November 2001, I was invited to present these ideas in New York to an international organisation of medical personnel involved in the care of marathon runners. A document, of which I am the first author, has since been submitted to the Board of Directors of that organisation for its review and has been published in the official quarterly journal of the International Association of Athletics Federations (*Paper 31*). Should the content of this document be accepted, these guidelines for fluid replacement during exercise and the manner in which collapsed athletes should be treated after exercise, will become the international standard. It is notable that these ideas, generated from our focused research over 20 years, have been preferred to those of the ACSM with which they are in conflict.

Besides appearing at length in *Lore of Running*, these very novel ideas have also been published in two of the most influential current textbooks in sports medicine, namely *Clinical Sports Medicine* by Brukner and Khan (2000) and the International Olympic Committee publication, *Endurance in Sport* (Shephard, 2000), and have extended beyond the confines of sports medicine to be included in the most recent issue of Conn's *Textbook of Medicine* (*Paper 32*).

[**Note added in preparation of this publication in November 2003**: On the weekend of the annual Boston Marathon footrace in April 2003, USATF announced that forthwith the guidelines described here for the medical management of running races including our guidelines for fluid ingestion during exercise (*Paper 31*) and which arose from the research programme described here (*Paper 33,* not my own work), would be applied to all running races in the United States. The important changes are that in future (i) athletes will be advised to drink according to the dictates of thirst rather than "as much as tolerable" and (ii) all collapsed athletes will no longer be presumed to be "dehydrated" and immediately treated with intravenous fluids. Rather they will be examined and treated selectively according to any specific medical conditions that may be diagnosed – as I had first suggested in 1988 (*Paper 24*) – seemingly confirming the general rule that it takes about 15 years before a novel (correct) idea is accepted into the medical mainstream to replace an incorrect dogma.

As a result in August 2003 I was invited to update *Paper 31* to include a series of new studies completed between 2001–2003 and which further showed that the mania for overdrinking especially in the United States, is the principal factor causing hyponatraemia (*Paper 34*). Then in November 2003, I came across *Papers 35–37* (not my own work) on a United States website for fist-time marathon runners. It is interesting how knowledge available in 1985 has now quite suddenly become the norm. It is also of interest that there is no reference to the source of these ideas; rather it appears as if only North Americans contributed to these ideas. Further, there is the commercial involvement by another company that manufactures non-steroidal anti-inflammatory drugs in the dissemination of this novel "health message".

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Finally it is of some historical interest that in 1998 I was privileged to be invited to attend the 224km Hawaiian Ironman World Championships in Kona, Hawaii. Medical staff at that race, which had been sponsored by the manufacturers of the United States sports drink, Gatorade, almost from its inception (but which sponsorship had been withdrawn for the 1998 race, thereby allowing my attendance for the first time), had consistently argued that the hyponatraemia of exercise is caused by dehydration (*Paper 38* – not my own work) and that intravenous fluid therapy is the cornerstone for the treatment of all collapsed Ironman Triathletes. There I presented the ideas detailed in *Papers 31* and *34* and in particular, (i) the technique of treating all collapsed athletes in the head-down (Trendellenberg) position; (ii) the need first to make an appropriate diagnosis before instituting any therapy including the use of intravenous fluid and (iii) that hyponatraemia results from fluid overload. The ideas were not especially well received even though they seemed to work well in the management of those athletes in whom they were tested in that race. Shortly before returning to South Africa after the race, one of the senior nursing staff informed me to the effect that "these ideas may well work in South Africa, but they do not work in Hawaii". *Paper 38* (not my own work) written by the medical director of that race indicates that 4 years later what works in South Africa now seems also to work in Hawaii!]

(iv) Challenging the scientific basis of the "plateau phenomenon" and the development of the Central Governor (Integrated Neuromuscular Recruitment) Theory of Exercise Physiology and Athletic Performance.

A core teaching in the exercise sciences is that an oxygen deficit develops during especially maximal exercise and it is the resulting anaerobiosis that causes fatigue and the termination of exercise. This hypothesis stems from work undertaken by Nobel Laureate Archibald Vivian Hill between 1923 and 1925 at University College, London, following the work of another Nobel Laureate, Frederick Grover Hopkins at Cambridge University in 1907.

It was whilst researching certain material for the first edition of Lore of Running that I was able to show with a retrospective analysis of his own data, that Hill's work had not ever established that an oxygen deficiency developed during exercise in his studies or that this explained what caused the termination of exercise (*Paper 39; Figure 2*).

The further development of this argument is described in detail in *Chapter 2* of *Lore of Running*. In brief, in 1996 I was invited to deliver the J.B. Wolffe Lecture at the annual meeting of the American College of Sports Medicine. For that lecture I chose to review what I considered to be a series of "creaking and ugly edifices" in the exercise sciences including the concept that muscles become anaerobic during maximal exercise and that it is the metabolic products of this anaerobiosis that causes a peripherally-based, metabolite-induced fatigue of skeletal muscle. At the conclusion of that lecture, I proposed

> "...an alternate physiological model ..... in which skeletal muscle contractile activity is regulated by a series of central, predominantly neural, and peripheral, predominantly chemical, regulators that act to prevent the development of organ damage or even death during exercise in both health and disease and under

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demanding environmental conditions."

"Regulation of skeletal muscle contractile function by central mechanisms would prevent the development of hypotension and myocardial ischemia during exercise in persons with heart failure, of hyperthermia during exercise in the heat, and of cerebral hypoxia during exercise at extreme altitude" (*Paper 40*).

This represented one of the first novel proposals on this topic in 75 years in the exercise sciences.

Interestingly, the article from this lecture was, unbeknown to me before its appearance, published together with a rebuttal that presented the conventional Hill model of exercise physiology. That article concluded with the following two paragraphs:

"...When we weigh the scientific evidence on both sides of the issue, it appears that Hill's views were amazingly accurate. Scientific investigations in the 70 years since Hill have served mainly to reinforce his paradigm and confirm that his scientific "hunches" were correct. Only relatively minor refinements to his theories have been needed."

"In contrast, Noakes' views are not supported by strong scientific evidence, and they raise numerous paradoxes and unresolved dilemmas."

However when I again re-read Hill's work, I discovered two crucial component of his theory that had lain forgotten for 75 years. First, Hill had realized that if the active skeletal muscles do indeed become anaerobic during exercise as a result of a limiting blood flow, then the first organ to be affected by this inadequate blood flow would in fact be the heart itself. Hence Hill's model required that the heart first develop an inadequate blood supply (myocardial ischaemia) during exercise. Second, Hill understood that this ischaemia would be damaging to the heart. He therefore proposed that there would need to be a "governor" existing either in the heart or the brain that would reduce the activity of the heart so that the heart would be prevented from damage, especially during maximal exercise.

When I read that article, I immediately realized that Hill's proposed "governor" would not be in heart but in the brain and that it would function, not to reduce the pumping capacity of the heart during exercise, but the work output of the active skeletal muscles. For any reduction in the work output of the muscles would also reduce the work of the heart thereby protecting the heart from damage (*Papers 41* and *42*).

Accordingly I proposed the Central Governor Theory (*Papers 43* and *44*) to explain how the body functions during exercise. The importance of this novel interpretation is that it sees the function of the body during exercise as a regulated process, the aim of which is to prevent the development of bodily damage. In contrast, the traditional model is based on the belief that exercise terminates only after one or more limitations are reached, in other words, after the system has already failed. The "failure" models (*Paper 42*) that are especially popular are the failure of oxygen delivery to the exercising muscles causing a lactate and pH-dependant inhibition of muscle contraction during high intensity exercise, or the depletion of muscle glycogen stores causing an inability to generate ATP sufficiently rapidly during more prolonged exercise. Note that both these "limitations models" exclude

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any possible role of the brain in the regulation of exercise performance. In contrast, the Central Governor Model opens the possibility that the brain is the central regulator and integrator of all the physiological processes that happen during exercise.

At a special symposium organized at the 2001 Annual Congress of the American College of Sports Medicine, Professors Vicki Lambert, Alistair St Clair Gibson and I presented these novel ideas in a more complete form for the first time. The scientific papers based on that symposium are currently in the final stages of preparation. We have realized that the final test of the Central Governor Model will *not* be provided by any evidence that muscles do or do not become anaerobic during exercise but rather by the extensive evidence that it is not possible to recruit all the skeletal muscle motor units during any form of voluntary exercise. Since complete motor unit recruitment is not possible during voluntary exercise, the conclusion has to be that the final control of exercise performance resides in the brain. I have since presented this more complete theory as the Key Note Lecture in 3 international conferences in 2002; the Annual Congress of the Canadian Sports Medicine Association in Mount Tremblant; the Ninth World Symposium of Biomechanics and Medicine in Swimming in Saint-Etienne, France; and the Twelfth Commonwealth International Sport Conference in Manchester, England.

If this theory is correct, it is a seminal contribution since it fundamentally alters the focus of research in exercise physiology from the traditional approach that has been followed ever since Hill's original and incorrect thesis was first developed in 1923.

Some of the implications of these new ideas that I had already realized at the time of completing the book, are discussed in greater detail in *Lore of Running*. Pages that will be of especial interest are the following:

Chapter 1	Pages 3–4	Box 1.1
Chapter 2	Pages 30–44	
Chapter 3	Pages 119–122	Box 3.1
Chapter 3	Pages 137–147	Box 3.3
Chapter 3	Pages 182–186	Box 3.9
Chapter 4	Page 225	Box 4.1
Chapter 8	Page 687	Box 8.1
Chapter 8	Page 701	
Chapter 13	Pages 951–953	Box 13.3
Chapter 13	Page 965	Figure 13.3

An obvious criticism at this time is that I have developed a theoretical model for which, at present, I have presented little firm scientific evidence myself. Rather I have used the published work of others to substantiate my theory.

In fact at present we are involved in specific tests of this hypothesis by having athletes exercise to exhaustion in a chamber in which the fraction of oxygen in the inspired air is greater than normal (up to 66%). To our knowledge, this is the first time that such exercise

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has been performed in a chamber; other experiments have had athletes inhale from a gas bag which contains the enriched oxygen. Our preliminary studies showed that this technique is invalid since the increased resistance to breathing from the gas bag introduces a spurious result which is the opposite of the result when the exercise is performed in the oxygenated chamber. The results of these studies suggest that, under these conditions of maximal exercise at sea level, the central governor is responding to something other than the oxygen tension of the inspired air or of a specific tissue. We are currently involved in the next series of experiments to test the theory that it is sensory feedback from the respiratory muscles, specifically related to the amount of work they are performing, which provides the signal to the brain to terminate progressive maximal exercise.

But more to the point, we have published two other studies that, in my opinion, clearly establish the action of a governor during prolonged exercise since they provide further evidence that there is incomplete skeletal muscle motor unit recruitment at exhaustion. The research protocol used in *Paper 45* was designed by myself as part of a research contract with an industrial partner. Although I did not personally conduct the study, there were 3 crucial methodological advances that were introduced in that study and to which I made a significant contribution. First we allowed the subjects to pace themselves throughout the time trial. Second we included repetitive bouts of all-out sprints in the body of the prolonged exercise (100km) bout. Third we measured electromyographic activity in the vastus lateralis muscle for the duration of the exercise. The clear evidence from that study is that muscle recruitment by the brain falls progressively during the successive sprint bouts indicating central, not peripheral regulation of the exercise response. This is entirely compatible with my hypothesis first proposed in the 1996 J.B. Wolffe Lecture to the effect that:

> "... skeletal muscle contractile activity is regulated by a series of central, predominantly neural, and peripheral, predominantly chemical, regulators that act to prevent the development of organ damage or even death during exercise in both health and disease and under demanding environmental conditions."

However in reflection, it is not the skeletal muscle contractile activity that is regulated by the Central Governor, but rather the number of skeletal muscle motor units (mass of skeletal muscle) that are recruited during exercise.

Equally importantly, these findings have been independently confirmed by our Australian collaborators who used a slightly different protocol but came to the same conclusion as had we (*Paper 46*). Both these papers can only be interpreted as evidence for the action of a central governor that regulates the amount of work that the body will be allowed to do throughout a bout of exercise. In addition are two recent publications from other laboratories showing the action of a central governor in explaining the fatigue that develops during exercise in the heat (L. Nybo, B. Nielsen. Hyperthermia and central fatigue during prolonged exercise in the heat. *Journal of Applied Physiology* 91; 1055–1060, 2001) and another showing that high concentrations of lactate improve isolated skeletal muscle function rather than the opposite (O. Nielsen, F. de Paoli and K. Overgaard. Protective effects of lactic acid on force production in rat skeletal muscle. *Journal of Physiology*, 536, 161–166, 2001). This latter study is especially important since it removes a final pillar of the traditional theory which holds that lactate acts as *the* peripheral

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regulator or governor of performance by directly inhibiting skeletal muscle contractile function whenever muscle lactate concentrations increase above some specific value.

[**Note added in preparation of this document in May 2004**: Three of our most recent papers addressing this question have recently been accepted for publication – *Papers 47–49*. The first two (*Papers 47* and *48*) show that during exercise in the heat, the brain acts to regulate the rate at which body heat is produced and stored, specifically to ensure that dangerous hyperthermia does not result. This confirms that the brain acts "in anticipation" of an event, and does not wait until catastrophe occurs, before it acts. The second study (*Paper 48*) shows that the brain acts in this way by altering skeletal muscle motor unit recruitment, thereby altering the athlete's pace, exactly as predicted by the Central Governor Model. Another recently completed study shows that the same occurs during self-paced exercise in hyperoxia. The marginally increased power output in hyperoxia is associated with increased skeletal muscle recruitment, shown by increased electromyographic (EMG) activity in the existing muscles. The third paper (*Paper 49*) establishes that anticipatory pacing also occurs during maximal exercise lasting 30 seconds.]

It is an exciting time in the evolution of this theory and novel concepts are being developed very rapidly. The ideas that have been developed so far in *Lore of Running* are really only the most primitive, initial ideas. Perhaps an important advance is the understanding that fatigue is purely an emotion that is perceived in the brain not in the active muscles (*Paper 50*, added in May 2004) and that as this sensation increases, the body responds by altering its pacing strategy during exercise (*Figure 13.3 and Box 13.3 in Lore of Running*).

What is called fatigue historically in the "limitations" models of exercise physiology, is seen by us as a change in a predetermined pacing strategy, the specific goal of which is to insure that the body does not exceed the limitations set by any bodily system. That is, that the body does not ever venture out of homeostasis. Indeed one of the great paradoxes of the exercise sciences is that we teach that the key feature of resting human physiology is the maintenance of bodily homeostasis. Next we explain fatigue on the basis of a loss of that homeostasis during exercise; yet there is no published evidence showing that homeostasis is lost during exercise. Rather the remarkable feature is how well homeostasis is maintained during exercise, regardless of its duration, intensity or the environmental conditions in which it is undertaken.

Thus our most current interpretation is that the sensation of fatigue is in some way related to the neural effort required to maintain homeostasis; that is, that fatigue is the conscious expression of those subconscious integrative processes undertaken by the central governor in its attempts to insure that homeostasis is maintained during exercise.

These ideas have fundamentally changed the focus of our future research from searching for limitations, to trying to understand how the central governor integrates prior knowledge with information coming from sensors within the body, most of which have still to be identified, and so to produce the pacing strategy during exercise that will optimize performance whilst protecting the athlete's body from irreversible harm.

The historical value of this work may well be that it is the first since the work of A.V. Hill

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in the early 1920s, fundamentally to change our understanding of whole body human exercise physiology. The critical changes that it suggests are the following:

A change from the "limitations" models of exercise physiology to one that recognises the integrative role of a central governor, the function of which is to insure that homeostasis is maintained during all forms of human exercise.

The proposal that fatigue is purely a sensation and not a physical event but that it is an alteration in the centrally-determined pacing strategy that we have erroneously called fatigue in the past.

The proposal that the physiology of pacing rather than the development of fatigue is the more important characteristic of human exercise.

Since humans pace themselves through every activity they perform throughout their lives, we can presently only guess at the ultimate importance of this novel insight.

[**Note added in preparation of this publication in May 2004:** A series of five papers documenting the totality of these novel ideas that were first presented at the 2001 Annual Congress of the American College of Sports Medicine have been accepted for publication in the *British Journal of Sports Medicine.* The titles of the 5 papers in this series are the following:

1. From catastrophe to complexity: A novel model of integrative central neural regulation of effort and fatigue during exercise in humans. Introduction.
2. Logical limitations to the "Catastrophe" Models of Fatigue during Exercise in Humans.
3. Evidence for complex system integration and dynamic neural regulation of skeletal muscle recruitment during exercise in humans.
4. Complex systems model of fatigue: integral control and defence of homeostasis during exercise in humans.
5. From catastrophe to complexity: A novel model of integrative central neural regulation of effort and fatigue during exercise in humans. Summary and conclusions.

These papers reflect the final break with the past and are co-authored by Professors Vicki Lambert and Zig St. Clair Gibon who have been pivotal in the further development, expansion and refinement of this model from its uncertain origins in 1988 (*Paper 39*). The scope of these novel ideas has been well described in a recent article in New Scientist (*Paper 51*, not my own work).

Finally, the letter to the Editor (*Paper 52*) raises the possibility that the perception of fatigue, quantified as the Rating of Perceived Exertion (RPE), is a measure of the duration of exercise that can still be sustained at that exercise intensity and in those specific environmental conditions by that specific individual, without risking failure of homeostasis (*Paper 51*).]

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(c) One set of copies of work to be submitted for the degree (with additional papers added prior to publication in May 2004).

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MEDICAL INTELLIGENCE

AUTOPSY-PROVED CORONARY ATHEROSCLEROSIS IN MARATHON RUNNERS

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With the assistance of Nico J. Schepers, M.Med., and Robert Dowdeswell, M.B.

THE relation between coronary-artery disease and marathon running is controversial. In 1961, the *Journal* published an article in which Currens and White discussed the autopsy findings on "Mr. Marathon"; the diameter of the coronary arteries was described as two to three times normal, and there was only minimal atherosclerosis.[1] This description was adduced in support of the contention that athletes capable of covering the marathon distance (42 km, or 26.2 miles) are immune to coronary atherosclerosis.[2,3] Two recent autopsy reports on marathon runners appear to support this hypothesis: in one, fatal myocardial infarction developed but the coronary arteries were normal[4]; in the other, ventricular hypertrophy with histologic features of hypertrophic cardiomyopathy developed, but again the coronary arteries were normal.[5] Several other reports[6] purporting to show coronary atherosclerosis in autopsied marathon runners have been erroneous.[7,8]

On the other hand, we have described four marathon runners with myocardial infarction and angiographically proved coronary-artery disease.[8] Autopsy data were unavailable, and our conclusions have been challenged.[9] We now report on four cases of autopsy-proved coronary atherosclerosis in marathon runners. One runner with severe coronary atherosclerosis died during a 24-km road race. Another had an occlusive coronary-artery thrombus and died in hospital while awaiting coronary bypass for unstable angina. Of three other athletes, killed in an automobile accident, two had coronary atherosclerosis. Thus, marathon running cannot ensure protection from coronary atherosclerosis or fatal coronary-artery disease, although our findings provide no information on whether coronary disease and cardiovascular death are more or less frequent in the overall group of marathon runners.

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CASE REPORTS

Case 1

A 44-year-old man had been running long-distance events for 14 months. During this period he completed eight standard 42-km marathons, a 56-km race in five hours and 59 minutes, and, on May 31, 1978, the Comrades Marathon (90 km long and very hilly) in 10 hours and 10 minutes. In training, he ran from 48 to 80 km per week. He was a nonsmoker and a social drinker. There was no relevant history of serious disease. In 1970 he received life insurance from two companies at a normal premium — indicating the absence of any apparent cardiovascular abnormality.

In July, 1978, he ran a 50-km race in four hours and 59 minutes, and on August 13, 1978, a standard 42-km marathon in four hours and two minutes. At about that time, he visited a general practitioner and complained of a nonspecific lack of energy. There were no symptoms or signs of ischemic heart disease. The blood pressure was described as normotensive, although the actual value was not recorded. The fasting serum cholesterol level was 7.65 mmol per liter (296 mg per deciliter), the high-density lipoprotein fraction 0.43 g per liter (43 mg per deciliter), and the triglyceride level 1.63 mmol per liter (145 mg per deciliter). The blood count and erythrocyte sedimentation rate were normal. Electrocardiography was not performed.

On September 16, 1978, the athlete competed in the 24-km

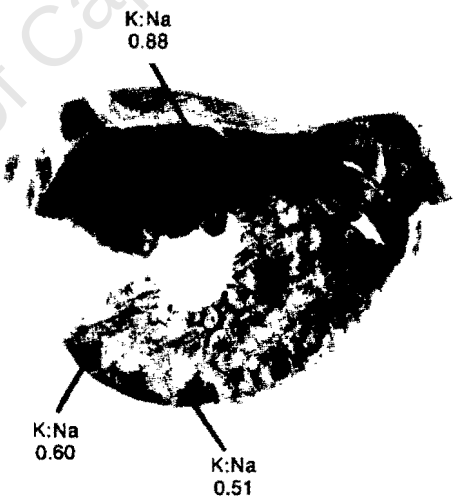

Figure 1. Transverse Slice of Both Ventricles from Case 1 after Incubation with Nitroblue Tetrazolium.

The healed anteroseptal infarction is represented by the white scarred area in the lower portion of the picture. Note loss of enzyme staining throughout the anterior left ventricular wall and in the subendocardial posterior wall, a small zone in the epicardial posterior wall at the site of the biopsy and the right ventricular posterior wall. The potassium-sodium ratios were reduced as indicated.

Reprinted from the *New England Journal of Medicine*
301:86-89 (July 12), 1979

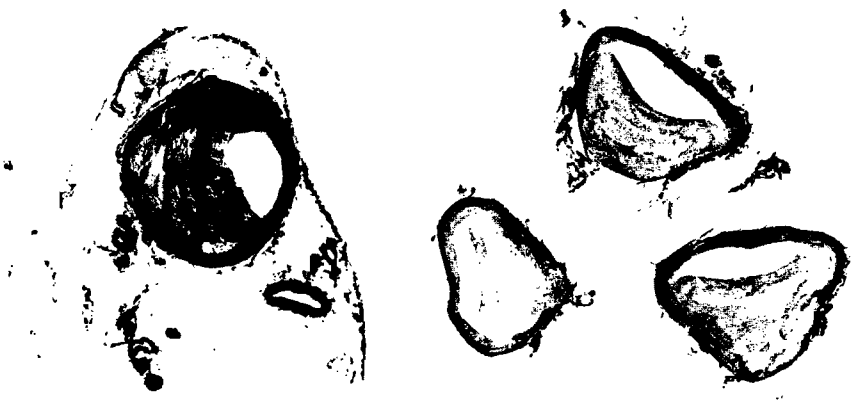

Figure 2. Anterior Descending and Circumflex Branches of Left Coronary Artery from Case 1.
In the left panel, the anterior descending branch of the left coronary artery 5 mm from its origin shows Grade 4 (75 to 100 per cent) atherosclerotic narrowing (elastin stain by van Gieson, × 7.5). In the right panel, the left circumflex coronary artery shows Grade 4 (75 to 100 per cent) eccentric atherosclerotic narrowing 3.5 cm from its origin (hematoxylin and eosin stain, × 7.5).

Simba road race. He was running without distress at the 19-km mark, when he stopped to adjust a loose shoelace. Bending down, he suddenly lost consciousness and fell to the ground. The first runner to reach him noted that he was immobile and pulseless and that facial pallor rapidly developed. All attempts at resuscitation failed.

At autopsy 48 hours after death, there were no extracardiac findings to explain the cause of death. The heart and some skeletal muscle were removed from the body, placed in ice and flown directly to us for further analysis. Fifty-six hours after death, drill-biopsy specimens were taken from the macroscopically normal left ventricular epicardium and from the skeletal muscle for analysis of potassium-sodium ratios [10]

The heart weighed 357 g, and there was an extensive anteroseptal infarction (Fig. 1). This healed infarction appeared to be of at least three to six months' duration and consisted of a mature scar devoid of inflammatory cells. Sections for microscopical examination were taken at 10-mm intervals along the course of the three arteries. About 5 mm from its origin the anterior descending branch of the left coronary artery showed Grade 4 (75 to 100 per cent) atherosclerotic narrowing of the lumen (Fig. 2, left panel), and 15 mm from its origin the artery was occluded by a completely organized thrombus, in which some recanalization had occurred. The extent of atherosclerosis in the circumflex coronary artery is shown in the right panel of Figure 2. Light microscopy revealed fibrosis of the papillary muscle. There was no evidence of coagulative necrosis, but in the subendocardium of the left ventricular posterior wall cytoplasmic contraction bands,[10-12] as well as focal fibrosis, were observed. In this portion of subendocardium no enzyme activity was detected with nitroblue tetrazolium[13] (Fig. 1). Contraction bands were also present in the posterior wall of the right ventricle, which likewise showed no dehydrogenase enzyme activity. The atrioventricular node and the bundle of His were microscopically normal. The sinoatrial node was not included with the heart received for examination.

In biopsy specimens from the macroscopically normal epicardial left ventricular wall, the potassium-sodium ratios were much reduced (0.63±0.06, mean ± S.E.M. in six specimens), whereas values in the skeletal muscle were normal (2.40±0.19 in eight specimens) — a combination found in sudden cardiac death.[14]

Case 2

This 41-year-old man had been running marathons for two years when in March, 1976, he had an acute myocardial infarction, as previously described.[8] In short, coronary angiography in July, 1976, confirmed inferior myocardial infarction and showed complete occlusion of the circumflex coronary artery, 50 per cent narrowing of the proximal portion of the right coronary and minor luminal irregularities of the anterior descending coronary artery. He was treated with propranolol, 40 mg twice a day, and clofibrate for mild, Type IIb hyperlipidemia, with cholesterol 6.85 mmol per liter (265 mg per 100 ml) and triglycerides 2.35 g per liter (235 mg per 100 ml). For exercise rehabilitation, he was advised to continue jogging but not to participate in marathon races. He had smoked three pipefuls of tobacco and two to three cigarettes per day for 20 years, but he stopped one month after infarction. He gradually increased his training and on March 5, 1977, approximately a year after myocardial infarction, he completed a 50-km race in five hours and 36 minutes. Two weeks later he ran a 42-km marathon in four hours and 45 minutes. He ran additional marathons in April and September, 1977, and in August, 1978, he ran a 42-km marathon in four hours and five minutes. In the 28-month period between his myocardial infarction and this race, he had run 3624 km and completed five marathons, as documented in his running logbook made available to us by his widow. The logbook also records numerous episodes of pain in the chest, jaws or left arm during training runs, but he did not seek medical advice.

In September, 1978, he was readmitted to hospital for two episodes of unstable angina. In October, 1978, a repeat coronary angiogram showed complete occlusion of the circumflex coronary artery (as noted before), total occlusion of the right coronary artery (progression from a 50 per cent lesion found in 1976) and more than 80 per cent stenosis of the anterior descending coronary artery (progression from minor luminal irregularities found in 1976). On the evening of October 17, while awaiting coronary bypass, he began to have severe chest pain, and electrocardiography revealed acute anterolateral ST-segment elevation with increasing size of the Q waves in V_5 and V_6. Despite therapy, the heart stopped within 1½ hours, and resuscitation failed. Consent was given for only

a partial post-mortem examination undertaken 58 hours after death.

The heart weighed 344 g. Drill-biopsy specimens were taken from the macroscopically normal left ventricular free wall and septum for analysis of potassium-sodium ratios. The three major epicardial coronary arteries were sectioned transversely at 3-mm intervals. The mainstem of the left coronary artery was free of noteworthy disease, but its anterior descending branch showed up to Grade 4 (75 to 100 per cent) narrowing. Total occlusion by a fresh thrombus superimposed on Grade 4 atherosclerotic luminal narrowing was seen 50 mm from its origin (Fig. 3). In the left circumflex artery there was up to Grade 4 narrowing, and 40 mm from its origin the vessel was totally occluded by a long-standing organized thrombus. In the right coronary artery there also was up to Grade 4 narrowing, and 23 mm from its origin the vessel was totally occluded for 6 mm by a recently organized thrombus.

The healed infarct of the left ventricular inferior wall was composed of mature, hypocellular fibrous tissue. Numerous dilated, thin-walled blood vessels were present, but there were no inflammatory cells. These appearances were in keeping with a healed infarction of over two years' duration. Incubation of a transverse slice of the heart through both ventricles with blue tetrazolium[13] showed deficient enzymatic activity only in the scarred wall of the left ventricle. Although there were neither histologic nor enzymatic changes of fresh infarction, hyperacute infarction was strongly suggested by the clinical features and the recent thrombus. The sinoatrial node was not present in the heart specimen submitted. The atrioventricular node showed mild interstitial fibrosis, but the bundle of His was normal. The descending thoracic aorta showed moderate atherosclerosis, and lung sections revealed acute edema.

Case 3

A 36-year-old man began serious long-distance running in January, 1971, and in the seven years before his death had run approximately 80 km a week. Each year he had competed in four or more standard marathons or longer races, including three 90-km Comrades Marathons and a 160-km track race. For the nine years up to 1969, he had smoked approximately 10 cigarettes per day, but had not smoked again after that date. In February, 1976, a routine medical examination revealed no symptoms or signs of cardiovascular disease. His blood pressure was 130/80 mm Hg, and the resting and submaximal-effort electrocardiograms (to a heart rate of 150 beats per minute) were both normal. On April 30, 1978, while

Figure 3. Anterior Descending Coronary Artery from Case 2.
The artery is totally occluded by a fresh thrombus superimposed on Grade 4 (75 to 100 per cent) atherosclerotic luminal narrowing 5 cm from its origin.

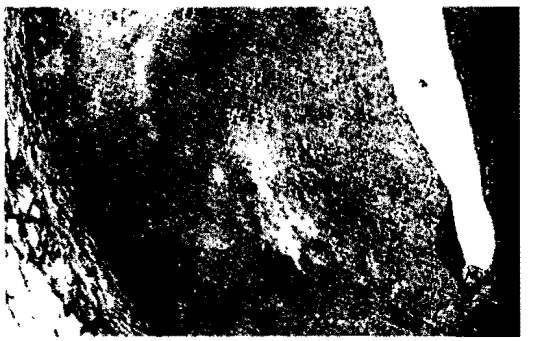

Figure 4. Diagonal Branch of the Left Anterior Descending Coronary Artery from Case 3.
Severe luminal reduction is indicated by concentric intimal fibrosis. Scanty lipid is present. Note that this marathon runner was asymptomatic, had been running for seven years and was only 36 years old (hematoxylin and eosin stain, × 50).

on a long training run in preparation for the 1978 Comrades Marathon, he and two other runners (Cases 4 and 5) were instantly killed by an automobile. Forensic autopsies were performed.

The heart weighed 360 g, and the myocardium was normal. The anterior descending branch of the left coronary artery and one of its large diagonal branches (Fig. 4) showed advanced luminal narrowing by concentric atherosclerosis of the intima. The left circumflex branch and the right coronary artery showed milder atherosclerotic narrowing. The small coronary vessels were normal. Histologic study of the ventricular myocardium showed no evidence of infarction or fibrosis. The only additional abnormality detected was a localized area of fibrous thickening on the contact area of the anterior mitral leaflet

Case 4

A 27-year-old man had been an active athlete at school and had excelled at rugby, football and middle-distance running. In February, 1977, he began long-distance running, and in the following 14 months he completed three 42-km standard marathons or longer races. One week before his accidental death he completed a 56-km marathon in five hours and 34 minutes. There was no important medical history. For the previous three years he had smoked an average of 10 cigarettes per day. At autopsy, the heart weighed 350 g, and there was evidence of subendocardial interstitial fibrosis in the left ventricle. The right ventricle showed adipose infiltration and scanty subendocardial myofibrillar degeneration. The left anterior descending branch of the left coronary artery showed 25 to 50 per cent atherosclerotic narrowing. The circumflex branch, the mainstem of the left coronary artery and the right coronary artery had no appreciable narrowing.

Case 5

Before his accidental death, this 38-year-old man had been running regularly for three years and had participated in one standard marathon and numerous shorter races. For the five years before his death, he had smoked five to 10 cigarettes per day. The coronary arteries and myocardium were normal.

Discussion

Bassler has stated that "until there is autopsy evidence of fatal atherosclerosis among marathon runners, it seems prudent to advise this life-style for the prevention of this disease."[9] We have described two autopsy-proved cases of fatal coronary atherosclero-

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sis in marathon runners. In the first runner cardiac death occurred during a road race and was shown by the abruptness of his death, the extensive coronary atherosclerosis together with a previous myocardial infarction (Fig. 1 and 2), the decreased potassium-sodium ratio in the myocardium in the presence of a normal ratio in skeletal muscle[14] (an especially noteworthy finding because the potassium-sodium ratio does not fall below 1 in the normal heart even many days after death[15]), the loss of blue tetrazolium staining[13] in the subendocardial posterior left ventricular wall and the presence of contraction bands.[10-12] Contraction bands can be found in a variety of acute myocardial injuries,[11] including sudden death[12] and early infarction[10]; combined with a decreased potassium-sodium ratio and loss of blue tetrazolium staining, these bands strongly suggest an early infarction. The blue tetrazolium staining is lost an hour or more after the onset of infarction and can be detected even in hearts stored for three days.[13] The small area of the subendocardial zone involved (Fig. 1) may explain why this runner had no cardiac symptoms before his death.

In the second athlete, inferior myocardial infarction and angiographic evidence of circumflex coronary-artery occlusion developed despite marathon running.[8] After recovery from his infarction, this runner continued to compete in long-distance races against medical advice. His symptoms worsened, and repeat angiography showed progression of the coronary-artery disease to complete occlusion of the right coronary artery and critical stenosis of the anterior descending coronary artery. He died in hospital with recent electrocardiographic evidence of acute anterolateral transmural myocardial ischemia, and autopsy confirmed extensive coronary atherosclerosis with superimposed fresh and long-standing occlusive thrombi (Fig. 3). This case argues against another statement made by Bassler, that "it is biologically impossible for atherosclerosis to progress in anyone capable of even walking the 42 km distance."[16]

Although our autopsy data provide firm evidence to disprove the "Bassler hypothesis," a number of important reservations are involved. First of all, the wider hypothesis that marathon running could give partial protection against ischemic heart disease must still be considered. Secondly, we cannot prove that marathon running did not reduce the rate of progression of coronary atherosclerosis in these or other athletes. Nor can we prove that if these men had not been marathon runners, they would not have died sooner. On the other hand, our data also do not exclude the possibility that marathon running hastened their deaths. In addition, coronary-artery disease has many causes, and undetected risk factors other than exercise could conceivably have had a role; Case 2 had mild hypertriglyceridemia, and Case 1 had a high-density lipoprotein fraction that was normal when compared with control values but low when compared with Wood's values for athletes.[17] It should also be noted that the greater alcohol intake of Wood's athletes could account for part of the elevation in high-density lipoproteins.[18]

Our data also illustrate the problems of arguing on the basis of isolated autopsy reports. An isolated report can only disprove a dogmatic statement, such as the assertion that marathon runners are immune to fatal atherosclerosis. But a single case report supplies little evidence for or against the more general thesis that marathon running or other prolonged exercise decreases the risk of fatal atherosclerosis. Indeed, the real weakness of the "Bassler hypothesis" is that it purports to establish epidemiologically valid conclusions from isolated autopsy data, whereas a proper epidemiologic survey would be required to settle the real relations between marathon running, coronary-artery disease and cardiovascular fatalities.

We are indebted to the wives, friends and doctors of the deceased runners for their willing co-operation in providing the case histories.

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CORONARY HEART DISEASE IN MARATHON RUNNERS

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Unforeseeing one! Yes, he fought on the Marathon day: So, when Persia was dust, all cried "To Akropolis! Run Pheidippides, one race more! The meed is thy due! "Athens is saved, thank Pan," go shout! He flung down his shield,
And Athens was stubble again, a field which a fire runs through,
Till in he broke "Rejoice, we conquer!" Like wine through clay,
Joy in his blood bursting his heart, he died—the bliss!

"Pheidippides"
Robert Browning
1879

INTRODUCTION

The marathon race commemorates the immortal run of an unknown soldier, fully armored and "hot from battle," to Athens to inform the Greek capital that the invading Persians had been defeated on the plains of Marathon. Had the Athenians in their unguarded capital remained ignorant of the Persian defeat, they might have surrendered without resistance to a direct seaborne invasion; thus the reason for the run.

Legend has it that, having delivered his news "Rejoice, rejoice, Victory is ours!', the messenger died suddenly from what Browning considered to be a cardiac death. Thus, in legend at least, the marathon race links extreme physical exertion with sudden cardiac death.

A recent hypothesis suggests this relationship to be unproven because "there are no documented deaths from coronary heart disease among marathon finishers of any age." [1] Thus far this hypothesis has been characterized by repetitive statement [1-27] but without any published documentation. In addition,

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it has not always been entirely clear what this "Bassler hypothesis" entails[28] because marathon running has variously been described as providing immunity to coronary heart disease,[1-10] to ischemic heart disease,[11, 12] to fatal myocardial infarction,[13-15] to "loafers heart,"[16] and to coronary atherosclerosis.[17-26]

In this paper we report six cases of myocardial infarction in highly-trained marathon runners. Four of these athletes had coronary artery disease demonstrated angiographically and considered indistinguishable from coronary atherosclerosis.

Case Reports

Case 1

A 35-year-old man had been running for at least 10 years before his death in February 1974. His athletic achievements included a best standard marathon time of 2 hours 33 minutes in April 1973, a time of 3 hours 24 minutes in April 1972 for 33 miles, and in May 1971 he finished the 56 mile Comrades Marathon in 45th position out of 925 competitors in a time of 6 hours 51 minutes. During 1972 and 1973 he ran a total of 4783 miles.

There was no family history of heart disease. His running logbook records that he went running on 11 occasions during the first three weeks of January 1974. On six of these runs reference is made to the presence of chest pain and/or pain between the shoulder blades. This was severe enough to force him to stop running on a number of occasions. During one 4½-mile time trial, at which his wife was present, she recalls that he was forced to stop running five or six times. A friend advised him to see a doctor but he declined attributing his problems to "unfitness." In this period he ran 27- and 40-mile training runs. During this longer run he had severe chest pain that frequently forced him to stop.

On the day of his death, he went to work as usual but telephoned home at 4 P.M. to say he was going surfing. However, he arrived home 50 minutes later saying that he was "too breathless" to surf properly. He went inside the house and 20 minutes later asked his wife to take him to the doctor immediately as he had severe chest pain. His wife recalled that he looked pale but was not sweating and did not complain of nausea. During the car ride to the doctor he requested his wife to drive faster as the chest pain was getting worse and that it was now present in his left hand, which felt paralyzed.

He was seen by a general practitioner who gave him an injection and informed his wife that he had had a heart attack. The patient was driven to hospital immediately where he was admitted to the Intensive Care Unit. A diagnosis of acute myocardial infarction was made on the clinical features and the absence of signs of rupture of aortic aneurysm or massive pulmonary embolus or other causes of acute severe chest pain.

The patient died at 6:40 P.M. and the diagnosis on the death certificate was coronary thrombosis. No postmortem was performed and an incorrect report in a letter[29] was discounted on further investigation.

An electrocardiogram was taken on admission to hospital (Figure 1) and later reported as showing changes of acute inferior subendocardial ischemia.

In view of the clinical picture and the supportive evidence of the ECG, it is believed that this constitutes a fatal myocardial infarction occurring in an

active marathon runner. Scaff's claim [30] that the ECG was that of heat stroke could readily be discounted because the patient had not been running on the day of his death. Our case thus disproves at least one of Bassler's statements.[13-15]

As no autopsy was performed, Bassler rejected this case as disproving his hypothesis. He modified his previously ambiguous statements by clarifying that marathon running provided immunity only to coronary atherosclerosis.[23, 27] However, coronary atherosclerosis need not present only as sudden death. Thus, for his hypothesis to be epidemiologically valid, marathon runners who develop other clinical manifestations of coronary atherosclerosis such as exertional chest pain or myocardial infarction must be shown to be free of this disease. In four

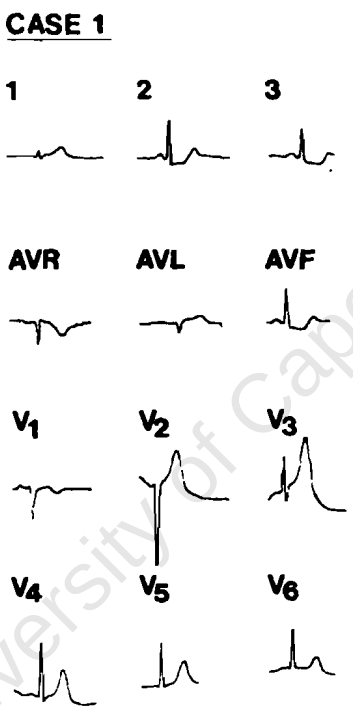

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FIGURE 1. Case 1. ECG taken shortly before death showing ST changes compatible with acute inferior subendocardial ischaemia.

marathon runners with myocardial infarction we have shown the presence of significant coronary artery disease considered angiographically indistinguishable from coronary atherosclerosis. A fifth runner who has sustained a documented myocardial infarction, has an ischemic response to submaximal exercise but declined coronary angiography.

Case 2

A 39-year-old White male participated in rugby football and amateur boxing in which he was nationally ranked until the age of 18, after which he became

physically inactive. Apart from occasional acute attacks of gout from 1963 onwards (for which he took allopurinol), he had no cause to seek medical attention. In January 1974 he took up long distance running and in the course of the following 27 months completed two Comrades Marathons, a number of standard marathons and had run 4050 miles in training. By the end of March 1975, he was in full training for the Comrades Marathon and was running more miles at a faster pace than at any previous time in his life. However, having completed his usual Sunday morning run of 26 miles uneventfully, he became aware of a sharp stabbing pain in his right elbow after he had run about 1 mile of a planned 8-mile training run on Monday, March 28. The pain persisted and after a further 2 miles was followed by the onset of moderately severe, cramping, anterior chest pain. These pains became progressively worse until he was forced to walk. Within a minute of walking these pains disappeared only to reappear immediately on jogging. The patient returned home and although he felt sluggish, he had no further chest pain. On the following 2 days the patient walked and ran a total of 18 miles and was again troubled by the same pains. On Thursday morning, the patient was awakened by severe, crushing precordial chest pain radiating to the right elbow. There was associated sweating and nausea.

He was seen in Casualty at Bloemfontein National Hospital where the electrocardiogram showed a hyperacute inferolateral myocardial infarction with marked ST-segment elevation in leads II, III, AVF, V5, and V6, with pathological Q waves in III, AVF, and V6. On admission to the Intensive Coronary Care Unit, the only abnormal findings were a jugular venous pressure raised 2 cms above the manubrium sterni and a third heart sound. He was treated with digoxin, furosemide, and supplemental potassium for mild right ventricular failure.

Cardiac enzymes were elevated the day after admission, creatine phosphokinase 510 units/ml (normal up to 50); lactate dehydrogenase 283 units/ml (normal up to 90). Enzymes returned to normal values within 4 days. He was discharged from hospital on propranolol (40 mgs three times daily) and on sulphinpyrazone.

On the day of his hospital discharge (against his physician's advice) he walked half a mile without chest pain and returned to work the following morning, 12 days after myocardial infarction.

Over the next 3 weeks he increased his daily walking distance to 2 miles at which stage he resumed jogging. For a period he developed elbow and chest pain when jogging, but always walked immediately when any chest pain started. By the end of June he was jogging without symptoms up to a distance of 6 kilometers. In mid-July 1976 he was admitted to Groote Schuur Hospital for assessment of coronary risk factors and evaluation of the desirability of his continued marathon running.

There was no family history of heart disease or hypertension, but one maternal aunt had died from diabetes in her forties. He abstained from alcohol but had smoked three pipefuls of tobacco and two to three cigarettes from the age of 18 until one month after his myocardial infarction.

The patient was a small (5′6″), muscular White male (somatotype 2:6½:1 Heath-Carter, percentage body fat 13.6%). There were no stigmata of hyperlipidemia. The patient was normotensive (blood pressure 110/70 mmHg) and the resting heart rate was 50 beats per minute. The apex beat was not displaced and there were no abnormal auscultatory findings. All peripheral

pulses were present. Other features, including urine and blood count were normal, and the ESR was 5 mm/hr (Westergren).

The glucose tolerance test was normal, serum uric acid was greater than 12 mgs per 100 ml, and a fasting lipogram was classified as a type IIb hyperlipidemia; cholesterol 265 mg/100 ml, triglyceride 235 mg/100 ml (normal up to 150 mg/100 ml), chylomicrons 16 mg/100 ml (normal up to 12 mg/100 ml), pre-beta-lipoproteins 177 mg/100 ml (normal up to 150 mg/100 ml),

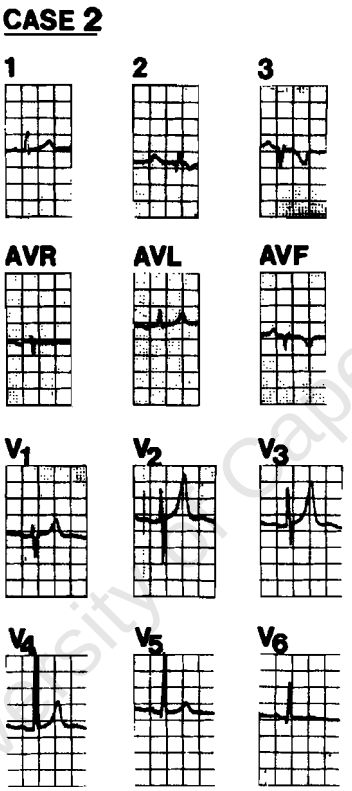

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FIGURE 2. Case 2. Resting ECG 3 months after acute myocardial infarction showing Q waves in leads 2, 3, and AVF. The tall T wave in V_2 and V_3 is normal for athletes.[56] Heart rate: 52/min.

and beta-lipoproteins 513 mg/100 ml (normal up to 480/100 ml). Chest X ray was normal and a resting electrocardiogram showed an old inferior myocardial infarction (FIGURE 2). The effort electrocardiogram did not reveal any symptoms, arrhythmias or ST changes up to a heart rate of 130 per minute while on propranolol 40 mg *b.d.*

The echocardiogram showed normal sizes and movement of heart chambers and no thickening of the posterior ventricular wall. The patient was Holter-monitored during a 30-minute jog, and no arrhythmias were found.

FIGURE 3. Left coronary angiogram in right anterior oblique (R.A.O.) showing complete occlusion of the circumflex artery (black arrow) and luminal irregularities in the anterior descending coronary artery (open arrows).

Left heart catheterization showed an increased left ventricular end-diastolic pressure (20 mmHg).

Angiography revealed complete occlusion in the distal circumflex artery just after the origin of the obtuse marginal branch (FIGURE 3), with a small segment of the more distal vessel filling later by means of bridge collateral. The left anterior descending artery had minor luminal irregularities (FIGURE 3). There was a 50% narrowing of the right coronary artery, which involved the origin of the right ventricular branch; the rest of the vessel was of good caliber with some luminal irregularities (FIGURE 4). Cineangiography of the left ventricle showed good contraction except for an area of inferior and infero-basal hypokinesia.

Treatment for the patient's gout and hyperlipidemia was instituted and the patient was advised against running extreme distances such as the 56-mile Comrades Marathon.

Case 3

A 48-year-old White male had been physically active throughout his life and was a nonsmoker. There was a family history of heart disease, his father had died suddenly at the age of 60 and a paternal uncle had died of "heart failure."

There was no past history of significance. He had been a long distance runner for 10 years and during this period had completed seven Comrades Marathons and more than 20,000 miles in training. After completing the 1975 Comrades Marathon in 9¾ hours, he maintained a heavy training schedule until the end of October 1976 when he traveled to Greece to run the Sacred Marathon on the course over which the legendary Marathon was run. For 6 weeks prior to this event he had been training 80–90 miles a week, including 25 mile runs at the weekend. He had never trained as hard as this in his life.

This Sacred Marathon was run in adverse environmental conditions, it being dry and hot, with the race starting at 1 PM. Facilities to supply the runners with fluid replacement were inadequate and in contrast to his usual practice, the patient was forced to drink very little fluid during the first 20 miles of the race. At about this point the patient began to feel nausea and was aware of a dull pain, feeling like a wind, in the epigastrium. The pain forced him to walk and he soon began vomiting. There was no chest pain.

Despite this discomfort and the regular occurrence of vomiting, the patient insisted on completing the last 6 miles of the course, which he did in two hours.

After the race the patient returned to his hotel where he continued to vomit and was unable to eat or drink. Four hours after finishing the

FIGURE 4. Case 2. Right coronary angiogram showing stenosis of the proximal right coronary artery (black arrow).

marathon, the patient was pain free and was seen by a marathon-running physician (J.M.) who prescribed an antiemetic to control the vomiting and advised the patient to drink fluids as he was dehydrated. During the night he passed urine but remained ill. For the next 24 hours his condition remained unchanged, but on the evening of the following day the epigastric pain radiated up both sides of the chest and into the back. A cardiologist was called and a diagnosis of acute myocardial infarction was made; the patient was admitted to the Intensive Care Unit of a local Athens hospital where an ECG showed an anteroseptal myocardial infarction. The patient was given two liters of intravenous fluid rapidly as he was dehydrated and anuric; this treatment relieved both the epigastric and chest pains. His further course was uncomplicated and he flew back to South Africa 4 days later in the company of J.M. From the plane he went to a hospital where he remained for 8 days.

Four days after discharge (against medical advice) he began walking 4 to 5 miles a day, and within a further 3 weeks he commenced jogging again. In January 1976 he was running 25 miles a week and by the beginning of March he had doubled this and thereafter continued at this level of activity.

In August 1976 he was admitted to Groote Schuur Hospital for investigation. Systemic interrogation did not reveal any additional features. On physical examination there were no stigmata of hyperlipidemia. The patient's somatotype was endo-mesomorphic (4:5½:2 Heath Carter) and he had an estimated 22.5% body fat indicating more adiposity than is usually associated with marathon runners. The resting pulse rate was 52 beats per minute and the blood pressure 130/90 mmHg. While the apex beat was not displaced there was a palpable fourth heart sound and on auscultation at the apex, in the lateral decubitus position, a systolic click and a late systolic murmur were audible. Phonocardiography at the mitral area showed third and fourth heart sounds, and there was an intermittent nonejection click. No definite systolic murmur was recorded.

The electrocardiogram showed the pattern of an old transmural anterior myocardial infarction with lateral T wave abnormality (FIGURE 5). The chest X ray showed mild cardiomegaly with a cardiothoracic ratio 52%. The lung fields were clear. A glucose tolerance test was within normal limits. The fasting lipogram showed cholesterol of 268 mg/100 ml and triglycerides of 107 mg/100 ml. Echocardiography showed that the left ventricular internal diameter was increased; the percentage of fractional shortening was normal; and no increased thickening of the posterior left ventricular wall was detected.

At cardiac catheterization, the left ventricular end-diastolic pressure was markedly elevated (30 mmHg at rest).

Coronary angiography showed a 2-cm area of 50%–75% narrowing in the mid-portion of the left anterior descending artery, but with good filling of the normal distal vessel (FIGURES 6a & b). The mainstem and circumflex vessels were free of disease. The right coronary artery was unobstructed, dominant, and of large caliber.

The left ventricular angiogram showed an enlarged left ventricle with an extensive akinetic area involving the apical, anterolateral, and inferior surfaces.

The patient easily ran 18 miles with one of us (T. N.) without the development of symptoms or undue fatigue. In view of this, he was advised to maintain running up to 8 miles a day with a single run of up to 15 miles on weekends. He was advised how to avoid dehydration while running[31] and was dissuaded from running in competitive marathons.

Case 4

A 50-year-old White male had been running for 10 years and had participated in competitive long distance running since 1969. He had completed 18 standard marathons and on average, had run more than 40 miles a week during this period.

His best marathon time was 3 hours and 36 minutes and in October 1974 he ran the Albuquerque, New Mexico Marathon in an attempt to qualify for

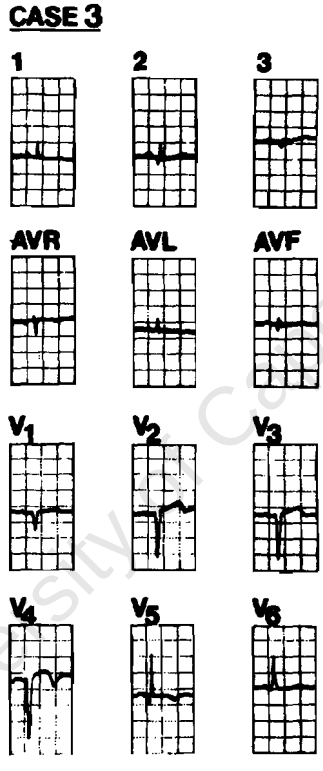

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FIGURE 5. Case 3. Resting ECG 9 months after acute myocardial infarction showing Q waves and loss of R amplitude in V leads.

the 1975 Boston Marathon (Qualifying Standard: 3 hrs 30 mins). After 15 miles of this marathon he became aware of vague chest discomfort which he attributed to altitude and dehydration. Although he did not feel particularly ill, he was reduced to walking the last 7 miles of the race and finished in 5 hours and 10 minutes.

After the race he continued to feel ill and in the plane flying home, he again felt chest discomfort, which was not severe enough to cause him alarm. At work the next day he was troubled by a vague malaise and at noon on the following day, 48 hours after the marathon, he developed severe precordial

FIGURE 6a. Case 3. Left coronary angiogram in R.A.O. showing a 2-cm segment (arrowed) of the anterior descending coronary artery with 50%–75% narrowing and good distal filling.

chest pain radiating down the left arm into the fingers, associated with marked dyspnoea.

He went immediately to the local hospital where he was admitted to the Coronary Care Unit. On admission, the patient was normotensive (110/80), and except for a prominent fourth heart sound, a gallop rhythm, and a pericardial friction rub, the cardiovascular examination was normal. The chest X ray was normal and the electrocardiogram was compatible with acute inferior myocardial infarction. Serial enzyme and electrocardiographic changes confirmed this diagnosis. Serum lipids were normal (cholesterol 216 mg/ml, triglycerides 114 mg/ml). The patient's hospital course was uncomplicated and he was discharged from hospital on the ninth day post-infarction. The following day, against medical advice, he recommenced jogging.

In November 1974, one month after myocardial infarction, the athlete was admitted to the Good Samaritan Hospital for assessment of his cardiovascular status. Five years previously, the patient had been admitted to hospital with severe chest pain, but as the electrocardiogram and serum enzymes were normal, a firm diagnosis could not be established.

Additional interrogation revealed that the patient was a nonsmoker, that his father had suffered from hyperlipidemia and had died from a heart attack; his

mother had suffered from hypertension and had died from a cerebrovascular accident.

A maternal uncle suffers from diabetes.

The patient was normotensive. On palpation at the apex a systolic bulge was noted, and on auscultation a third and fourth heart sound was heard. Phonocardiography confirmed these findings. The remainder of the cardiovascular examination was normal.

The electrocardiogram showed the pattern of an old transmural inferolateral myocardial infarction (FIGURE 7). The chest X ray was reported as normal. Echocardiography showed both the left ventricular internal diameter and the posterior wall thickness to be normal.

At cardiac catheterization, the right atrial, right ventricular, the pulmonary arterial and pulmonary "wedge" pressure were all normal as was the left ventricular end-diastolic pressure. Parameters of left ventricular function, specifically cardiac output and the tension-time index were all normal.

Selective coronary angiography showed the left coronary artery to be normal (FIGURE 8). The right coronary artery was dominant with only minor segmental lesions in its proximal extent (FIGURE 9a), but there was an area of significant stenosis more distally (FIGURE 9b).

FIGURE 6b. Case 3. Left coronary angiogram in left anterior oblique (L.A.O.) showing narrowed segment (arrowed).

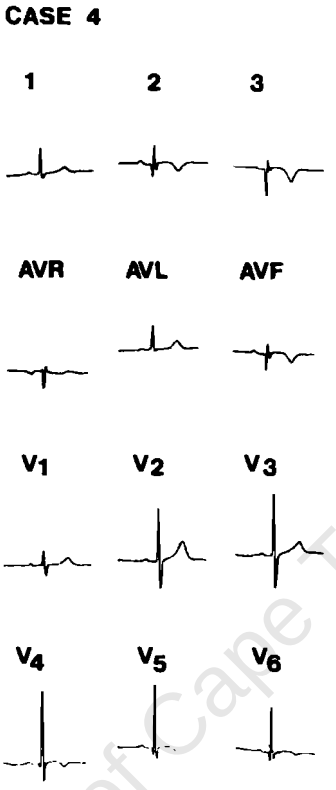

FIGURE 7. Case 4. Resting ECG one month after acute myocardial infarction showing Q waves in leads 2, 3, and AVF and anterolateal T wave inversion.

After nitroglycerin administration, there was no change in the luminal diameter of the coronary arteries.

The left ventricular angiogram showed a normal-sized left ventricle, but a dyskinetic area was shown at the apex of the left ventricle (FIGURES 10a & 10b).

In January 1975, two months after myocardial infarction, the patient completed the Fiesta Bowl Marathon in 4 hours 13 minutes. He has subsequently completed a further five marathon races and has returned to his preinfarction training status.

Case 5

A 37-year-old White male, who was a nonsmoker and who had no family history of heart disease, began jogging regularly in 1967 in order to improve his health and to lose weight. At the urging of a friend, in late 1971, he increased his training mileage with a view to running the 1973 Comrades Marathon. In 1972 he ran approximately 1500 miles in training.

During 1972 a routine medical examination for insurance purposes revealed

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T-wave inversion in the inferior leads (leads 2, 3, & AVF). He received insurance only at a loaded premium and was told that he had the Billowing Mitral Leaflet Syndrome (Barlow's Syndrome).

In 1973 and 1974 he completed the Comrades Marathon in 7 hr 17 min and 7 hr 20 min, respectively. During this period he ran about 2000 miles in training annually. His best time for the standard marathon was 2 hr 51 min. In the 5 months before the 1976 Comrades Marathon he had run a further 1200 miles.

During the race itself, he passed the halfway mark of the course in 3 hr 19 minutes and was lying amongst the top 100 runners. He was feeling "strong" and considered it very likely that he would complete the distance in under 7 hours. However, after a further 6 miles of running, he suddenly felt very tired, nauseous and noted that he was sweating profusely. He chose to walk for a period of 20 minutes after which he was again able to run. This sequence recurred three times but there was no chest pain nor did he vomit.

He completed the race in 7 hr 33 min but as he continued to feel ill after the race, he was referred for admission to a local hospital. Overnight he was treated with intravenous fluids and the following morning was found to be grossly edematous, with a jugular venous pressure raised 8 cm above the manubrium sterni, a third heart sound, dullness to percussion at both lung bases, and a 3-cm hepatomegaly with gross abdominal ascites. An ECG at the time showed an acute inferior myocardial infarction and serial enzyme changes were compatible with this diagnosis. The patient responded well to conservative therapy and was discharged from hospital 11 days later.

FIGURE 8. Case 4. Left coronary angiogram showing a normal left coronary artery in R.A.O. view.

FIGURE 9a. Case 4. Right coronary angiogram in R.A.O. showing dominant right coronary artery with minor segmental irregularities in its proximal and middle thirds.

FIGURE 9b. Case 4. Right coronary angiogram in L.A.O. showing a distal stenotic lesion in the late filling phase (arrow).

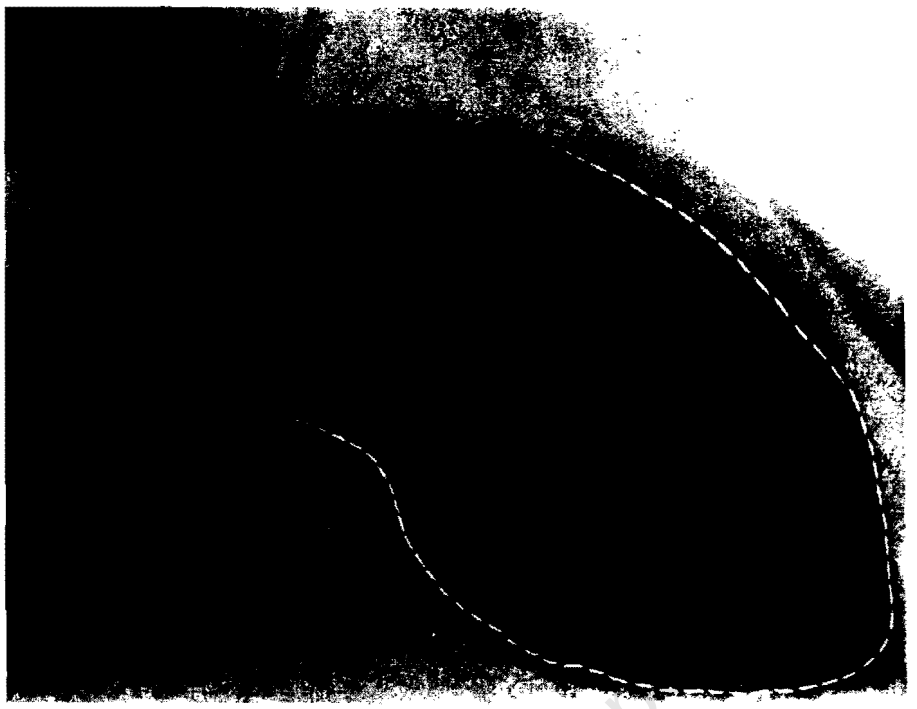

FIGURE 10a. Case 4. Ventriculogram during diastole. Part of the apex and inferior surface of the ventricle has been outlined in white.

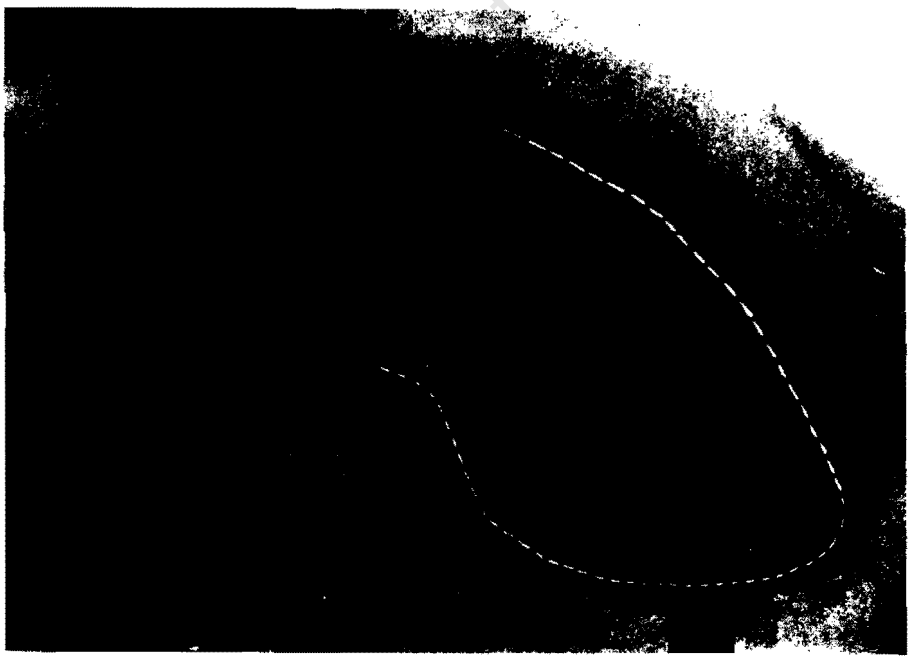

FIGURE 10b. Case 4. Ventriculogram during systole showing an area of inferior and apical dyskinesia (black arrows).

He commenced regular walking on discharge from hospital and two months later began jogging 3 to 5 miles, four times a week.

He was seen at Groote Schuur Hospital 19 months after his initial hospitalization. An ECG confirmed an old transmural inferior myocardial infarction (FIGURE 11). Clinical examination was entirely normal, there being no stigmata of hyperlipidemia; the patient's blood pressure was 130/90, the heart sounds were normal, and all pulses were present. The chest X ray was normal.

Echocardiography revealed all the heart chambers to be of normal size. The movement of the mitral valve was also normal, and was not considered compatible with Barlow's Syndrome.

During the exercise stress test, segmental ST depression first appeared at a heart rate of 160 beats/min and became progressively more severe in the anterior lead up to a heart rate of 190.

Immediately after exercise, ST depression was present in leads V4, V5, and V6 (FIGURE 12). Together with the inferior myocardial infarction, this could suggest diffuse coronary artery disease.

The patient declined to have coronary angiography performed.

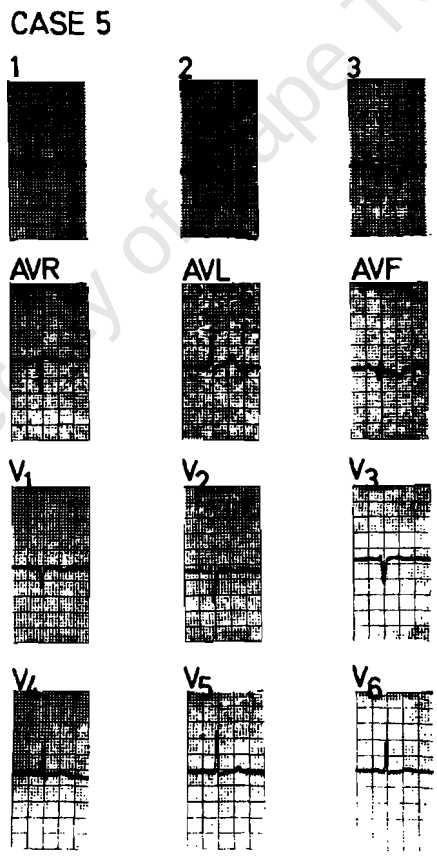

FIGURE 11. Case 5. Resting ECG, 19 months after inferior myocardial infarction.

CASE 5

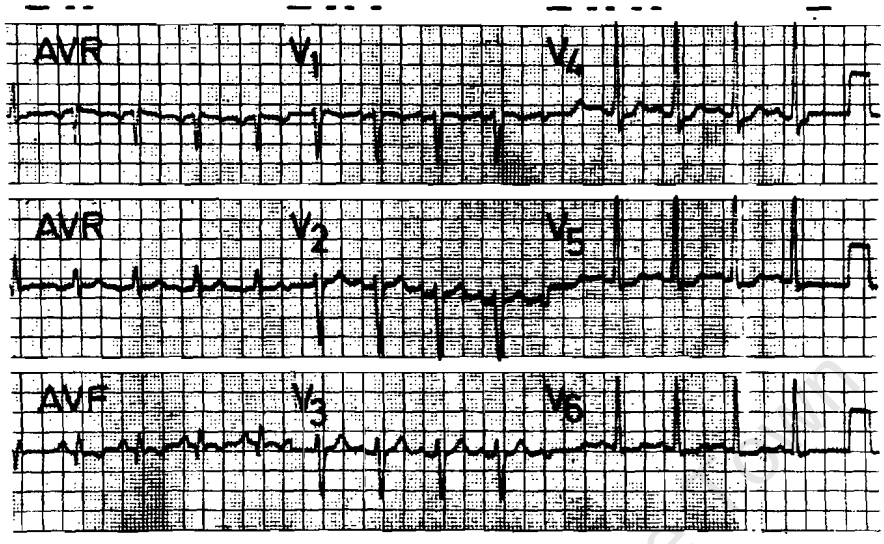

FIGURE 12. Case 5. ECG 5 minutes after exercise showing ST depression in leads V4, V5, and V6.

Case 6

A 46-year-old White male athlete was first seen in 1972 with a complaint of pain in the left groin while running. He was fully examined, including an ECG (FIGURE 13) and no cardiovascular abnormality was reported.

The patient was next seen in December 1974 with the complaint that while running 5 days previously, he had developed a severe pain across the front of his chest. On this occasion he had refused to stop and, despite chest pain, had run on 3 of the following 4 days, including a 10-mile time trial. An ECG at the time showed changes of anteroseptal myocardial infarction (FIGURE 13). The patient refused hospitalization. He was allowed to rest at home but persisted in physical activity, including mowing his lawn, for 5 hours, with severe chest pain.

In February 1975, an effort electrocardiogram, a glucose tolerance test, a fasting lipogram, and serum uric acid estimation were all normal. The patient was allowed to start careful jogging but was advised against any future competitive running. However, in September 1975, he completed a 17-mile road race without difficulty and in April 1976 he ran 93 miles in a 3-day race.

Two years after the original diagnosis of myocardial infarction, the patient was admitted to Groote Schuur Hospital for cardiac evaluation as he wished to run his 15th Comrades Marathon in 1977.

Special interrogation revealed that the patient was known to have retinitis pigmentosa, leaving him with moderately impaired vision. There was a family history of heart disease, his father dying suddenly at the age of 51 from

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myocardial infarction. His mother had died at 53 from diabetes and was a carrier of an X-linked gene for retinitis pigmentosa.

The patient was a teetotaler and had never smoked. He had always been extremely physically active, representing his Province at swimming while still a schoolboy. Failing vision forced him to turn to rowing, and in 1958 he was selected to represent South Africa as an oarsman at the Empire Games. In 1960 he took up long distance running and between 1961 and 1974 had completed 14 consecutive Comrades Marathons and had run more than 30,000 miles in training.

Systemic interrogation revealed only that the patient frequently developed exertional chest pain, particularly when running uphill or before he had "warmed up." When on the flat he was able to "run through" his chest pain, but was often reduced to a walk on the uphill. On physical examination, there were no stigmata of hyperlipidemia. The pulse rate was 65 beats per minute with the occasional irregular beat. The blood pressure was 130/90. The apex was impalpable and there were no abnormal auscultatory findings. All peripheral pulses except the dorsalis pedis on both sides were present and there were no bruits.

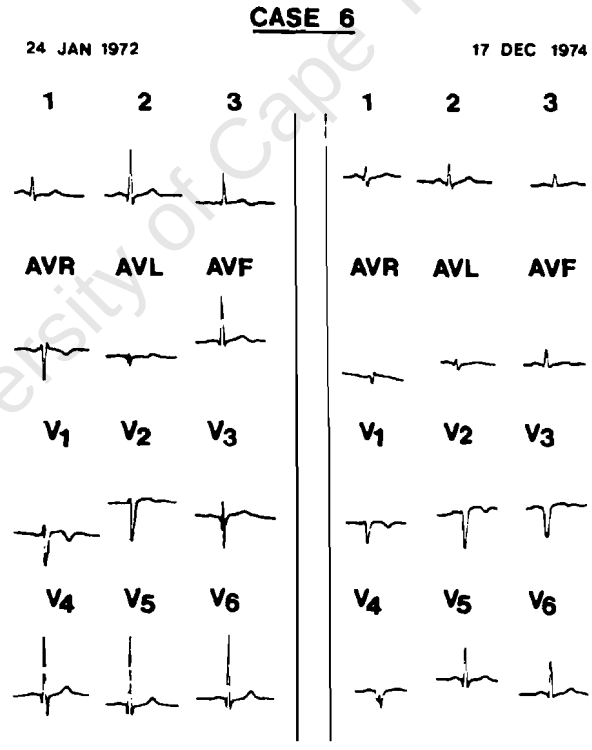

FIGURE 13. Case 6. Resting ECGs taken 2 years apart. The 1972 tracing shows diminishing R waves in V1–V2 and narrow Q waves in V3 suggestive of old anterior infarction. The more recent tracing, taken 4 days after the onset of chest pain, shows Q waves with loss of R waves in V2–V4.

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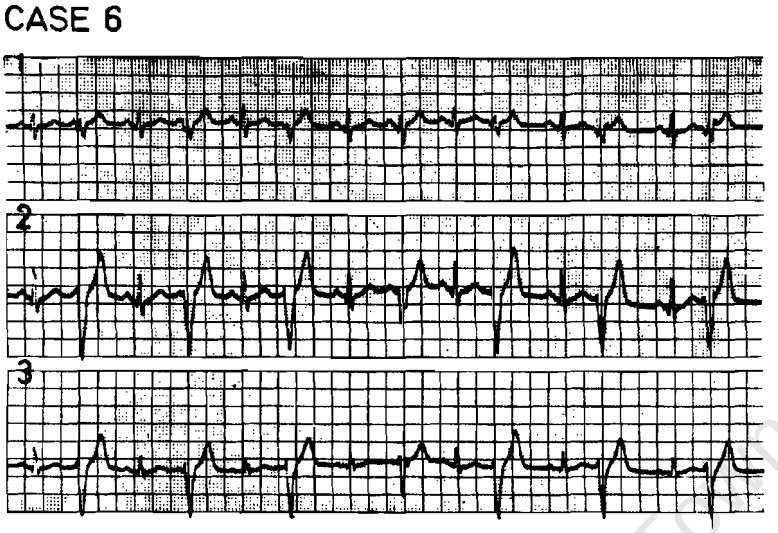

FIGURE 14. Case 6. ECG taken 4 minutes after exercise showing ventricular bigeminy.

The chest X ray was normal and the resting ECG was unchanged from that shown in FIGURE 13.

An effort electrocardiogram was unchanged up to a heart rate of 174 beats per minute but at 4 minutes postexercise, a run of ventricular bigeminy appeared lasting for 1 minute (FIGURE 14).

Left heart catheterization showed all the pressures to be normal.

Coronary angiography revealed a dominant right coronary artery with mild proximal disease and a 70% area of narrowing in the posterior descending artery (FIGURE 15). The distal left anterior descending coronary artery was seen to fill retrogradely.

The mainstem left coronary artery was free of disease but the circumflex artery had mild, diffuse disease (FIGURE 16a). The left anterior descending artery was narrowed by approximately 80% in at least three areas of its proximal and midportions with the distal vessel filling late (FIGURE 16b). A large diagonal branch, supplying a significant area of myocardium, was present (FIGURES 16a and 16b).

The left ventricular angiogram showed a large akinetic area involving the anterolateral, apical, and diaphragmatic segments with good contraction of the inferobasal and anterobasal segments (FIGURES 17a and 17b).

DISCUSSION

Marathon Running and Immunity to Coronary Atherosclerosis

Strong epidemiological evidence exists to suggest that regular physical activity may be beneficial in terms of favorably altering coronary risk profile,[32] in reducing the incidence of ECG abnormalities compatible for myocardial

FIGURE 15. Case 6. Right coronary angiogram showing the right coronary artery in L.A.O. with mild proximal disease and a 70% area of narrowing in the posterior descending artery (arrow).

ischemia,[33] and in reducing coronary mortality [34, 35] and, in particular, the incidence of sudden death.[36]

This report of coronary heart disease amongst highly-trained marathon runners in no way refutes these important studies nor does it alter the belief stated previously by two of the present authors, in the benefits of regular physical activity.[37, 38] However, neither the mechanism whereby exercise may protect nor the amount of exercise required for protection has been established. The Bassler hypothesis has had the unfortunate effect of promoting marathon running as the method by which anyone, regardless of precursor pathology or risk factors for coronary heart disease, can achieve total immunity to coronary atherosclerosis. In addition, it has left many with the impression that other less vigorous sports may have no place in coronary heart disease prevention.

We report six cases of myocardial infarction in highly-trained marathon runners. Four of these athletes had coronary artery disease demonstrated

FIGURE 16b. Case 6. Left coronary artery in R.A.O. showing an area of stenosis in the circumflex branch (open arrow). The anterior descending coronary artery is narrowed by approximately 80% in at least three areas (black arrows).

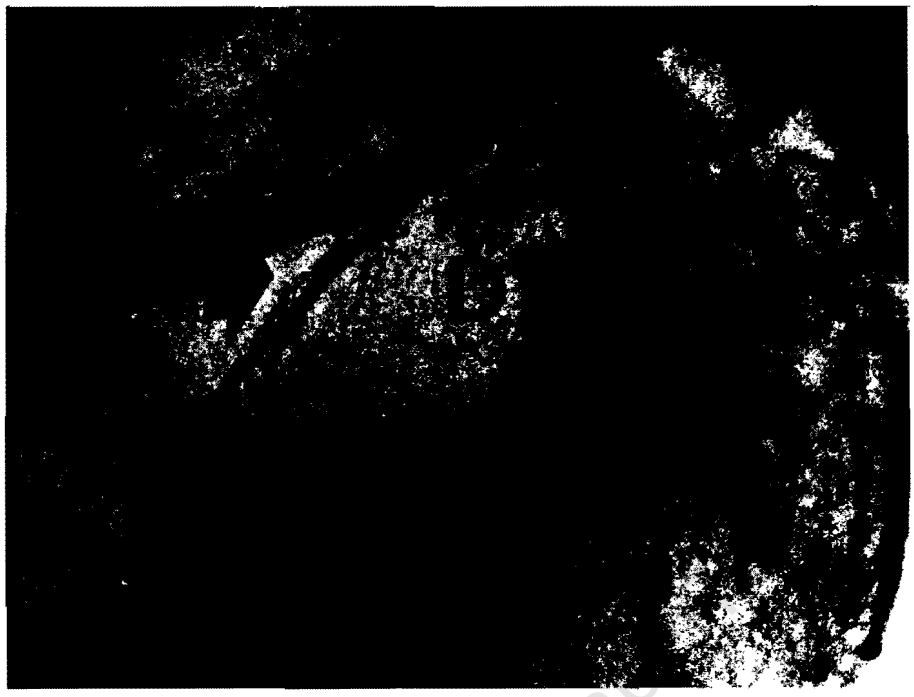

FIGURE 16a. Case 6. Left coronary artery in L.A.O. showing a severely diseased left anterior descending artery (L.A.D. in diagram), a large diagonal branch (D in diagram) and diseased circumflex artery.

FIGURE 17a. Case 6. Ventriculogram during diastole.

FIGURE 17b. Case 6. Ventriculogram during systole showing a large apical akinetic area.

angiographically and considered indistinguishable from coronary atherosclerosis. All athletes developed myocardial infarction despite continued high levels of physical activity. This contrasts with Bassler's statement that "immunity to heart disease is synonymous with physical fitness" [1] and is in accord with the findings of Vouri and his colleagues [39] and Jokl [40] that high levels of physical fitness do not guarantee the absence of significant cardiovascular disease.

Recently the sudden death of a veteran long distance runner has been reported. Although technically not a marathon runner, he had completed a 23-mile training run the day before his death, he had been running regularly since his teens, he was a nonsmoker, and within the year before his death he had won the National A.A.U. Masters 25-kilometer race. The finding of significant coronary atherosclerosis of the anterior descending coronary artery at autopsy supplies additional evidence against the Bassler hypothesis.[41]

Exertional Symptoms

All six athletes had warning symptoms. Four athletes developed exertional chest pain but in two the onset of predominantly gastrointestinal symptoms caused a delay in diagnosis.

Despite symptoms, three athletes completed marathon races, one athlete ran more than 20 miles after the onset of exertional discomfort to complete the 56 mile Comrades Marathon. The athlete who died continued training for 3 weeks, including a 40-mile run, with chest pain which he ascribed to "unfitness." Two other athletes continued to train with chest pain.

It is possible that the exaggerated claims for the protective effect of marathon running, widely publicized in lay athletic journals, may have contributed to athletes continuing running despite symptoms.

Competitiveness appeared to be a factor, in that four athletes were undergoing particularly rigorous training in attempts to improve on their previous best marathon times. In a previous study of sudden death amongst sportsmen, both competitiveness and a denial of symptoms were apparent.[42] Thus marathon runners, like other sportsmen,[42] need to be warned of the serious significance of the development of exertional symptoms. It is possible that competitiveness and over-training may have contributed to the subsequent development of myocardial infarction in some of these runners.

Marathon Running and "Normal Coronary Arteries"

An over-emphasis of the role of marathon running might play in the prevention of coronary heart disease may have obscured important facts about the dangers of marathon running in persons with apparently normal or mildly diseased coronary arteries. Thus Green *et al.*[43] have reported a fatal myocardial infarction occurring during a marathon race in an athlete with normal coronary arteries at autopsy, while Frick and his colleagues [44] report a runner with angiographically normal coronary arteries, ischemic electrocardiographic changes during exercise testing, and a demonstrable area of myocardial underperfusion. Cantwell [45] has recently described a veteran marathon runner who collapsed during exercise and required cardiopulmonary resuscitation. A subsequent exercise stress test provoked couplets of ventricular premature beats at a heart rate of 100 beats per minute. At angiography, the coronary arteries of this athlete were reported to be normal.

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Myocardial Infarction during Marathon Racing

The absence of coronary artery occlusion in two athletes (Cases 3 & 4) who developed infarction during marathon racing, raises questions regarding the mechanisms by which transmural myocardial infarction can occur without coronary artery occlusion. It has been argued [46] that recanalization of an occluding thrombus may occur in the period between infarction and coronary angiography; thus at angiography the vessels may appear patent. Case 4, who had mild coronary artery disease, underwent coronary angiography only 1 month after infarction suggesting that if this was the mechanism, recanalization occurred rapidly. Case 3 first underwent coronary angiography three months after infarction and at that stage, his angiogram was unchanged from that reported here and done 6 months later. (We thank Professor E. Chesler of Durban for details.)

Coronary artery spasm has been evoked to explain why some persons with angiographically normal coronary arteries can develop angina pectoris or even myocardial infarction [47, 48] and this mechanism has been offered to explain this association in the Billowing Mitral Leaf Syndrome.[49]

The third explanation postulates biochemical factors in the myocardium leading to an imbalance of adenosine triphosphate (ATP) supply and demand.[50] ATP production is dependent on an adequate oxygen supply to maintain oxidative phosphorylation (which is presumably normal in persons without coronary artery disease), but the rate of ATP breakdown (hydrolysis) may be influenced by factors other than the rate of mechanical work. Thus during marathon running a continual rise in heart rate, in body temperature, in circulating free fatty acids, and in catecholamines might all be expected to exert a deleterious effect on the myocardium or to increase myocardial oxygen consumption or to "waste ATP." [42, 51]

In addition, dehydration, which occurs to an alarming extent in marathon runners,[52] might increase viscosity and decrease coronary blood flow, thus reducing myocardial oxygen delivery or predispose to coronary thrombosis.[53]

Regardless of the mechanism, the finding of transmural myocardial infarction occurring during marathon running in athletes without occlusive artery disease re-emphasizes the complexity of the relationship of exercise, coronary atherosclerosis, and sudden death or myocardial infarction.

Conclusions

Firm evidence for the benefits of marathon running in the prevention of coronary heart disease will only result, as has been suggested by Werkö,[54] from carefully controlled epidemiological studies that take into account all the factors discussed in this section of the Marathon Symposium. Only then will it become apparent whether it is marathon running by itself or the favorable alteration in the other coronary risk factors, simultaneously advocated by Bassler, that influences coronary mortality. Until such time as this data is available, we strongly support Dayton [55] in calling for a moratorium on public assertions that marathon running prevents coronary heart disease.

Summary

Six highly trained marathon runners developed myocardial infarction. One of the two cases of clinically diagnosed myocardial infarction was fatal, and

there were four cases of angiographically-proven infarction. Two athletes had significant arterial disease of two major coronary arteries, a third had stenosis of the anterior descending and the fourth of the right coronary artery.

All these athletes had warning symptoms. Three of them completed marathon races despite symptoms, one athlete running more than 20 miles after the onset of exertional discomfort to complete the 56 mile Comrades Marathon. In spite of developing chest pain, another athlete who died had continued training for three weeks, including a 40 mile run. Two other athletes also continued to train with chest pain.

We conclude that the marathon runners studied were not immune to coronary heart disease, nor to coronary atherosclerosis and that high levels of physical fitness did not guarantee the absence of significant cardiovascular disease. In addition, the relationship of exercise and myocardial infarction was complex because two athletes developed myocardial infarction during marathon running in the absence of complete coronary artery occlusion. We stress that marathon runners, like other sportsmen, should be warned of the serious significance of the development of exertional symptoms.

Our conclusions do not reflect on the possible value of exercise in the prevention of coronary heart disease. Rather we refute exaggerated claims that marathon running provides complete immunity from coronary heart disease.

Acknowledgments

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[**Note added in proof.** Against our advice, Cases 2, 3, and 6 have all subsequently completed marathon races. Thus of the 6 runners, only Case 1 (deceased) and Case 5 (jogging 20–30 miles per week) have not returned to marathon running.]

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cessfully, have died within a year. After considering these data and the favorable results with the bypass operation, persons at the workshop decided that lesions in the left main coronary artery do not seem suitable for the procedure. Moreover, it was recommended that investigators avoid lesions due to arteriospasm.

As with all new technics, the complications and risks, as well as the benefits, are difficult to quantify. However, if patients are carefully selected by the criteria listed above, and if surgical treatment is available if needed, the risk to life would seem to be low. Most investigators at the workshop felt that the risk would increase unacceptably if strict criteria were not used.

The participants in the workshop, recognizing not only the value but also the poorly defined risks of the procedure, unanimously agreed that it should be attempted only as an investigational procedure. Physicians who attempt percutaneous transluminal coronary angioplasty should follow the guidelines established by pioneers in the field who have demonstrated its safety and efficacy only under certain circumstances.

Collection of data on patients and the results of treatment is essential. To make this information most useful, the workshop advised that a registry be continued. However, the workshop participants felt that a randomized collaborative clinical trial would be premature at this time. This view was based on the rapid changes in the technic, the continuing modification of equipment and the small number of patients thought to satisfy the current criteria. It was estimated at the workshop that less than 5 per cent of patients now undergoing coronary-bypass operations are potential candidates for this procedure. Whether a randomized clinical trial will ultimately be possible remains to be determined. For the present there is clearly a need for careful collection and analysis of clinical experience and for prompt dissemination of this information to minimize adverse effects while taking advantage of the value of the technic. The responsibility should be shared by investigators, institutions and their review boards and the manufacturers of the devices.

The NHLBI is ready to meet its responsibilities without interfering with the developments that have brought the technic to its present status and without imposing limitations on other activities for which it has responsibility. Thus, the NHLBI will explore possible sources of funding for the continued existence of a registry and will make every effort to stimulate laboratory and clinical research with this technic.

When first reported two years ago,[7] percutaneous transluminal coronary angioplasty was greeted with amazement by investigators treating patients with cardiovascular disease, and it is still regarded as an innovative approach. Its limitations are becoming increasingly apparent, but its promise remains considerable for a limited group of patients. Only through meticulously conducted and evaluated clinical studies will the true value of this procedure be fully clarified and its potential utility in medical practice defined.

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CARDIOMYTHOLOGY AND MARATHONS

Two questions about long-distance running are addressed in this issue of the *Journal:* If people who go in for protracted, strenuous exercise have healthier cardiovascular systems, is the exercise itself responsible or are other factors, such as a different constitutional endowment? Secondly, does the exercise involved in running marathons confer immunity to death from coronary-artery disease?

Whether one compares railway switchmen with railway clerks, postal carriers with postal clerks, bus conductors with their companion drivers, college athletes with their more sedentary classmates or farmers and longshoremen with the rest of the community, the active member of each pair will have less clinical evidence of coronary-heart disease. Paffenbarger has reasonably argued that vigorous exercise reduces the rate of fatal heart attack, i.e., that it is protective.[1,2] The association, he believes, is not due to a selective process that makes those with symptoms of cardiovascular distress more sedentary. Paffenbarger has, however, pointed out that what is missing in most studies is an analysis of the factors that go into work selection: it is surely reasonable to suspect that those who choose to be longshoremen, bus conductors or athletes differ before they begin to work from those who select sedentary occupations, and that these constitutional factors have at least some role in shaping subsequent events.

The paper by Siegel and his colleagues in this

week's *Journal* attempts to come to grips with this problem and provides at least some preliminary evidence that constitutional factors have a role: marathon runners reported a paternal history of coronary-heart disease less frequently than did matched nonrunners. For a rigorous evaluation of such an important question, we would have liked some approach other than a mailed questionnaire, which produced a mere 61 per cent return and a response that was never validated. Perhaps direct evaluation of the pairs for risk factors apart from age and a family history of diabetes and a longitudinal study showing whether running reduces known risk factors would provide more convincing evidence. Such detailed, prospective studies are required before any final conclusion can be drawn.

We still do not know, then, whether physical or psychologic attributes separate runners, before they take up running, from the indolent rest. Why some of us run and, especially, why some run marathons are also unknown. In 490 B.C., after the Athenians' inspired charge across the plain of Marathon had driven the Persians back into their ships, Miltiades had an urgent need to get a message to his city, lest it surrender prematurely. The runner who was sent the 35.1 km (21 miles, 1470 yards) to carry the news to the Athenian agora is said to have arrived, collapsed and died. None of us know the cause of death. Some believe that his name was Pheidippides, even though Miltiades had, a few days beforehand, dispatched this same man, "by profession and practice a trained runner," in a fruitless attempt to get help from the Spartans. Pheidippides had reached Sparta "the very next day after quitting the city of Athens," despite the distance (240 km, or 150 miles), the rugged terrain and an encounter with the god Pan.

Shortly afterwards the Athenians organized a "torch race" to celebrate all this in the name of Pan, but the world had to wait until 1896 when Michael Bréal thought up a "Marathon" race for the modern Olympic games. In 1908, the British Olympic Committee, taking a properly imperial view, redefined the distance between battle ground and agora as that distance between the royal residence at Windsor Castle and the royal box at the White City Stadium: 42.2 km or 26 miles, 385 yards.

Whatever its origins may have been, a marathon is an ordeal that goes on too long for comfort. The Athenians had good reasons for long-distance running, but why do so many of us do it now? There were 320 marathons in the United States in 1978 and 60,000 entrants.[4] We run for fun and for reasons ranging from the transcendental through the esthetic to the competitive. Some of us certainly run because of a modern-day myth — that marathon running provides complete immunity from coronary-artery disease.[4]

As pointed out as recently as October, 1978, this notion is widely held; the evidence concerning this simplistic hypothesis has been debated most notably by Bassler (for) and Milvy (against),[5-8] with more repetition than documentation being offered in support.[8,9] The paper by Noakes and his colleagues, in this issue, unequivocally destroys it.

Now we know what most have suspected: coronary-artery disease does develop in at least some marathon runners. We do not know, although we strongly suspect, that the frequency is reduced in runners, and we can only guess at the mechanisms responsible for the protection. Pickering[10] has listed ways by which endurance training could improve our coronary lot. Surely, as Milvy has pointed out, a reduced frequency would be anticipated from the fact that marathon finishers as a group tend to be skinny, young, nonsmokers. They may also have inherited a different constitution, as suggested by Siegel and his co-workers.

Does this mean that the *Journal* is taking an anti-exercise stance? Far from it. We merely point out that physicians who recommend ambitious exercise programs for their patients must remember that proof that this approach will prevent or even delay cardiovascular death is not yet available. We suspect that Paffenbarger[1,2] is correct: everything else being equal, heart-attack rates decline with increasing activity. We also suspect that prospective, randomized trials of the prevention afforded by running will be practical only in those with coronary-artery disease. In a free society, how could adequate randomization of fit subjects be achieved? Unfortunately, even in highly motivated populations with advanced atherosclerosis, dropout rates of about 50 per cent are being reported.

The fundamental question of whether running does good things to the coronary arteries will not be answered simply by studying self-selected runners. Until the data are in, the exercisers' enjoyment of the activity and their pleasure in the way they feel and look should be sufficient. In exercise, as in good deeds, the reward must lie in the act itself.

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Physical Training Increases Ventricular Fibrillation Thresholds of Isolated Rat Hearts During Normoxia, Hypoxia and Regional Ischemia

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SUMMARY **The effect of exercise training on cardiovascular mortality is controversial. The purpose of this study was to determine the effect of a period of treadmill training on the ventricular fibrillation threshold of the isolated rat heart. Trained hearts had higher threshold values during standard, control perfusion conditions, and when exposed to hypoxia, hypoxia plus isoproterenol infusion, or when subjected to coronary artery ligation. Myocardial metabolic studies failed to define the mechanism for the effect of running training. However, in coronary ligated hearts, the content of the arrhythmogenic substance 3',5' cyclic adenosine monophosphate (cyclic AMP) was reduced in the ischemic zone of hearts from trained rats. Cyclic AMP levels were also lower in trained hearts during control perfusions. We conclude that running training increases the resistance of the heart to ventricular fibrillation by mechanisms that are largely unknown, although they may involve cyclic AMP.**

THE RELATION between exercise and ischemic heart disease remains controversial. Although even extreme exercise, such as marathon running, does not give total protection against coronary atherosclerosis or sudden cardiac death,[1, 2] there is strong epidemiologic evidence for an association between high levels of physical activity either at work[3] or in leisure time[4–7] and a reduced incidence of coronary heart disease and, in particular, sudden death. Paffenbarger[8] concluded that low levels of work energy output are a risk factor as powerful as cigarette smoking, a history of heart disease and high blood pressure, and more influential than obesity, abnormal glucose tolerance or high blood cholesterol.

Another possibility is that exercise training specifically protects against sudden coronary death. Thus, in the longshoreman studies reported by Paffenbarger and Hale,[3, 8] high energy output at work provided greater protection against sudden death than against death occurring 6 hours after the onset of symptoms. Similarly, in studies of British civil servants, not only were the overall coronary mortality rates lower in those who reported vigorous leisure time activity, but sudden death mortality and mortality from the first and subsequent heart attack were also lower.[4, 5, 7] These findings are compatible with a specific, training-related protection against rapidly fatal heart attack. Indeed, Paffenbarger[9] postulated that part of the myocardial adaptation to training may be a stabilization of cardiac rhythm, perhaps conferring a reduced risk of the development of that chain of events proceeding from ectopic ventricular activity to fibrillation and death.

Additional epidemiologic studies are required to settle these controversial issues; but further information can be obtained from animal models designed to investigate the effects of exercise training on the myocardial

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electrical stability during experimental interventions believed to mimic conditions present during myocardial infarction.

We chose the isolated perfused rat heart model to compare the ventricular fibrillation thresholds of hearts isolated from running-trained rats with those of hearts from control rats. We studied the effects of hypoxia and acute regional myocardial ischemia on the ventricular fibrillation threshold to determine whether exercise training could increase the myocardial electrical stability under these specified experimental conditions.

Materials and Methods

Three weeks after weaning, young male Wistar-Weissman rats were randomly assigned to either an exercising or a control group and were housed and fed under identical conditions. Rats assigned to the exercising group completed the following training program, which lasted at least 9 weeks. The rats exercised 5 days a week on a Quinton Model 42-15 treadmill (Quinton Instruments) set at a 15° incline. On the first and second training days, the rats ran for 15 minutes, on the third day for 30 minutes, on the fourth day for 45 minutes, and on the fifth day for 60 minutes. Thereafter, the running time was increased by 3 minutes daily until, at the end of the fifth training week, the rats were running for 2 hours daily, the first hour at up to 0.8 mph and the second at up to 1 mph. This exercise level was maintained until the rats were killed. This training program significantly increases myocardial myosin ATPase activity and the degree of myosin P light chain phosphorylation,[10, 11] but does not cause myocardial hypertrophy.[10]

Untrained rats were kept at normal cage activity. All rats were exposed to a 12-hour day/night cycle and were fed rat cubes and water ad libitum.

After 9 weeks of training, rats from either the control or trained group were anesthetized with ether in a vacuum bowl and, when asleep, 10 μl of heparin (Pularin, Glaxo-Allenbury (SA) (Pty) Ltd., 1000 U/ml) was injected into the femoral vein. The thoracic cavity was opened and the heart rapidly excised and immediately placed in ice-cold (4°C) Krebs-Henseleit[12] buffer. As soon as the heart stopped beating, it was removed from the buffer and mounted on the isolated Langendorff-perfused heart system used in this laboratory.[13] Hearts from trained and control rats were perfused alternatively so that an equal number of hearts from each group were studied on each experimental day.

The perfusate was a modified Krebs-Henseleit buffer solution[12] with a $CaCl_2$ concentration of 1.1 m*M*, aerated with either 95% O_2 and 5% CO_2 or with 95% room air and 5% CO_2 during studies of hypoxia. The perfusate substrate was 11.1 m*M* D(+) glucose (Merck) plus insulin (NUSO Neutral Insulin, Wellcome Foundation) at a concentration of 2 U/l. The perfusion pressure was always 100 cm H_2O. In experiments in which myocardial glycolytic rates were measured, ^{3}H-glucose (D-2-^{3}H(N))-glucose (New England Nuclear) was added to the perfusate in a concentration of 100 μl/l.

Experimental Protocols

Ventricular Fibrillation Threshold Measurements During Control Perfusions

The technique for measuring the ventricular fibrillation threshold in the isolated perfused rat heart has been described in detail.[13] After mounting the heart on the aortic cannula of the isolated perfusion system, thin platinum electrodes were inserted into the apex and base of the left ventricle with the anode at the apex, for the delivery of square-wave stimuli of 2 msec duration (Grass S88 physiologic stimulus generator). For hearts used in the studies of regional ischemia, a 5-0 silk suture with an atraumatic needle was passed deep to the left main coronary artery within 2 mm of where the artery emerges adjacent to the left atrium, according to the technique described by Kannengiesser et al.[14] The ventricular fibrillation threshold was measured by applying a single train of 10 stimuli at 200-msec intervals across the T wave, starting 10 msec after the onset of the R wave. The heart was stimulated every 30 seconds unless ventricular fibrillation occurred, in which case the next stimuli were only applied after 60 seconds. The current strength was increased by increments of 2.5 mA until ventricular fibrillation, consisting of six or more repetitive ectopic cycles with irregular form, developed. The ventricular fibrillation threshold was defined as the lowest current that produced ventricular fibrillation on three occasions, and that did not produce fibrillation at a current of 0.5 mA lower.

The hearts stabilized for 15 minutes before measurement of heart rate, from the oscilloscope, and coronary flow rate by collection, in a graduated measuring cylinder, a timed sample of coronary effluent from the heated chamber below the heart. The ventricular fibrillation threshold was then measured, which was taken to represent the value for the control perfusion.

A separate series of nine trained and eight control hearts was frozen for biochemical analysis of ATP, phosphocreatine and cyclic AMP levels after 15 minutes of Langendorff perfusion but before determination of their ventricular fibrillation thresholds.

Ventricular Fibrillation Threshold Measurements During Acute Regional Ischemia

After the ventricular fibrillation threshold had been measured under control conditions, hearts from 12 trained and 14 control rats were exposed to acute regional ischemia by abruptly tightening the ligature surrounding the left main coronary artery. Beginning 5 minutes after ligation, ventricular fibrillation thresholds were measured every 30 seconds for 10 minutes in hearts from six trained and seven control rats, and for 15 minutes in another six trained and seven control rat hearts.

In the group perfused for 20 minutes of regional ischemia, the experiments were terminated by removing the hearts from the aortic cannula after injection of

disulphan blue dye into the perfusate through the aortic cannula. This technique differentiates the ischemic from the nonischemic zone of the left ventricle.[15] The ischemic zone was then dissected out, weighed and recorded as a percentage of the total left ventricular wet weight.

In the group of hearts perfused for 15 minutes of regional ischemia, the experiments were terminated by freeze-clamping the hearts in Wollenberger tongs[16] precooled in liquid nitrogen. Hearts were then individually stored in liquid nitrogen until biochemical analysis.

Ventricular Fibrillation Threshold Measurements During Hypoxia and During Hypoxia with Catecholamine Stimulation

After measurement of the control ventricular fibrillation thresholds, a further series of hearts from eight trained and eight control rats was exposed to 15 minutes of hypoxic perfusion, during which the ventricular fibrillation thresholds were measured every 30 seconds.

After the initial 15 minutes of hypoxic perfusion, $1 \times 10^{-8}M$ isoproterenol (Isuprel, Winthrop Laboratories) was infused for 15 minutes while hypoxia was maintained. Ventricular fibrillation thresholds were again measured. The experiments were terminated by freeze-clamping the hearts in precooled Wollenberger tongs.

In these experiments, coronary effluent was sampled every 5 minutes and its ^3H_2O content was measured to calculate myocardial glycolytic rates.

Biochemical Measurements

The tissue contents of ATP, phosphocreatine, glycogen, lactate and 3',5' cyclic AMP were measured in freeze-clamped hearts homogenized under liquid nitrogen by methods previously described.[13]

The coronary effluent ^3H_2O content of hearts perfused with D-2-^{3}H glucose was measured according to the methods of Neely et al.[17] Ion exchange resin (Resin Dowex 1 × 4-200, Sigma Chemical Company) was prepared according to instructions provided by Professor M.J. Rovetto of the Department of Physiology, Jefferson Medical College of the Thomas Jefferson University, Philadelphia. After preparation, the resin was placed over glass wool in Pasteur pipettes to a column height of 2.5 cm. The resin was thoroughly rinsed with distilled water before being dried with compressed air. A 0.5-ml aliquot of coronary effluent was then carefully washed through the resin with 3 volumes of distilled water, 0.5 ml per passage, into 10 ml of scintillation fluid (Insta-Gel, Packard Instrument Company). Standards and blanks were prepared from aliquots of perfusate that had not passed through the heart. Standards were prepared by adding 0.5 ml of perfusate plus 1.5 ml of distilled water directly to the scintillation fluid without passage through the column, whereas blanks were prepared by the passage of the perfusate aliquot through the resin columns.

After the perfusate or coronary effluent had been washed through the column with distilled water, the resin columns were again dried with the passage of compressed air. The scintillation vials were then spun to ensure complete mixing, wiped clean, and their radioactivity was determined by counting in a liquid scintillation counter (Beckman Instruments).

Statistical Methods

Data are presented as mean ± SEM. An unpaired *t* test was used to compare means between groups. A *p* value of less than 0.05 was considered significant.

Results

Ventricular Fibrillation Thresholds During Acute Regional Ischemia

Figure 1 shows the ventricular fibrillation thresholds in trained and control hearts before and after coronary artery ligation. At all times after coronary artery ligation, the ventricular fibrillation thresholds were significantly higher in hearts from trained rats ($p < 0.05$).

Table 1 is a list of additional observations made in these experiments. There were no differences in heart rates or coronary flow rates either before or after coronary artery ligation, and the infarct sizes expressed as a percentage of total left ventricular wet weights were similar in both groups. However, ventricular fibrilla-

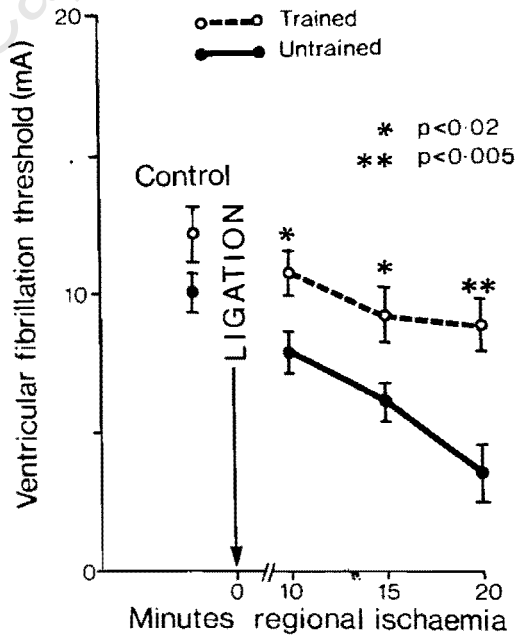

FIGURE 1. *Effect of acute regional ischemia caused by coronary artery ligation on ventricular fibrillation thresholds of isolated hearts from trained and control rats. At all times after coronary artery ligation, ventricular fibrillation thresholds are significantly higher in hearts from trained rats. Values are mean ± SEM.*

TABLE 1. *Heart Rates, Coronary Flow Rates, Times to Decrease in Ventricular Fibrillation Thresholds and Infarct Sizes of Hearts from Trained and Control Rats Exposed to Acute Regional Ischemia*

	Time to fall in VFT (min)	Control heart rates (beats/min)	Heart rates after 20 min regional ischemia (beats/min)	Control coronary flow rates (ml/min)	Coronary flow rates after 20 min regional ischemia (ml/min)	Infarct sizes (%)
Trained rats	11.5 ± 1.0 (12)	185.3 ± 5.6 (12)	172.5 ± 8.4 (12)	7.9 ± 0.4 (12)	5.3 ± 0.4 (12)	36.9 ± 1.8 (12)
Control rats	8.4 ± 0.8 (14)	180.6 ± 6.1 (14)	172.4 ± 6.1 (14)	8.4 ± 0.6 (14)	5.1 ± 0.5 (14)	39.3 ± 2.3 (14)
p	<0.05	NS	NS	NS	NS	NS

The heart rates, coronary flow rates and infarct sizes are not different between trained and control hearts, but the mean time to the initial fall in VFT is significantly longer in trained hearts.

Values are mean ± SEM; numbers in parentheses indicate the number of measurements.

Rats weighed 230–330 g; fresh weights of perfused hearts were 0.5–0.6 g.

Abbreviation: VFT = ventricular fibrillation thresholds.

tion thresholds fell significantly sooner after coronary ligation in control than in trained hearts.

Table 2 is a list of the tissue levels of ATP, phosphocreatine, glycogen, lactate and cyclic AMP in trained and control hearts clamped after 15 minutes of regional ischemia. The only significant difference was that tissue cyclic AMP levels were lower in the ischemic left ventricular zone of hearts from trained rats ($p < 0.02$). In hearts clamped after 15 minutes of Langendorff perfusion before determination of ventricular fibrillation thresholds, cyclic AMP levels were also significantly lower in trained hearts (0.21 ± 0.02 vs 0.28 ± 0.03 nmol/g, $p < 0.03$), whereas ATP and phosphocreatine levels were not different.

Ventricular Fibrillation Thresholds During Hypoxia and During Hypoxia with Catecholamine Stimulation

The ventricular fibrillation thresholds were significantly higher in hearts from trained rats during the control perfusions, during hypoxia, and during hypoxia combined with isoproterenol infusion (fig. 2).

Table 3 is a list of additional observations made during these experiments. There were no significant differences between trained and control rats in heart rates or coronary flow rates during either the control perfusions or during hypoxia or during hypoxia combined with isoproterenol infusion. There were also no significant differences in any metabolic measurements between hearts from trained and control rats (table 4).

Ventricular fibrillation thresholds in trained hearts were significantly higher during control perfusions in this, but not in the first experimental series (fig. 1). The rats used in this series of experiments had been trained for 12–16 weeks, whereas in the first study, the rats had been trained for 9–12 weeks. However, regression analysis failed to show a significant correla-

TABLE 2. *Tissue ATP, Phosphocreatine, Glycogen, Lactate and Cyclic AMP Levels in Normal and Ischemic Zones of Hearts from Trained and Control Rats After 15 Minutes of Regional Ischemia*

	ATP (μmol/g)	PCr (μmol/g)	Glycogen (μmol glucose Eq/g)	Lactate (μmol/g)	cAMP (nmol/g)
Normal tissue					
Trained rats	4.0 ± 0.1 (6)	5.8 ± 0.4 (6)	21.0 ± 1.1 (6)	1.4 ± 0.5 (6)	0.36 ± 0.1 (6)
Control rats	4.3 ± 0.5 (6)	6.1 ± 0.8 (6)	20.2 ± 1.2 (6)	2.1 ± 0.5 (6)	0.41 ± 0.1 (6)
p	NS	NS	NS	NS	NS
Ischemic tissue					
Trained rats	2.9 ± 0.2 (6)	2.5 ± 0.5 (6)	18.1 ± 1.5 (6)	15.1 ± 2.0 (6)	0.38 ± 0.1 (6)
Control rats	3.5 ± 0.3 (6)	2.7 ± 0.6 (6)	17.4 ± 1.7 (6)	16.6 ± 3.2 (6)	0.48 ± 0.1 (6)
p	NS	NS	NS	NS	<0.02

Cyclic AMP levels are significantly lower in the ischemic left ventricular zone of trained hearts. Values are mean ± SEM; numbers in parentheses indicate the number of measurements.

Abbreviations: PCr = phosphocreatine; cAMP = cyclic AMP.

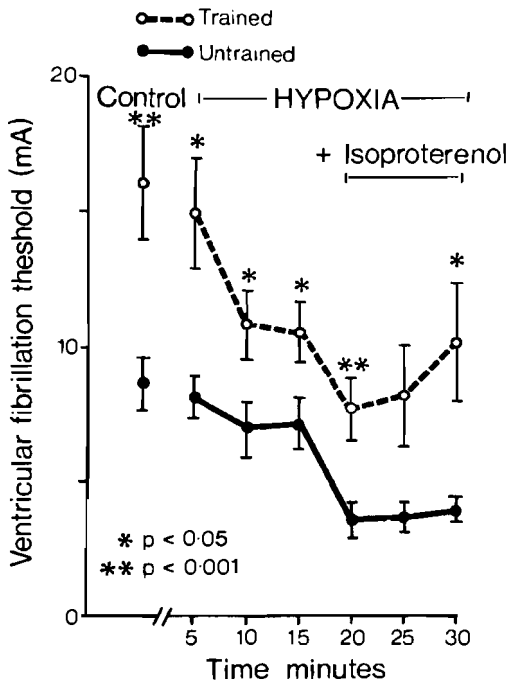

FIGURE 2. *Effect of hypoxia and hypoxia combined with isoproterenol infusion on ventricular fibrillation thresholds of trained and control hearts. At all times, ventricular fibrillation thresholds are higher in trained hearts.*

tion between the ventricular fibrillation threshold measured during the control perfusion, and the number of training sessions each rat had performed. Thus, the higher ventricular fibrillation thresholds of the trained hearts used in this series of experiments are probably not because they trained more.

Discussion

These studies show that ventricular fibrillation thresholds are increased in hearts from trained animals during control perfusions, during hypoxia and during acute regional ischemia. The only previous report that has relevance to this study is that of Ammann et al.,[18] who reported that in response to acute circumflex coronary artery ligation, eight of eight untrained dogs developed ventricular fibrillation, whereas only eight of 16 trained dogs did so.

In this study, the increased thresholds in trained hearts during either acute regional ischemia or during hypoxia could not be explained on the basis of differences in heart rates, in coronary flow rates, or in tissue levels of high-energy phosphates, glycogen or lactate. There was also no evidence that, in this model, exercise training caused reduced infarct sizes in response to coronary artery ligation, as reported by McElroy et al.,[19] or increased coronary flow responses to hypoxia, as reported by Spear et al.[20]

Cyclic AMP accumulation in the ischemic left ventricular zone was, however, significantly less in trained hearts, a finding consistent with the work of Kleitke et al.,[21] who reported that in response to acute global ischemia, hearts from swimming-trained rats had significantly lower cyclic AMP levels than those from control rats. In view of the hypothesis linking myocardial cyclic AMP levels and ventricular fibrillation thresholds in this model,[13] decreased formation of myocardial cyclic AMP in response to coronary artery ligation in trained animals would explain the beneficial effects on ventricular fibrillation thresholds caused by exercise training.

Cyclic AMP levels were significantly lower in trained hearts during the control perfusion. Although in absolute terms these changes were small, changes of a similar magnitude have been used to explain the antiarrhythmic effects of amiodarone in the same isolated heart preparation.[15] The possibility that cyclic AMP is compartmentalized within the heart cell[22] could explain why relatively small changes in cyclic AMP might have relatively large effects. On the other hand, cyclic AMP changes could not explain the differences in ventricular fibrillation thresholds between trained and control rats when the hearts were exposed to hypoxia and isoproterenol infusion, although these values, measured after 30 minutes of hypoxic perfu-

TABLE 3. *Heart Rates and Coronary Flow Rates of Hearts from Trained and Control Rats During Control Perfusions and During Hypoxia*

	Control heart rates (beats/min)	Heart rates during hypoxia (beats/min)	Heart rates during hypoxia plus isoproterenol infusion (beats/min)	Control coronary flow rates (ml/min)	Coronary flow rates during hypoxia (ml/min)	Coronary flow rates during hypoxia plus isoproterenol infusion (ml/min)
Trained rats	187.4 ±6.9 (8)	198.3 ±12.4 (7)	274.8 ±17.7 (8)	7.5 ±0.5 (8)	15.7 ±0.8 (8)	21.7 ±0.8 (8)
Control rats	198.8 ±8.5 (8)	184.8 ±11.3 (8)	252.4 ±11.3 (7)	8.4 ±0.5 (8)	16.0 ±1.7 (8)	21.1 ±1.2 (7)
p	NS	NS	NS	NS	NS	NS

Values are mean ± SEM; numbers in parentheses indicate number of measurements.

TABLE 4. *Tissue ATP, Phosphocreatine, Glycogen and Cyclic AMP Levels in Hearts from Trained and Control Rats After 30 Minutes of Hypoxic Perfusion, Combined with Isoproterenol Infusion**

	ATP (μmol/g)	PCr (μmol/g)	Glycogen (μmol glucose Eq/g)	cAMP (nmol/g)	Peak glycolytic rate (μmol glucose Eq/min)
Trained rats	3.1 ± 0.2 (8)	4.7 ± 0.3 (8)	16.0 ± 0.6 (8)	0.35 ± 0.04 (8)	2.9 ± 0.2 (8)
Control rats	3.3 ± 0.1 (7)	4.7 ± 1.4 (7)	14.3 ± 0.7 (7)	0.41 ± 0.03 (7)	2.5 ± 0.3 (7)
p	NS	NS	NS	NS	NS

Values are mean ± SEM; numbers in parentheses indicates the number of measurements.
*Hearts were clamped for biochemical analysis after 30 minutes of hypoxic perfusion according to the protocol shown in figure 2.
Abbreviations: PCr = phosphocreatine; cAMP = cyclic AMP.

sion, may not have been representative of the levels that were present after 20 minutes of perfusion, when ventricular fibrillation thresholds were lowest (fig. 2).

The mechanisms whereby exercise training reduces the resting levels of cyclic AMP and its accumulation during ischemia could include reduced catecholamine turnover at rest and in response to ischemia, increased parasympathetic activity, or alterations in the density of β-adrenergic receptors. Ostman et al.[23] found that the rates of myocardial noradrenaline turnover measured both at rest and during exercise in hearts of swimming-trained rats were half those of control rats, but similar studies have not been performed under ischemic conditions. An increase in parasympathetic tone has been found in some athletes, to such an extent that varieties of conduction abnormalities have been reported.[24] Radioligand binding studies have shown that there is no alteration in either β-adrenergic or muscarinic cholinergic receptor numbers or affinities after swimming training;[25] no data are available on running rats.

Whatever the mechanism for the reduced levels of cyclic AMP in trained hearts during ischemia, a consequence may be reduced calcium ion entry by the slow calcium current.[26] Thandroyen[27] showed that calcium ions may be important in the genesis of ventricular fibrillation. Further investigations on the effects of running training on calcium ion flux in the ischemic heart are warranted. Under conditions of maximal heart work, we found indirect evidence for increased trans-sarcolemmal calcium entry[10, 11] in trained hearts.

The finding that exercise training increased myocardial resistance to ventricular fibrillation in this model may not be applicable to man, in whom ventricular fibrillation occurs spontaneously and not in response to exogenous electrical stimulus. Nevertheless, these data from animal studies give experimental support for the epidemiologic data linking exercise training with decreased sudden cardiac death.[3-5, 7, 8]

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Exercise Training After Experimental Myocardial Infarction Increases the Ventricular Fibrillation Threshold Before and After the Onset of Reinfarction in the Isolated Rat Heart

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Previous work has shown that exercise training increases the ventricular fibrillation threshold of the isolated perfused rat heart. The aim of our study was to determine whether exercise training that begins after myocardial infarction can similarly increase the ventricular fibrillation threshold. Rats that had suffered an experimental myocardial infarction were subject to a running training program. Thereafter, the ventricular fibrillation threshold was measured before and after the onset of acute reinfarction induced by a second coronary artery ligation. Ventricular fibrillation thresholds were significantly elevated in trained rats during normoxia (13.7 ± 2.2 vs. 4.7 ± 0.8 mA, $p<0.01$) and during acute ischemia (6.8 ± 1.6 vs. 3.0 ± 0.7 mA, $p<0.02$). The myocardial cyclic AMP level was lower in the nonischemic zone of the trained hearts (0.21 ± 0.01 vs. 0.28 ± 0.01 nmol/g, $p<0.05$), which also had lower cyclic AMP levels after epinephrine challenge (0.50 ± 0.05 vs. 0.73 ± 0.09 nmol/g, $p<0.01$; 1.41 ± 0.11 vs. 1.85 ± 0.09 nmol/g, $p<0.02$ after epinephrine 10^{-7} M and 5×10^{-6} M injection, trained vs. untrained). Both propranolol 10^{-6} M and epinephrine 5×10^{-7} M attenuated the difference in ventricular fibrillation thresholds before and after second coronary artery ligation and eliminated any difference in cyclic AMP content of both the nonischemic and ischemic myocardial tissue. We conclude that exercise training increases the ventricular fibrillation threshold of the previously infarcted isolated rat heart before and after the onset of reinfarction and that the training effect may be mediated by a decrease in myocardial sympathetic tone, an increase in parasympathetic tone, or both. (*Circulation* 1989;80:138–145)

Epidemiologic evidence shows an association between exercise and a reduced incidence of sudden cardiac death.[1–4] We have previously shown that the exercise-trained rat heart has an increased resistance to ventricular fibrillation during normoxia, hypoxia, and acute regional ischemia,[5] suggesting that training may act directly on the myocardium to increase myocardial resistance to lethal cardiac arrhythmias.

The aim of our study was to determine whether exercise training in the presence of an established previous myocardial infarction can also influence myocardial resistance to ventricular fibrillation. Epidemiologic evidence[3,6,7] suggests that exercise as part of a comprehensive rehabilitation program after myocardial infarction may reduce the incidence of subsequent sudden cardiac death.[8] In conscious postinfarct dogs, when further temporary myocardial ischemia is applied during exercise, the risk of ventricular fibrillation is decreased by prior exercise training, suggesting that postinfarct training in humans could prevent sudden death.[8] However, the underlying cellular biochemical mechanisms for the benefits of postinfarct training have not been clarified.

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The purpose of our study was to determine whether exercise training after experimental myocardial infarction influences the ventricular fibrillation threshold (VFT) of the isolated perfused rat heart. Groups of rats that had suffered a surgically induced acute myocardial infarction were randomly assigned to either an exercising or a nonexercising control group. After a 10-week period, isolated perfused hearts from both trained and untrained rats were subject to a second acute coronary artery ligation before and after which the VFT was measured.

Previous studies[5,8–10] have suggested that the increased myocardial resistance to ventricular fibrillation after exercise training might be related to altered autonomic nervous system activity. Myocardial biochemical studies were performed to determine whether trained hearts had altered levels of cyclic AMP (cAMP). Myocardial cAMP concentrations served as an indicator of myocardial sympathetic activity. The additional effects of β-adrenergic antagonism and stimulation were also studied.

Methods

In Vivo Coronary Artery Ligation

Male Long-Evans rats (250–300 g) were anesthetized with intraperitoneal Ketalar (ketamine HCl 100 mg/ml, Parke Davis) (1 mg/g body wt). Lidocaine (10 mg) was sprayed onto the epiglottis to prevent laryngospasm during intubation. A modified laryngoscope was used to intubate the rats, which were ventilated with a Harvard apparatus rodent respirator (Protea Holdings) on a 2:1 oxygen-halothane mixture (Maybaker [SA]).

A skin incision approximately 5 cm long was made from the sternum to the left shoulder. The left pectoral muscle was incised to expose the ribs. Next, an incision was made through the rib cage, care being taken to avoid damaging the underlying lungs. A chest miniretractor was used to expose the heart, and the thymus gland was held to one side with a fine artery forceps. The pericardium was gently dissected away and the left atrium elevated to establish clearly the origin of the left main coronary artery. A 6-0 Ti-Cron suture (Davis and Geck) was inserted into the left ventricle halfway down the course of the left anterior descending coronary artery. After ligation, the ventricular mass below the ligature became pale, corresponding to the area of acute ischemia, which represented approximately 25–35% of the left ventricular mass.

The chest and skin were closed with 3-0 Ti-Cron (Davis and Geck). Ventilation was changed to room air, which was maintained until spontaneous breathing returned. Aseptic procedures were not used and postoperation sepsis was not noted. Neither antibiotic nor antiarrhythmic therapy was instituted, and preoperative ketamine provided adequate analgesia.

A mortality of approximately 25% resulted from the acute coronary artery ligation.

Training Program

After a 1-week convalescent period, the rats were randomly assigned to either an exercising or nonexercising group. Exercising rats completed a 10-week training program on a Quinton Model 42-15 treadmill (Quinton Instruments, Seattle, Washington). The rats exercised 5 days a week at a speed of 1.3 km/hr (15% elevation) for an initial period of 10 minutes increasing to a maximum of 60 minutes at the end of 2 weeks. This duration was maintained for the remainder of the training program. The treadmill is designed to provide electrical shocks via an electrical wire grid at the back of the running lanes to those rats that do not maintain their running speeds. In practice, the rats were shocked less than one shock every few minutes.

The untrained rats were maintained at normal cage activity for the 10-week period. Both groups were housed under the same conditions and were given food and water ad libitum.

As the trained rats were subjected to intermittent electrical shocks during the training program, an untrained group was placed on the electrical wire and prevented from running. These rats received intermittent shocks of the same frequency and intensity as did the trained rats for an identical period of time. After 10 weeks, rats from the untrained, untrained but shocked, and trained groups (three groups) were killed for the experimental studies.

Experimental Protocols

Measurement of "training effect." MAXIMUM OXYGEN CONSUMPTION (VO_{2max}). Before the start of training and after 10 weeks of training, rats were subject to a running performance test using the apparatus and methods previously described from this laboratory.[11] Rats ran in a bottomless Plexiglas chamber (9.5×32.5×11.5 cm) that was suspended on a custom-built single-lane treadmill. Ambient air was drawn through the chamber at a flow rate of 5.0–7.5 l/min (STPD), depending on the mass of the rat. The flow rate was calibrated before and after each test with a Tissot spirometer. Samples of the extracted air were directed to an O_2 (Applied Electrochemistry S-3A/1) and a CO_2 (Applied Electrochemistry P-61B) analyzer, which were interfaced with an Alpha microcomputer. Oxygen consumption was calculated every minute as previously described.[11] Before and after each test, the O_2 and CO_2 analyzers were calibrated with gases of known O_2 and CO_2 composition.

Each VO_{2max} test was conducted after a day of rest according to the testing procedure previously described from this laboratory.[11] The test protocol involved increasing the treadmill speed and elevation every 3 minutes until the rat could no longer maintain his position on the treadmill belt. The highest VO_2 measured was recorded as the VO_{2max}.

SUBMAXIMAL RUNNING ENDURANCE. The submaximal running endurance was determined by running the rats at a speed of 20 m/min with no inclination or, in a separate series, at an inclination of 15°. The time taken to reach exhaustion represented the submaximal running endurance. Exhaustion was determined as the inability of the rats to maintain their position on the treadmill belt.

Measurement of ventricular fibrillation thresholds. VENTRICULAR FIBRILLATION THRESHOLD MEASUREMENTS DURING CONTROL PERFUSIONS. The rats were anesthetized with ether in a glass vacuum bowl. When adequately sedated, 10 μl heparin (1,000 units/ml) was injected into the femoral vein. The thoracic cavity was opened, and the heart rapidly excised and immediately placed into ice-cold Krebs-Henseleit[12] buffer. The perfusate was a modified Krebs-Henseleit buffer solution with a concentration of 144 mM Na^+, 5.9 mM K^+, and 1.1 mM $CaCl_2$ aerated with 95% O_2-5% CO_2. Insulin (NUSO Neutral Insulin Wellcome Foundation) was added at a concentration of 2 IU/l. Once the heart had stopped beating, the aorta was cannulated and retrograde perfusion was commenced within 90 seconds via an isolated Langendorff system at a perfusion pressure of 100 cm H_20.

The VFT of the isolated rat heart was measured as previously described.[13] The heart was mounted on the aortic cannula, and two thin platinum electrodes were inserted into the base and apex of the left ventricle. These electrodes recorded the electrocardiogram on an oscilloscope and delivered square-wave stimuli of 2-msec duration (Grass S88 Physiologic Stimulus Generator). The VFT was measured by applying a single train of 10 stimuli of 200-msec duration across the T wave starting 10 msec after the onset of the R wave. The heart was stimulated every 60 seconds unless ventricular fibrillation occurred, in which case the next stimulus was only applied after 120 seconds. The current strength was increased by 2 mA every 60 seconds until ventricular fibrillation consisting of six or more repetitive ectopics of irregular form developed. The VFT was defined as the lowest current that produced ventricular fibrillation on three occasions and did not produce fibrillation at a current of 0.5 mA lower.

The first VFT measurements were made after a 15-minute stabilization period during which both coronary flow and spontaneous heart rate were measured. At the completion of the experiment, heart mass and size of the in vivo infarct were measured.

VENTRICULAR FIBRILLATION THRESHOLD MEASUREMENTS DURING ACUTE ISCHEMIA. In a separate series of experiments, VFT measurements were made during acute ischemia. After cannulation (as previously described), a 6-0 Ti-Cron suture with an atraumatic needle was passed deep to the left main coronary artery as it emerges adjacent to the left atrium, according to the technique described by Kannengieser et al.[14] This ligature was necessary for the development of acute ischemia (see below). Once initial control VFT measurements had been performed, acute regional ischemia was induced by abruptly tightening the ligature that had previously been placed around the left coronary artery.

Beginning 2 minutes after ligation, VFT measurements were made for a period of 15 minutes. Thereafter, disulphan blue was injected into the aortic cannula to perfuse the coronary arteries. This dye distinguishes between oxygenated and nonoxygenated tissue and was, therefore, used to differentiate normal from ischemic or infarcted myocardial tissue. The hearts were then freeze-clamped with Wollenberger tongs[15] that had been precooled in liquid nitrogen. The frozen tissue was separated into normal and ischemic/infarcted tissue and stored in liquid nitrogen pending cAMP and biochemical analysis.

VENTRICULAR FIBRILLATION THRESHOLD MEASUREMENTS DURING ACUTE ISCHEMIA IN HEARTS PERFUSED WITH PROPRANOLOL 10^{-6} M AND EPINEPHRINE 5×10^{-7} M. An identical protocol was used for two further sets of experiments. Hearts from trained and untrained rats were perfused separately with propranolol 10^{-6} M (Inderal, ICI Laboratories) and epinephrine bitartrate 5×10^{-7} M (Petersen Ltd). VFT measurements were performed as before and the hearts were freeze-clamped after 15 minutes of ischemia for cAMP and biochemical analyses.

cAMP measurements after catecholamine stimulation. In these experiments, VFT measurements were not performed. Hearts from trained and untrained rats with previous myocardial infarction were mounted on the perfusion apparatus as previously described. After the 15-minute stabilization period, the aortic cannula was cross-clamped and a 1 ml bolus of epinephrine bitartrate was injected into the aortic perfusate over a period of 2 seconds. Epinephrine bolus concentrations of 10^{-8} M, 5×10^{-8} M, 10^{-7} M, and 5×10^{-6} M were used. Ten seconds later, the hearts were clamped and the noninfarcted tissue segments were stored for cAMP analysis.

Tissue Analysis

Measurement of acute ischemic zone and infarct size. Hearts were removed from the aortic cannula after the injection of disulphan blue into the aortic perfusate. The ischemic and infarcted tissues failed to stain with dye. Assessment of ischemic tissue was made after the scar tissue from the in vivo infarct had been excluded, and a zone of apparently normal periinfarct tissue was also excluded. Measurements of in vivo infarct size were performed in a separate series of experiments where no secondary ischemia was induced. The infarcted tissue was dissected out, and its mass was recorded as a percentage of the total left ventricular mass.

Myocardial biochemical and cyclic AMP measurements. The tissue contents of ATP, phosphocreatinine, glycogen, lactate, and cAMP were mea-

TABLE 1. Effect of Training on Exercise Program

Test	Untrained (n=6)	Trained (n=6)
VO_{2max} (ml O_2/kg/min)	68.5±2.0	74.8±1.7*
Run time to exhaustion during submaximal test (min)	19±4	69±7†
Run time to exhaustion during maximal test (min)	15.0±0.6	26.4±0.8†

Mean±SEM.
*p<0.05.
†p<0.01.

sured in freeze-clamped hearts homogenized under liquid nitrogen by standard methods, as previously described in a report from this laboratory.[5]

Statistical Methods

Data are presented as mean±SEM. A 2×2×4 factorial analysis of variance (three-way ANOVA) was used to analyze VFTs. A multifactorial analysis of variance with repeated-measures design and a Student's unpaired t test modified for multiple comparisons were used for analysis of biochemical data.

Results

Effect of Training on Exercise Performance

Exercise training significantly increased mean VO_{2max} in trained rats (Table 1). Running time to exhaustion also increased significantly with training during the maximal test. Similarly, exercise training significantly increased the time taken to reach exhaustion during the submaximal running tests.

Effect of Training on Rat Mass, Heart Mass, Infarct Size, Spontaneous Heart Rate, Coronary Flow, and Ventricular Fibrillation Threshold

Trained rats had lower body mass than untrained rats (Table 2). Heart mass was not different between groups. True infarct size, spontaneous heart rate, and coronary flow were not affected by training.

Exercise training significantly increased mean VFT in trained rats. There was no difference in VFT values between shocked and unshocked animals.

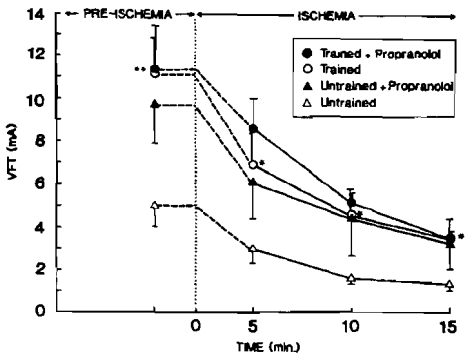

FIGURE 1. *Effect of acute regional ischemia caused by second coronary artery ligation on ventricular fibrillation thresholds of previously infarcted trained and untrained rat hearts perfused with no drug or propranolol 10^{-6} M. Mean±SEM,* n=8. *p<0.05 *trained vs. untrained with no drug.* **p<0.01 *trained vs. untrained with no drug.*

Ventricular Fibrillation Threshold Measurements During Acute Ischemia

At all times during coronary artery ligation, the VFT was higher in hearts from trained rats (Figure 1). As in the previous experiment, trained rats were lighter but there were no differences in heart mass, spontaneous heart rate of the isolated heart, or total coronary flow (data not presented).

Ischemia caused tissue ATP, phosphocreatinine, and glycogen levels to fall, whereas lactate levels rose. cAMP levels rose in the ischemic tissue, but this increase was not significant. Tissue levels of ATP, phosphocreatinine, glycogen, and lactate were not different between the trained and untrained groups after 15 minutes of regional ischemia (data not presented).

Myocardial cAMP levels were lower in the normal zone of the hearts from trained than untrained rats, but cAMP levels in the ischemic zone were unchanged by training.

Ventricular Fibrillation Threshold Measurements During Acute Ischemia in Hearts Perfused With Propranolol 10^{-6} M or Epinephrine 5×10^{-7} M

Hearts perfused with propranolol 10^{-6} M. Propranolol significantly elevated the VFT value prior

TABLE 2. Measurement of Rat Mass, Infarct Size, Heart Rate, and Coronary Flow During Control Perfusions of Hearts From Untrained Ligated, Trained Ligated, and Untrained Ligated Shocked Rats

Rats (n=8)	Rat mass (g)	Heart mass (g)	In vivo infarct size* (% LV)	Spontaneous heart rate (beats/min)	Coronary flow (ml/min)	VFT (mA)
Untrained, ligated	503±24†	2.05±0.07	27.3±3.2	261±19.5	18±2.6	4.9±0.8‡
Trained, ligated	462±19	2.11±0.15	27.0±1.7	274±8.0	17±1.1	13.7±2.2
Untrained, ligated, shocked	512±16†	2.08±0.04	28.0±2.4	273±11.0	19±2.5	4.8±0.8‡

Mean±SEM.
*For limitations of method, see Anversa et al.[31]
†p<0.05 vs. trained, ligated.
‡p<0.01 vs. trained, ligated.

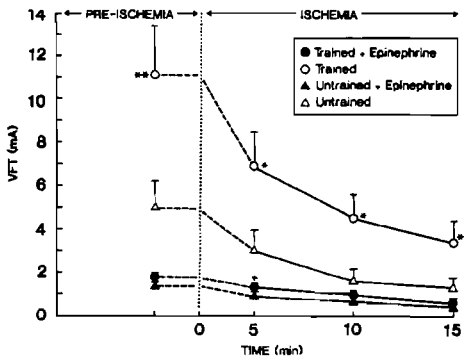

FIGURE 2. *Effect of acute regional ischemia caused by second coronary artery ligation on ventricular fibrillation thresholds of previously infarcted trained and untrained rat hearts perfused with no drug or epinephrine 5×10^{-7} M. Mean±SEM,* n=8. *p<0.05 *trained vs. untrained with no drug.* **p<0.01 *trained vs. untrained with no drug.* †p<0.05 *trained + epinephrine vs. untrained + epinephrine.*

to second coronary artery ligation of untrained but not of trained hearts (Figure 1). After coronary artery ligation, VFT during ischemia was elevated but not significantly in hearts from both trained and untrained rats. The net effect of propranolol was to attenuate the difference in VFT previously found between hearts from trained and untrained rats before and after second coronary artery ligation.

Propranolol caused a reduction in spontaneous heart rate and an increase in coronary flow. As before, there were no differences in heart mass, spontaneous heart rate, or coronary flow between hearts from the trained and untrained rats (data not presented).

Ischemia caused equivalent changes in ATP, phosphocreatinine, glycogen, and lactate levels in both trained and untrained hearts. cAMP levels in either the nonischemic or ischemic tissue of the hearts from trained and untrained rats were also not different (Table 2).

Hearts perfused with epinephrine bitartrate 5×10^{-7} M. Epinephrine caused a significant reduction in VFT values of hearts of both trained and untrained rats before and after second coronary artery ligation (Figure 2). Epinephrine attenuated the difference in VFT between the hearts from trained and untrained rats before ligation and after 10 and 15 minutes of ischemia. After 5 minutes of ischemia, the VFT of the hearts of trained rats was higher, however ($p<0.05$).

Epinephrine caused an increase in spontaneous heart rate and coronary flow. There were no differences in heart mass, spontaneous heart rate, or coronary flow between the hearts from trained and untrained rats (data not presented).

There were no differences in tissue levels of ATP, phosphocreatinine, glycogen, and lactate between the two groups of hearts after 15 minutes of regional ischemia. There were no differences in cAMP levels of either the nonischemic or ischemic tissues of the hearts (Table 3).

cAMP Measurements After Catecholamine Stimulation

cAMP levels were lower in the hearts from trained rats 10 seconds after epinephrine 5×10^{-6} M and 10^{-7} M stimulation (Figure 3). There were also no differences in cAMP concentrations between hearts from trained and untrained rats with epinephrine concentrations of 5×10^{-8} M and 10^{-8} M.

Discussion

The present study shows that the training protocol used, although less vigorous than that used for

TABLE 3. **Tissue ATP, Phosphocreatine, Glycogen, Lactate, and Cyclic AMP in Nonischemic and Ischemic Zones of Hearts From Trained and Untrained Rats With a Prior Myocardial Infarct Perfused With no Drug, Propranolol 10^{-6} M, and Epinephrine 5×10^{-7} M After 15 Minutes of Ischemia**

Group		ATP (μmol/g)	Phosphocreatinine (μmol/g)	Glycogen (μmol glucose Eq/g)	Lactate (μmol/g)	Cyclic AMP (nmol/g)
Trained and no drug (n=8)	Nonischemic	2.46±0.26*	4.56±0.35*	24.23±2.09*	4.35±0.46*	0.21±0.01†
	Ischemic	1.19±0.13	2.24±0.28	14.70±2.25	10.44±2.07	0.26±0.04
Untrained and no drug (n=8)	Nonischemic	2.83±0.20*	4.61±0.36*	20.86±1.44*	3.73±0.60*	0.28±0.01
	Ischemic	1.29±0.25	1.77±0.22	10.31±1.37	9.79±2.22	0.29±0.02
Trained and propranolol 10^{-6} M (n=8)	Nonischemic	3.91±0.17*	4.46±0.19*	23.38±1.63*	5.22±0.57*	0.28±0.01
	Ischemic	2.64±0.13	1.19±0.22	15.44±1.16	10.62±1.24	0.29±0.13
Untrained and propranolol 10^{-6} M (n=8)	Nonischemic	3.90±0.18*	4.43±0.37*	23.56±1.39*	6.11±1.48*	0.28±0.01
	Ischemic	3.04±0.32	1.38±0.13	15.63±1.45	13.51±3.20	0.32±0.02
Trained and epinephrine 5×10^{-7} M (n=8)	Nonischemic	3.00±0.16*	4.59±0.25*	17.16±2.60*	6.00±0.27*	0.71±0.03*
	Ischemic	1.37±0.15	1.68±0.40	5.31±1.09	15.14±2.09	0.52±0.04
Untrained and epinephrine 5×10^{-7} M (n=8)	Nonischemic	2.81±0.13*	5.14±0.63*	11.57±1.50*	6.39±0.65*	0.71±0.07*
	Ischemic	1.18±0.18	1.24±0.18	4.43±1.05	15.10±2.54	0.46±0.06

*$p<0.05$ ischemic vs. nonischemic.
†$p<0.05$ trained nonischemic vs. untrained nonischemic.
Mean±SEM.

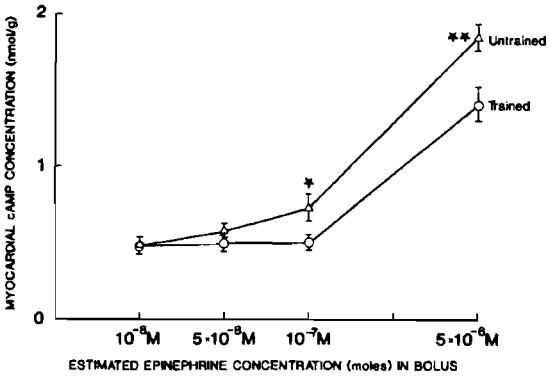

FIGURE 3. *Myocardial cyclic AMP concentrations 10 seconds after epinephrine stimulation. Mean±SEM, n=8. *p<0.01. **p<0.02.*

rats without myocardial infarction,[5] was sufficient to produce a training effect. This was shown by the increased VO_{2max} and increased running times to exhaustion during submaximal and maximal exercise in trained rats (Table 1). More important, this study establishes that training of rats after previous experimental myocardial infarction elevates VFTs before and after the onset of acute regional ischemia produced by a second coronary artery ligation. Trained hearts also had lower cAMP levels in the nonischemic left ventricular zone and in the normal myocardium after catecholamine stimulation. Both propranolol 10^{-6} M and epinephrine 5×10^{-7} M attenuated this difference in VFT before and after second coronary artery ligation and eliminated any difference in cAMP content of both the nonischemic and ischemic myocardial tissue.

The present study, therefore, extends our previous work[5] in which we showed that exercise training increased the VFT of isolated hearts from normal rats. Our data are in agreement with two additional animal studies. Verdouw and Schaffer[10] found that exercise-trained noninfarcted pigs had a reduced incidence of ventricular fibrillation after acute myocardial ischemia during an open-chest anesthetized procedure, whereas Billman et al[8] found that conscious dogs who were exercise trained after a previous myocardial infarction had a reduced incidence of ventricular fibrillation during subsequent acute ischemia, also in the conscious state.

In combination with ours, these studies provide strong experimental evidence that in very different experimental systems, exercise training increases myocardial resistance to lethal arrhythmias that occur either spontaneously[8,10] or in response to electrical stimulation either before or after coronary artery ligation[5] or after reinfarction as shown by this study.

It should, however, be noted that there are some apparent differences between the findings of our present and the previous study.[5] In the present study, there is a lower level of cAMP in the nonischemic tissue of the trained rats, whereas the previous study showed lower concentrations of cAMP in the ischemic regions. Possible interpretations of these findings might relate to the difference in protocols in the two studies. In the present study, the rats were trained after myocardial infarction, whereas in the previous study healthy rats were trained. However, in both studies, mean cAMP levels are lower in both regions of the myocardium of trained rats, although not all values are significantly lowered. Furthermore, in the previous study, cAMP rose significantly in the ischemic zone in untrained rats, whereas in this study it did not (the increase was not significant). Because cAMP had not risen in the ischemic zone, training could not have been expected to reduce it.

Our findings of the effect of propranolol and epinephrine on the VFT also support the hypothesis that exercise training decreases myocardial sympathetic drive with a consequent increased resistance to the development of ventricular fibrillation. Trained and untrained hearts perfused with either propranolol or epinephrine had similar ventricular fibrillation thresholds and similar myocardial cAMP levels. Possibly the effects of propranolol or of epinephrine were to eliminate training-induced differences in myocardial sympathetic balance.

Lubbe et al[16] also found that propranolol attenuated the decrease in the VFT of the isolated perfused rat heart during ischemia. Vulnerability to ventricular fibrillation in early myocardial ischemia was related to changes in cAMP content of the ischemic myocardium and appeared to be independent of the depletion of myocardial high-energy phosphate stores. Additional studies support this conclusion.[17,18] Nonetheless, propranolol acted without decreasing myocardial cAMP levels.

In addition, hearts from trained rats had lower myocardial cAMP concentrations in nonischemic tissue after an epinephrine challenge. However, there was no difference in cAMP concentrations in the nonischemic tissue between hearts from trained and untrained rats subject to epinephrine stimulation and acute myocardial ischemia. It, therefore, appears that while exercise attenuates the increase in myocardial cAMP after catecholamine stimula-

tion, this effect is not present during both epinephrine stimulation and acute myocardial ischemia.

Possible Role of Altered Autonomic Function

The mechanism for this protective effect of exercise is presently unclear. One possibility is that exercise training alters the myocardial response to sympathetic stimulation. Enhanced sympathetic activity increases myocardial predisposition to ventricular fibrillation.[19-21] Acting at a cellular level, high circulating catecholamine concentrations are considered to be potently arrhythmogenic and to cause lowering of the ventricular fibrillation threshold in the isolated rat heart.[13] The proposed intracellular messenger of the arrhythmogenic effect is cAMP.[22] The chronic effects of exercise on the sympathetic nervous system are well documented.[23-25] In particular, there is decreased activity of the sympathetic nervous system, so that at comparable workloads the heart of a trained subject is exposed to lower levels of sympathetic stimulation.[26,27] A training-induced reduction in myocardial catecholamine "sensitivity" is, therefore, a possible explanation for the higher VFT measured in hearts from trained subjects.

In this and our previous study,[5] training was associated with a reduced concentration of cAMP in the nonischemic myocardium. In the present study, we also show that hearts from trained rats had lower myocardial cAMP levels after catecholamine stimulation. Lower cAMP levels could be explained either by chronically reduced whole-body catecholamine levels at rest or by alterations in the density or sensitivity of the β-adrenergic receptors. Although the isolated rat heart was used without an intact autonomic nervous system, the decreased levels of cAMP in the hearts from trained rats could indicate decreased myocardial sympathetic tone. A training-induced alteration in baroreceptor reflex control of heart rate and in autonomic actions paralleled the increased protection against ventricular fibrillation.[8,28,29]

The training effect found by Billman et al[8] could be explained by an increase in parasympathetic activity, a decrease in sympathetic activity, or both. The importance of changes in baroreflex control is emphasized by two recent studies. In one, mortality in postinfarct patients was associated with decreased baroreflex sensitivity.[28] In the other study, dogs with a prior myocardial infarction were subject to acute ischemia during exercise; ventricular fibrillation developed more easily in dogs with a low baroreflex sensitivity.[29] We did not assess baroreflex sensitivity but measured myocardial cAMP levels as an end-point of cardiac autonomic activity. The level of cAMP, the second messenger of adrenergic stimulation, is influenced by additional hormone systems, in particular, the parasympathetic nervous system in which acetylcholine may counteract the catecholamine effect both before and after the adrenergic synapses. Postsynaptic acetylcholine may act both directly and indirectly via raised cGMP levels to reduce cAMP levels.[30] Increased parasympathetic activity could, therefore, decrease cAMP levels. An alternative interpretation of the above findings would be that training elevates VFT by increasing parasympathetic activity. However, this conclusion would not explain the reduced cAMP response to epinephrine infusion (Figure 3).

Limitations to Study

There are three important limitations to this study. First, we used the rat model of electrically induced ventricular fibrillation rather than the development of spontaneous ventricular fibrillation. Limitations inherent in the Langendorff model of retrograde perfusion include a denervated isolated heart with low afterloads and coronary artery perfusion pressures that are not in the physiologic range of an intact preparation.

A second limitation concerned the inaccuracies inherent in the measurement of the ischemic zone, the infarct size, and coronary flow. Although coronary flow rates were similar in hearts from trained and untrained rats, the smaller reduction in VFT during acute ischemia in the trained rats could possibly reflect an improved collateral circulation so that the ischemic insult was smaller. Accurate measurement of infarct size in the rat model requires careful morphometric techniques, similar to those developed by Anversa et al.[31] We cannot exclude that exercise training altered ultimate infarct size. Third, the measurements of cAMP on freeze-clamped hearts could have been on a mixture of infarcted and noninfarcted tissue, as well as of ischemic and nonischemic tissue. Hence, the differences shown in Table 3 could have been influenced by a considerable sampling error. It remains true that a comparison of the values of ATP, phosphocreatine, glycogen, and lactate found between ischemic and nonischemic tissue shows that the separation technique was at least sufficiently adequate to achieve major differences.

Conclusions

The data obtained support the hypothesis that altered autonomic activity occurs with training, specifically, that the reduced sensitivity of the myocardium to catecholamines could improve the myocardial resistance to ventricular fibrillation. These data, therefore, provide experimental support for the possibility that exercise training after myocardial infarction might be associated with a reduced incidence of sudden death in humans.[32]

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10
Fluid Replacement During Exercise

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HISTORICAL INTRODUCTION

Included among the "Don'ts" in a 1909 monograph titled "Marathon Running" [152] was the admonition: "Don't get in the habit of drinking and eating in a Marathon race; some prominent runners do, but it is not beneficial." The advice of Arthur Newton, a leading ultramarathon runner of the first half of this century, who held world records for running distances from 50–130 miles [117] was similar: "Even in the warmest English weather, a twenty-six mile run ought to be manageable with no more than a single drink, or at most two" [115].

In 1957, the then holder of the world's four fastest times for the 42-km marathon footrace wrote: "There is no need to take any solid food at all (during a marathon race) and every effort should be made to do without liquid, as the moment food or drink is taken, the body has to start dealing with its digestion and in so doing some discomfort will almost invariably be felt" [135]. Another famous ultra-distance runner who set world records at 30, 40, and 50 miles in 1954 confirmed that this advice was widely accepted: "In those days it was quite fashionable not to drink, until one absolutely had to. After a race runners would recount with pride 'I only had a drink after 30 or 40 kilometres.' To run a complete marathon without any fluid replacement was regarded as the ultimate aim of most runners, and a test of their fitness." (J. Mekler, 1991, personal communication). This athlete, who once competed in a 100-mile race in which he first drank only after 75 miles, confirmed that this approach was still popular when he had run his last competitive ultramarathon race in 1969.

That these ideas could *ever* have held credence, let alone so recently, may seem absurd to the modern exercise physiologist. But the fluid requirements of athletes has attracted scientific interest only since the early 1970s. Virtually all of the textbooks of exercise physiology and sports medicine published before 1970 contain little or no reference to this topic [2, 12, 44, 52, 57, 89, 164]; one of the first to include a section on fluid replacement during exercise was the monograph by Costill [31]. Yet many studies showing the importance of adequate fluid replacement especially during industrial and military activities in the heat had already been published.

The building of the Hoover Dam near Boulder City, Nevada in the 1930s stimulated the first systematic studies of fluid (and electrolyte) requirements during work in temperatures ranging between 90–120°F. One early study described the clinical and biochemical features of so-called "heat cramps" in seven workers on this project [157]. Another study measured fluid intake and urine output during both work and rest [156] and concluded that construction work could be undertaken without major health risks even in these severe environmental conditions provided subjects were accommodated in air-conditioned lodgings [46]. Yet another early study showed that sweat sodium concentration fell within days of exposure to extreme heat becoming so low that "10 litres per day may be secreted without the necessity of an abnormal salt intake" [46].

More detailed studies by Adolph and Dill [7] showed that the daily fluid intakes of construction workers averaged about 4 liters/day but rose as a linear function of increasing maximum daily temperature. Sweat rates increased from a resting value of 400 ml/hr when sitting in shade, to maximum rates of 1500–1700 ml/hr during 1–2 hr of exercise in the heat. Subjects showed relatively little desire to drink during exercise; fluid ingestion was greatest immediately after exercise and with meals. In the absence of food ingestion, drinking stopped when approximately one-half of the fluid loss had been corrected. The authors suggested that: ". . since some solute as well as water was lost, only enough water was required by the subject to render the concentration of the body fluids equal to their previous state." They also noted that all the water ingested an hour before exercise was lost in urine before the onset of exercise. But if the fluid contained sodium chloride "the water was retained for several hours before it was required for the formation of sweat." Subsequent studies suggested that 1 or more liters of fluid with a sodium chloride content of 0.5–0.9% (80–140 mmol/liter) ingested 2–3 hr before exercise would increase body fluid content [5].

Despite the clear reluctance of dehydrated subjects to replace their fluid losses fully during and immediately after exercise, their daily fluctuations in weight were no greater than those measured in winter climates, indicating that fluid imbalances were corrected diurnally: "All the deviations from water balance were on the negative side; water was expended and a debt built up, which was later paid off." In contrast, Dill [46] found that within minutes of being given water, the dog and the donkey (burro) replaced exactly all the fluid they had lost during exercise. In one case, a burro drank 12 liters in 5 minutes [46]. Among the mammals studied by then, therefore, dehydrated humans were unique in this inability to replace all the fluid lost during exercise, as soon as water was provided.

The demands of desert warfare during the Second World War stimulated the next and, possibly, the truly classic early studies of fluid

replacement during exercise [5]. These magnificent studies established for the first time, many of the concepts that continue to intrigue modern physiologists. Interestingly, at the time the studies commenced, it was believed that men, like marathon runners, should be "trained to do without water." Among the classic findings were the following:

1. Maximal sweat rates during exercise under the most severe environmental desert conditions were of the order of 1.7 liters/hr; much higher rates were reported during exercise in conditions of high humidity (jungle heat). Sweat rates during exercise in desert heat rose as a linear function of body weight and, hence, metabolic rate and environmental temperature.
2. Sweat rates during exercise were not influenced by the level of dehydration. Thus, the capacity for evaporative heat loss during low-intensity exercise was not impaired by progressive dehydration. Despite this, the rectal temperature rose during exercise as a linear function of the level of dehydration.
3. Urine flow was reduced when levels of dehydration exceeded 3% but did not increase dehydration levels of 7%. Thus, progressive dehydration did not induce fluid conservation by decreasing urine output. Anuria was not detected in any subject under any conditions. The constant urine output was needed to excrete the solutes contained in urine.
4. Chloride was present in virtually all urine samples measured. Thus, "salt deficiency in the desert was not common."
5. Even when given free access to adequate fluids during exercise, subjects developed a progressive weight loss, termed "voluntary" dehydration. Food ingestion greatly increased fluid intake; at least one-half of the fluid ingested daily was taken with meals. Conversely, without an adequate fluid intake, food intake during meals was also reduced. But body weight was usually restored after the evening meal.
6. Unless corrected, the progressive dehydration that developed during exercise in the heat impaired physical performance. At low levels of dehydration, physical performance was impaired only during high-intensity exercise. Subjects became syncopal, however, and were unable to exercise even at low exercise intensities when their levels of dehydration exceeded 7%. Feelings of well-being and the ability to walk returned within minutes of the resumption of drinking. Maximal levels of dehydration compatible with life were of the order of 20%.
7. The fluid lost in sweat did not originate equally from the different fluid compartments but came predominantly from the extracellular compartment. This would impair cardiovascular function.
8. Heart rate and rectal temperature increased and stroke volume fell as

a linear function of increasing levels of dehydration. Rectal temperature rose 0.3°C for each 1% increase in the level of dehydration.

9. The level of dehydration correlated most accurately with the rise in rectal temperature, the standing heart rate, and the reduction in salivary flow. Salivary flow ceased at dehydration levels greater than 8%.
10. Sodium ingestion during exercise tended to increase the amount of fluid ingested and reduced the urine output.

These studies, which clearly established the value of fluid ingestion during exercise, made little immediate impact on the athletic community. The studies of Pugh et al. [138] and Wyndham and Strydom [169] finally drew attention to the need for fluid ingestion also by *athletes* during prolonged exercise.

Pugh et al. [138] showed that competitors drank only 400 ml during a marathon race (0.12 liters/hr) and developed a mean weight loss of 2.9 kg (5.9% of initial body weight). As fluid loss, sweat rate, and postrace rectal temperature were highest in the race winner, Pugh et al. [138] concluded that "a high tolerance to fluid loss" seemed to be an important requirement for success in distance running. But they did not propose any role for fluid ingestion during exercise.

In their study, Wyndham and Strydom [169] found that athletes who became dehydrated by more than 3% during a series of 32-km foot races had elevated postrace rectal temperatures. As also found by Adolph [5], there was a linear relationship between the athletes' levels of dehydration and their postrace rectal temperatures, at least for levels of dehydration greater than 3%. The authors concluded that: (*a*) the level of dehydration was the most important factor determining the rectal temperature during prolonged exercise so (*b*) the avoidance of dehydration would be the critical factor preventing heat injury during prolonged exercise [168, 169]. Interestingly, the authors did not speculate that dehydration might influence running performance. Their finding that the race winners had the highest rectal temperatures and were the most dehydrated [119], may have dissuaded them.

Although the basis for some of their conclusions has been challenged [119, 121, 125], there is no doubt that it was especially the study of Wyndham and Strydom [169] that stimulated the modern interest in the role of fluid replacement during exercise.

MODERN STUDIES OF FLUID LOSS AND FLUID INGESTION DURING EXERCISE

There are two experimental models that have been used to study the effects of fluid loss and fluid intake on the physiological responses during exercise.

As emphasized by Coyle et al. [35, 36], fluid loss (hypohydration) induced either by the administration of diuretics, or exposure to sauna, or fluid restriction *before* exercise, produces physiological effects that are more marked than those that result from the form of dehydration that develops voluntarily *during* exercise when the rate of fluid loss exceeds the rate of fluid ingestion. In particular, the reduction in plasma volume and in physical performance for a given level of dehydration is greater with hypohydration [22, 35, 107].

For this reason, the result of the hypohydration studies that are reviewed in detail elsewhere [147] are perhaps most relevant for activities in which subjects deliberately dehydrate themselves before exercise, usually to make a specific competitive weight. These studies will not be considered further in this review; we will focus principally on studies of exercise-induced dehydration.

Effect of Exercise-induced Dehydration on Physical Performance

At least six studies [5, 15, 49, 91, 136, 151] have evaluated the effects of progressive exercise-induced dehydration on physical performance. Most have compared the performance of a group of subjects, usually military personnel, who either ingested fluid or restrained from fluid ingestion during prolonged exercise of relatively low intensity (walking) in dry heat. The measure of physical performance was the number of subjects in each group able to complete the prescribed exercise task.

Although few of the studies were subject to rigorous statistical analysis, the trend in all was for fewer subjects to complete the exercise task when they did not ingest fluid. Furthermore, performance was least impaired in subjects who maintained fluid balance during exercise. Fluid ingestion reduced rectal temperatures and heart rates during exercise; this effect was greatest when the rate of fluid ingestion equalled the sweat rate. In general, sweat rates were not influenced by fluid ingestion and fell only when the fluid deficit exceeded 2.5 liters [91]. Fluid ingestion also prevented the development of postural hypotension on cessation of exercise [49].

Most researchers observed that fluid ingestion had more obvious effects on the psyche than on the soma. The description of Bean and Eichna [15] is typical for subjects who did not ingest fluid during exercise: "An important change which the chart does not show was the actual condition of the men, their low morale and lack of vigor, their glassy eyes, their apathetic, torpid appearance, their 'don't-give-a-damn-for-anything' attitude, their uncoordinated stumbling, shuffling gait. Some were incapable of sustained purposeful action and were not fit for work. All they wanted to do was rest and drink" (p. 155). Eichna et al. [49] reported that dehydrated subjects were "reduced to apathetic, listless, plodding men straining to finish the same task" that they completed "energetically and cheerfully" when fully hydrated. Similarly,

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Strydom et al [151] reported that the fluid restriction caused their subjects to become morose, aggressive, and disobedient toward their superiors.

Since 1966, there have been relatively few studies that have looked specifically at the effects of fluid ingestion *alone* on athletic performance. Rather, the evaluation of *carbohydrate* ingestion has been emphasized [30, 36, 74, 75]. These studies generally show that carbohydrate ingestion enhances performance [30, 36] and the assumption is that this is due only to a metabolic effect. However, the addition of glucose to the ingested solution increases fluid absorption [66, 67]; hence, a part of the beneficial effect of carbohydrate ingestion during exercise could theoretically be due to an influence of the added carbohydrate on fluid balance.

Four modern studies have compared the exercise performance of subjects when they either ingested or did not ingest fluid during exercise. Maughan et al. [101] found that ingestion of either water or concentrated carbohydrate solutions did not increase endurance time at 70% $\dot{V}O_{2max}$, which exhausted subjects in 70–75 minutes. Endurance was prolonged, however, in subjects who ingested a dilute carbohydrate/electrolyte solution.

In contrast, Barr et al. [14] showed that subjects who did not ingest fluid during prolonged exercise at 55% $\dot{V}O_{2max}$ terminated exercise approximately 90 min earlier than when they ingested fluid. Levels of dehydration at exhaustion were >6%. Montain and Coyle [108] also found that, when they did not ingest fluid, subjects were less likely to complete exercise in the heat at 65% $\dot{V}O_2max$.

Two studies have assessed the effects of fluid ingestion or infusion at higher exercise intensities. Deschamps et al. [43] reported that intravenous saline infusion did not enhance performance at 84% $\dot{V}O_{2max}$, which exhausted subjects in approximately 21 min. Walsh et al. [163], however, found that subjects were able to exercise significantly longer during a subsequent exercise bout at 90% $\dot{V}O_{2max}$ when they ingested fluid during a preceding 1-hr exercise bout at 70% $\dot{V}O_{2max}$ in the heat. This effect was not because of differences in any measured physiological variable including rectal temperature, and occurred despited a difference in fluid balance of only 1.1 kg between dehydrated and fluid-repleted subjects. Ratings of perceived exertion were significantly lower when fluid was ingested.

In summary, the balance of evidence indicates that the ingestion of water enhances performances during both very prolonged exercise of low intensity and during exercise of somewhat higher intensity but shorter duration. However, this effect may be somewhat less than that achieved when the fluid contains carbohydrate either alone [166] or with electrolytes [30, 101]. Possibly the most consistent finding is that fluid ingestion markedly reduces the perception of effort during exercise of

both low [5] and high-intensity exercise [163]. It is also probable that exercise performance during high-intensity exercise is impaired at levels of dehydration that do not influence performance at lower exercise intensities [5].

Physiological Effects of Progressive Dehydration During Prolonged Exercise

The physiological effects of exercise-induced dehydration have been studied by comparing the physiological responses of athletes when they replace either none, some, or all of their fluid lost during prolonged exercise. More recent studies have infused fluid intravenously during exercise to reverse any dehydration-induced fall in plasma volume. These latter studies have attempted to differentiate the physiological effects caused by reduction in plasma volume from those caused by dehydration-induced changes in serum osmolality.

PLASMA VOLUME. Plasma volume falls at the initiation of exercise. This fall is influenced by the type and intensity of exercise, and by the posture adopted [35].

Thereafter, a progressive exercise-related fall in plasma volume is reduced in proportion to the amount of fluid ingested during exercise [14, 24, 100, 107, 108]. The change is least when most fluid is ingested [108] and can be prevented if the rate of fluid ingestion equals the rate of fluid loss [73].

There is some evidence that the ingestion of sodium-containing solutions during exercise may prevent the fall in plasma volume more effectively than the ingestion of pure water [23]; as discussed subsequently, water ingestion tends to reduce serum osmolality.

SERUM OSMOLALITY AND SERUM ELECTROLYTE CONCENTRATIONS. Serum osmolality rises if no fluid is ingested during prolonged exercise [24, 100, 101]. This rise is reduced by fluid ingestion [24, 100] and is least when the rate of fluid ingestion approximates the rate of fluid loss [108].

Changes in serum sodium concentrations parallel changes in serum osmolality because the serum sodium concentration is the major determinant of the serum osmolality. Hence, serum sodium concentrations rise with exercise-induced dehydration but are maintained when fluid is ingested [117, 120]. Interestingly, serum sodium concentrations and serum osmolality fall *only* when water is ingested during exercise [14, 23, 116]. This is a fundamental observation that invites explanation. No studies have yet reported that serum sodium concentrations fall in the absence of fluid ingestion during exercise; this would be unlikely as sweat is a hypotonic solution [32].

The rise in serum osmolality and serum sodium concentration correlates with the rise in esophageal temperature [108] and may be the stimulus for the reduction in sweating that develops at the higher levels of dehydration [91]. This suggests that an important goal of fluid

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ingestion during exercise may be to prevent changes in serum osmolality or serum sodium concentrations, as originally proposed by David Dill [46].

SWEAT RATE DURING EXERCISE. Some studies have shown that the sweat rate falls with increasing levels of dehydration [53, 71, 91, 149] whereas others have failed to show this effect [14, 24, 65, 73, 107, 108]. An early study found that sweat rate falls only above a certain level of dehydration [91].

Hypohydration studies indicate that sweat rate over the trunk but not the head may be selectively reduced by prior dehydration [25]. There may also be considerable individual variability in the effects of dehydration on sweat rates during exercise [149]; perhaps this explains the variable results reported in the literature. Hyperhydration prior to exercise increases sweat rate during subsequent exercise [110].

RECTAL OR ESOPHAGEAL TEMPERATURES DURING EXERCISE. The exercise-related rise in rectal temperature is attenuated by fluid ingestion during exercise [5, 14, 24, 33, 53, 65, 71, 73, 107, 108]. The rise is reduced in proportion to the amount of fluid ingested and is least when the rate of fluid ingestion approximates the sweat rate [71, 108]. Hence there is a linear relationship between the rise in esophageal temperature and the level of dehydration [107, 108] as also reported in some of the original field studies [5, 169].

Fluid ingestion reduces the rectal temperature response only after a minimum of 60–80 min of exercise [14, 73, 107, 108, 149, 150]. No effect of fluid ingestion on rectal temperature was found in a study of shorter duration but higher intensity [163], possibly because exercise terminated before 80 min.

The magnitude of this effect of fluid ingestion on the rise of rectal temperature is relatively small [122] so its real physiological relevance may be questioned. Most studies indicate that levels of dehydration of up to 5% (equivalent to a weight loss of 2–4 kg) usually increase rectal temperature by less than 1°C [14, 65, 73, 107, 108, 121]. Hyperhydration before exercise also decreases rectal temperature during subsequent exercise [111].

HEART RATE AND STROKE VOLUME. Heart rate is increased [5, 24, 71, 100, 149] and stroke volume reduced in proportion to the fluid deficit that develops during exercise [108]. Cardiac output and stroke volume do not fall when the rate of fluid ingestion is sufficient to prevent dehydration [73]. But heart rate is elevated even when dehydration is prevented by adequate fluid ingestion during exercise [73]; hence, dehydration is not the sole cause of the progressive increase in heart rate during prolonged exercise. Heart rate is also reduced by hyperhydration before exercise [110].

SKIN BLOOD FLOW. Fluid ingestion maintains higher rates of forearm blood flow during exercise [107, 108] and of forearm and calf blood flow

at rest during prolonged heat exposure [82]. The reduction of forearm blood flow is proportional to the level of dehydration [108]. Hence, fluid ingestion during exercise may attenuate the development of hyperthermia by maintaining skin blood flow [107].

PERCEPTION OF EFFORT. The perception of effort during exercise is increased in proportion to the fluid deficit [108]. Even partial fluid replacement has a significant effect on the perception of effort during exercise of high intensity [163]. The major psychic effects of fluid restriction during prolonged exercise of low intensity and their rapid reversal with fluid ingestion, have been described.

HORMONAL CHANGES. Plasma concentrations or activities of the fluid and electrolyte-regulating hormones, specifically, atrial natriuretic peptide (ANP), antidiuretic hormone (ADH—also arginine vasopressin—AVP), aldosterone, and renin, increase during prolonged exercise [9, 17, 64, 162]. With the exception of ANP, these concentrations may remain elevated for up to 31 hr after exercise [9]. In general, ADH activities rise in response to increasing serum osmolality [159, 162], whereas plasma renin activity may follow changes in either plasma or extracellular fluid volumes.

There is also a paradoxical increase in the plasma activity of the diuretic and natriuretic hormone ANP during prolonged exercise when plasma volume is reduced [9, 162]. The diuretic effects of ANP are probably inhibited by the increased activity of the renin-angiotensin-aldosterone axis and the increased serum ADH concentrations [9, 161].

Fluid ingestion during exercise reduces the hormonal activities and concentrations during exercise; concentrations are further reduced when subjects hyperhydrate before exercise [17]. Of these, the rise in plasma ADH activity is most affected by either hyperhydration before or fluid ingestion during exercise; this effect may be relatively independent of the nature of the fluid ingested. In contrast, the increased activity of the renin-angiotensin-aldosterone axis is reduced more by the ingestion of sodium-containing solutions compared with pure water [17]. Thrasher et al. [159] reported essentially the same findings in dehydrated dogs; water ingestion reduced plasma ADH activity, whereas ingestion of an electrolyte solution with the same composition as the extracellular fluid volume reduced plasma renin activity.

As described, water ingestion, especially during exercise, causes serum osmolality either to remain the same or to fall; this would reduce ADH secretion. Why the ingestion of sodium-containing solutions specifically reduces plasma renin activity and aldosterone concentrations is not known. Possibly, the effect is because of the maintenance of higher plasma volumes when electrolyte-containing solutions are ingested [17, 23].

FLUID INGESTION AND RENAL FUNCTION. Renal function during prolonged exercise like marathon running is unaffected by levels of

dehydration less than 4% [86–88] and is enhanced during recovery in those who retain fluid during exercise [85]. The classic studies also found that renal function was not influenced by levels of dehydration less than 7% [4]. Anuria has been reported in one runner who drank inadequately and lost 11% of her body weight during an 88-km ultramarathon [88].

Renal fluid and electrolyte excretion may be influenced by the nature of the fluid ingested during exercise, but this has been infrequently studied during exercise [14] or even at rest [20]. The renal response to the ingestion, during exercise, of fluids with different electrolyte contents will be influenced by a number of factors including the relative amount of sodium and water lost in sweat, the extent of the sodium movement from the interstitial space into the intestinal lumen [66, 67] and the relative rates of sodium and fluid absorption from the ingested solution. As yet, there are no studies that have addressed these issues, either singly or collectively.

GASTRIC EMPTYING AND INTESTINAL ABSORPTION. Dehydration impairs gastric emptying [113] and could theoretically limit fluid replacement during prolonged exercise. In contrast, intestinal absorption may increase when blood volume falls [148].

But gastric emptying should not limit fluid replacement during exercise as high rates of gastric emptying can always be achieved with the appropriate drinking patterns [127]. It is more probable that fluid absorption by the small bowel could limit fluid replacement especially when only plain water is ingested at high rates during prolonged exercise (see later).

INFLUENCE OF EXERCISE-RELATED FALL IN PLASMA VOLUME ON PHYSIOLOGICAL RESPONSES DURING EXERCISE. An important question is whether changes in serum osmolality or in plasma volume regulate the physiological responses to exercise-induced dehydration. The infusion of isotonic fluids that maintain plasma volume without altering serum osmolality can differentiate between these possibilities [62].

BODY TEMPERATURE, SKIN BLOOD FLOW AND SWEAT RATE. Fortney et al. [62] showed that the infusion of an isotonic saline solution reduced both the core temperature *and* total sweat output during exercise. The authors concluded that the maintenance of plasma volume increased skin blood flow thereby increasing convective heat losses. Hence, evaporative heat losses were reduced. In contrast, increased serum osmolality raises the temperature threshold at which skin blood flow increased and delayed the onset of sweating, thereby favoring heat retention [62, 63].

Montain and Coyle [107] infused a 6% dextran solution to increase plasma volume above the level maintained by fluid ingestion during exercise. Serum sodium concentrations and serum osmolality increased when subjects did not ingest fluid during exercise but were maintained at pre-exercise concentrations by saline infusion. Unlike the findings of

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Fortney et al. [63], plasma volume expansion alone did not influence either the esophageal or rectal temperature response to exercise, or forearm skin blood flow. Nor did fluid infusion prevent the rise in the rating of perceived exertion as effectively as did fluid ingestion.

Thus, maintaining or increasing plasma volume by fluid ingestion does not explain the temperature-lowering effect of fluid ingestion during exercise. Rather, fluid ingestion may influence thermoregulation by preventing the rise in serum osmolality or serum sodium concentrations [107] with maintenance of forearm blood flow [128]. These findings support Dill's [46] proposal that the goal of fluid ingestion during exercise should be the maintenance of serum osmolality and serum sodium concentrations.

Cardiovascular Drift

Compared with the findings when no fluid was ingested, cardiac output and stroke volume were higher with intravenous infusion; but this effect was less than that achieved by full fluid replacement [107].

The authors concluded that the cardiovascular drift shown by an increase in heart rate and a fall in stroke volume and cardiac output during prolonged exercise is not solely caused by the fall in plasma volume. Thus, the beneficial physiological effects of fluid ingestion during exercise cannot be due solely to the maintenance of plasma volume and central cardiovascular function.

Hamilton et al. [73] have also shown that ingesting fluid at rates that prevent dehydration maintains cardiac output and stroke volume during prolonged exercise. Other components of cardiovascular drift, in particular the rise in heart rate and in oxygen consumption, were prevented only by the addition of a glucose infusion. They have proposed that especially the rise in oxygen consumption during prolonged exercise results from a catecholamine-mediated stimulation of metabolism that is prevented by glucose infusion.

OPTIMUM RATES OF FLUID INTAKE DURING EXERCISE

The evidence so far presented suggests that the principal aim of fluid ingestion during exercise is to prevent any rise in serum osmolality or serum sodium concentrations. A secondary goal is also to prevent any change in plasma volume. Few studies have considered the interacting influences of the rates of fluid loss and fluid ingestion, and the composition of the ingested solution on changes in these variables during exercise. Rather, it has been assumed that the optimum rate of fluid ingestion is always that which equals the rate of fluid loss. It is clear, however, that most subjects do not voluntarily replace all the fluid lost during exercise [5]. Therefore, it is appropriate first to discuss the

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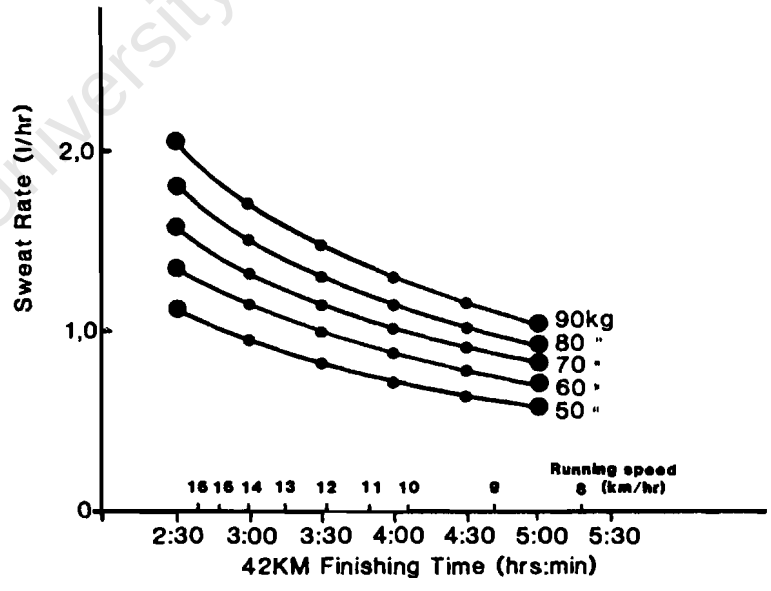
factors that influence the rates of fluid loss and fluid ingestion during exercise as this may identify those exercising conditions when the development of voluntary dehydration is more likely. The possible effects of the nature of the ingested fluid on changes in serum osmolality and plasma volume under these conditions will also be briefly considered.

Rates of Fluid Loss During Exercise

The rate of sweat loss, which is the principal determinant of fluid loss from the body during exercise, is determined mainly by the metabolic rate [32, 39, 40, 69, 70, 125, 171]. At least in running, the metabolic rate is determined by the body mass and the running speed; in nonweight-bearing activities like cycling, the velocity of movement becomes the principal determinant of the metabolic rate. Barr and Costill [13] have predicted sweat rates for subjects of different masses running at different speeds. Figure 10.1, drawn from their data, shows the interaction of body mass and running speed on sweat rate and predicts, for example, that heavier athletes running quite slowly can have sweat rates equal to those of smaller runners running much faster.

FIGURE 10.1

Predicted sweat rates of athletes of different masses running at different speeds. Drawn from the data of Barr, S.I., and D.L. Costill. Water: can the endurance athlete get too much of a good thing? J. Am. Diet. Assoc. *89:1629–1632, 1989.*



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The prediction of this figure is that sweat rates will seldom be greater than 1.2 liters/hr in runners weighing less than 70 kg. Such high sweat rates are probable only in runners weighing 80 kg or more running faster than 12 km/hr. Heavier runners probably achieve these racing speeds only infrequently, at least for prolonged periods, for example, in marathon races.

The finding that sweat rates measured in runners during longer distance races are seldom greater than 1.2 liters/hr (for review, see [125]) confirms the general accuracy of these predictions. Higher sweat rates are usually recorded only when the environmental conditions are more severe (dry bulb temperature > 25°C) or when the activity is held indoors without the benefit of adequate convective cooling. For example, compared with sweat rates measured at the same metabolic rate in wind-still conditions indoors, sweat rates of cyclists are reduced by up to 38% during outdoor exercise [20].

Therefore, it seems probable that the reports of much higher sweat rates measured in the laboratory [10, 105] could possibly be explained, in part, by the absence of adequate convective cooling during exercise indoors.

Rates of Fluid Ingestion During Exercise

Table 10.1 lists the reported rates of fluid intake in both competitive and experimental studies both outdoors and in the laboratory, in runners, cyclists, and triathletes competing over a wide range of distances. Table 10.2 lists the absolute and relative exercise-induced weight changes in subjects competing in the same or similar events.

Table 10.1 shows that the rates of fluid intake during exercise vary considerably but are seldom more than about 500 ml/hr except in subjects cycling in the laboratory when forced to ingest fluid at higher rates. One conclusion might be that subjects voluntarily choose to drink about 500 ml/hr during exercise with little likelihood that rates > 1 liter/hr will be achieved except under laboratory conditions.

Because these rates of fluid ingestion are less than sweat rates, voluntary dehydration develops (Table 10.2), at least during those activities lasting less than about 6 hr. In longer events, especially those lasting many days, there is a tendency for body weight to increase during exercise.

A striking feature of Table 10.2, not previously noted, is the remarkable constancy of the weight loss (2–3 kg) experienced by athletes during prolonged exercise. This appears to be relatively independent of either the type or duration of the activity. It is as if total weight loss during exercise is a regulated variable.

Athletes develop symptoms of discomfort when they attempt to drink at rates equal to the higher sweat rates. Thus, both runners [33] and cyclists [106] develop symptoms of "fullness" when ingesting fluid at

TABLE 10.1
Reported Levels of Dehydration Developing in Athletes Competing in Running, Triathlon, and Cycling Races of Different Distances

Race Distance (km)	*% Wt Loss*	*Kg Loss/Gain**	*Reference*
Running			
32	3.8	2.4	169
42	4.3	2.9	29
42	2.4	1.8	87
42	3.7	2.6	97
42	4.3	2.8	98
42	2.9	2.1	99
42	1.6–3.1	1.1–2.3	121
42	2.0	2.5	125
42	5.2	2.9	138
42	3.4 (male)†	2.5 (male)	140
	2.6 (female)	1.5 (female)	140
42	2.1	2.9	165
56	2.7	2.0	86
56	2.6–3.1	1.9–2.0	121
67	3.3 (male)†	2.4 (male)	139
	2.3 (female)	1.0 (female)	139
80	+0.3	+0.2	145
90	5.1	3.5	37
90	3.5	2.7	90
100–160	0.6	0.5	114
24-hr race (132–188 km)	3.6	2.3	61
24-hr race (121–242 km)	3.2	2.1	60
24-hr race (160–199 km)	3.6	2.7	123
960 km (5 days)	0.8	0.5	143
Triathlon			
52	4.0	2.9	105
52	1.7	1.2	134
110	3.3	2.3	158
113	2.8	2.1	134
160	4.5	3.2	160
174	3.2	2.2	61
226	4.1 (male)†	3.2 (male)	58
	2.4 (female)	1.4	58
226	3.6‡	2.8	59
226	3.7	2.8	134
Cycling race			
4800 km	+3.5	+2.8	96

*Weight gain during exercise.
†Note that weight loss is greater among males than females.
‡Most of weight loss in the triathlon occurred in the run section (1.6 kg vs. 0.7 kg in cycle section) despite the shorter duration of the run (04:34 vs. 06:08).

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TABLE 10.2
Reported Rates of Fluid Intake of Athletes Competing in Running, Triathlon, and Cycling Races of Different Distances

Distance/Intensity/Duration (km) (% $\dot{V}O_2max$) (hr:min)*	*Mean Rate of Fluid Intake (liters/hr)*	*Reference*
Running		
25	0.05	140
32	0.15	169
42	0.40	29
42	0.41	97
42	0.19	98
42	0.38	99
42	0.45–0.49	121
42	0.48–0.59	121
42	0.60	125
42	0.12	138
42	0.15	140
56	0.49–0.62	121
56	0.40–0.46	121
67	0.40 (male)	139
	0.31 (female)	139
80	0.50	145
90	0.48	37
960	0.83	143
Running (Laboratory)		
70% $\dot{V}O_2max$ × 02:00	0.08–0.12	16
70% $\dot{V}O_2max$ × 04:00	0.21	41
71% $\dot{V}O_2max$ × 02:00	0.88	33
75% $\dot{V}O_2max$ × 02:00	0.60	65
76% $\dot{V}O_2max$ × 30 km	0.48	166
Triathlon		
52	0.6	105
Cycling (Competition)		
8 800 km	0.62	96
55% $\dot{V}O_2max$ × 06:00	1.2	14
60% $\dot{V}O_2max$ × 03:00	0.9	26
60% $\dot{V}O_2max$ × 03:00	1.1	144
70% $\dot{V}O_2max$ × 02:00	0.8–1.6	106
Rest		
00:40	1.5	48

*$\dot{V}O_2max$ = maximum oxygen consumption.

rates equal to or greater than 800 ml/hr. Runners were unable to sustain these high rates even for 2 hr [33] whereas cyclists reported increasing levels of discomfort when ingestion rates were greater than 800 ml/hr [106]. One-half of the cyclists ingesting 1200 ml/hr and all subjects ingesting 1600 ml/hr were "visibly uncomfortable." Interestingly, 25% of subjects developed diarrhea when ingesting 1.6 liters/hr [106] indicating

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that this rate of fluid ingestion exceeded the combined maximum rate of fluid absorption of both the small and large bowels.

Brouns et al. [18] showed that the rate of fluid ingestion of subjects encouraged to drink as much as possible during a simulated triathlon, was two to three times higher in the cycling leg (600–800 ml/hr) than in the running leg (100–300 ml/hr). This suggests that running reduces the desire to drink more than does cycling [19].

Hence, peak rates of fluid ingestion under ideal conditions are seldom greater than 800 ml/hr. Feelings of abdominal fullness seem to prevent higher rates of ingestion, especially during running.

Whereas this upper limit of voluntary fluid ingestion during exercise may be set by progressive gastric distension due to impaired gastric emptying [106], another possibility is that fluid ingested at such high rates may also accumulate at other sites, including the colon. The assumption that the small bowel has an unlimited capacity for both fluid and energy assimilation is currently under review [45]. Indeed, Buddington and Diamond [21] have suggested: ". . . the intestine never possesses an enormous excess absorptive capacity. Instead, just enough intestine and transporters are synthesized to absorb the expected nutrient loads so that biosynthetic energy is not wasted on unneeded tissue and molecules but ingested nutrients are not wasted either. The intestine exemplifies the motto, 'enough but not too much.' "

Their suggestion is that the maximum absorptive capacity of the small bowel at least for glucose is approximately twice the usual carbohydrate intake. If this holds also for fluid absorption, and if the usual fluid intake in humans is 180–200 ml/hr [56], then the maximum rates of small bowel fluid absorption might be approximately only 360–400 ml/hr. Interestingly, this value approximates the voluntary rates of fluid ingestion of most subjects during exercise (Table 10.2), but is well below both their average sweat rates [121] and the maximum rates of fluid ingestion of some athletes who develop fluid retention during prolonged exercise [85].

At present, the maximum rates of small bowel fluid and glucose absorption either at rest or during exercise are not known. There is sufficient information however, to suggest that these rates may be sufficiently low to limit optimum fluid and carbohydrate replacement during exercise.

Thus, a number of studies [74, 75, 109, 139, 141] have shown that less than about 40% of the carbohydrate ingested during exercise is oxidized by the muscles, possibly because intestinal glucose absorption is limiting. Peak rates of exogenous glucose oxidation by muscle are approximately 1 g/min regardless of the type of carbohydrate ingested [75]. This rate is equal to that given historically as the maximum rate of glucose absorption from the small bowel [1, 72]. As glucose absorption stimulates water absorption [65, 66], such low rates of glucose absorption might indicate that water absorption also occurs relatively slowly. Indeed,

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Gisolfi et al. [66] have also calculated that only 37% of fluid infused into the duodenum and jejunum at rates of 900 ml/hr was absorbed; others have reported that the maximum rate of water absorption from an isotonic solution with a sodium concentration of 110 mmol/liter was only 800 ml/hr [42].

Similarly, studies in which fluid replacement either during [14] or after exercise [34] equalled fluid losses found that not all the ingested fluid could be accounted for by its appearance in the extracellular or intracellular fluid pools, suggesting that not all was rapidly absorbed [116]. Indeed, Costill and Sparks [34] suggested that: "a large fraction of the ingested water remained in the gastrointestinal tract or was shifted to the extravascular compartment."

In summary, the maximum rates of fluid absorption by the small bowel during exercise are not known but could be less than either the highest rates of fluid loss incurred by some athletes during more intensive exercise, or the highest rates of fluid ingestion of some less competitive runners especially during prolonged exercise [85]. Any unabsorbed fluid would accumulate in the large bowel where its presence might: (*a*) explain the symptoms of fullness experienced by some athletes ingesting large fluid volumes during prolonged exercise, and (*b*) lead to a potential "third space" effect that could be a factor in the etiology of the hyponatremia of exercise (see later).

Clearly, unless the maximum rates of fluid absorption by the small bowel are known, it is difficult to prescribe how much fluid should be ingested during exercise [116]. But, if intestinal absorptive capacity is regulated by demand and can increase when demand increases chronically [45], it follows that the chronic ingestion of large volumes of fluid either during or after exercise might increase intestinal absorptive capacity.

Influence of Changes in Serum Osmolality, Plasma Volume, and Other Factors on Drinking Behavior in Humans

In contrast to dogs [4, 159], the donkey (burro) [46], the monkey [11], and the Bedouin goat [27], only humans develop voluntary dehydration when given free access to fluid either during or after exercise in the heat; other mammals immediately replace all their fluid losses as soon as water is provided. The volume ingested by the dog appears to be regulated by receptors in the oropharynx [6, 159]. Drinking rapidly inhibits ADH release, probably in response to an orophanryngeal reflex [11].

Dill [46] proposed that humans develop voluntary dehydration during exercise because only they lose sodium chloride in sweat. As a result, serum osmolality rises less during exercise-induced dehydration in humans. But, as all mammals seemed to drink sufficiently to maintain a constant serum osmolality, Dill [46] postulated that the fluid intake of humans would always be inadequate to replace their sweat losses.

Nose et al. [130] have shown that the drinking behavior of dehydrated humans is regulated by changes in both serum osmolality and plasma volume. Hence, dipsogenic drive in dehydrated humans ceases when either osmolality *or* plasma volume is corrected by the ingestion of either plain water or a sodium-containing solution, respectively. Thus, the ingestion of plain water prematurely inhibits drinking by causing serum osmolality to return to isotonicity before either fluid or sodium losses are replaced; sodium chloride ingestion also terminates drinking prematurely by restoring plasma volume prematurely. But changes in osmolality and plasma volume during exercise-induced dehydration in humans are not independent of each other; the rising serum osmolality with dehydration acts to maintain plasma volume and to reduce the volume-dependent drive for fluid replacement [130]. The result is that whether or not they ingest plain water or sodium chloride solutions, dehydrated humans stop drinking before they are fully rehydrated.

In addition, water ingestion increases free water loss [130] whereas selective restoration of plasma volume with sodium-containing solutions inhibits secretion of sodium-retaining hormones [131], increasing osmotic diuresis.

Perhaps it is these complex interactions that also explain why humans are unable to prevent the development of voluntary dehydration during exercise. Others suggest that it is the rapid alleviation of the symptoms that initiate drinking including, among others, dryness of the mouth, which causes the premature cessation of drinking before full rehydration has occurred [84, 146]. Indeed, subjects can be classified as either "reluctant" or "avid" drinkers [153, 154] on the basis of the volume of fluid they ingest during exercise. Fluid ingestion during exercise is enhanced by drinking cold, sweet fluids [56, 84, 146]. Simultaneous food consumption also increases fluid consumption [5, 84].

There is a need to establish factors that will enhance fluid ingestion during exercise, thereby limiting the extent to which voluntary dehydration develops.

Role of Sodium Chloride Ingestion

The predictions of Adolph and Dill [7] that the fluid deficit that develops during exercise is corrected only when the sodium chloride deficit has been corrected so that "water cannot be held until the missing osmoles are made good" [92] has been confirmed by the detailed studies of Nose and colleagues [112, 129–131, 133]. The essential conclusion from these studies is that the sodium content of the extracellular space must regulate the extracellular fluid volume [112, 129]. As a result, the extracellular fluid volume must contract whenever a sodium deficiency develops. This explains why serum sodium concentrations remain constant (or increase slightly) during prolonged exercise when both

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sodium and water are lost, even if plain water in limited amounts is replaced [120].

There are two exceptions to this general rule that the extracellular fluid volume is regulated by its sodium chloride content so that serum sodium concentration will remain within a narrow range regardless of the degree of fluid or sodium deficit. The first is the condition of true sodium chloride deficiency [102–104]; the other is the hyponatremia of exercise [120]. These are discussed in subsequent sections. In both conditions, the volume of the extracellular space is increased out of proportion to its sodium chloride content.

Nose et al. [129] also found that, at any level of dehydration, the less sodium chloride lost in sweat, the greater the loss of fluid from the intracellular compartment. Thus, a reduction of sweat sodium losses with protection of the circulating volume is an important benefit of heat acclimatization and training.

It follows that an important benefit of ingesting sodium chloride during or after exercise might be better maintenance and more rapid restoration of the extracellular volume and possibly also the plasma volume [17, 23, 34, 116] although this is not always found [100, 137]. This effect would be enhanced by the addition of carbohydrate, which further increases the rate of fluid absorption from the solution ingested during exercise [67].

Figure 10.2 shows the rates of water, sodium, and carbohydrate absorption from different solutions ingested at rest. It shows that optimum fluid absorption occurs from isotonic carbohydrate/electrolyte solutions, whereas rates of absorption from water and electrolyte-containing solutions are not greatly different. Sodium absorption, however, is enhanced from electrolyte-containing solutions. This latter finding would explain why sodium-containing solutions are more likely to maintain plasma volume whereas the ingestion of water is more likely to influence plasma osmolality.

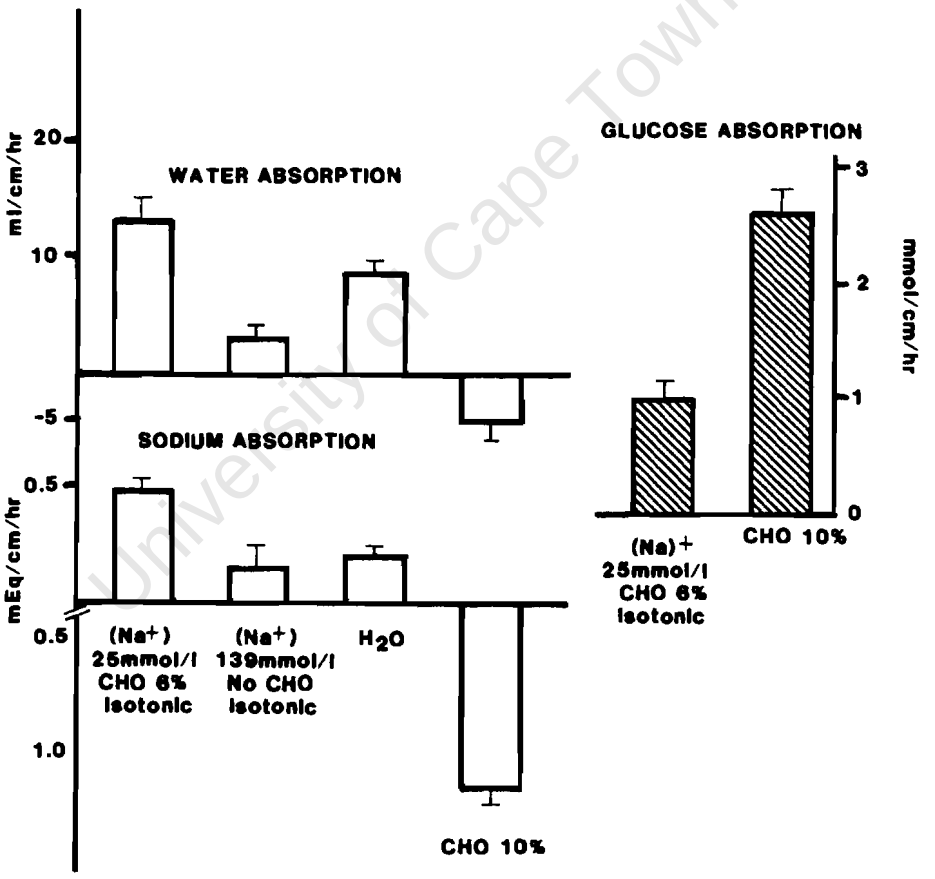
On the other hand, carbohydrate absorption is most rapid from concentrated (10%) carbohydrate solutions. But these solutions induce net water movement into the small bowel and could, therefore, be a factor contributing to the hyponatremia of exercise (see later).

APPLIED MEDICAL ASPECTS

"Salt-Deficiency" vs. "Water-Deficiency" Heat Exhaustion

An original classification of the heat illnesses distinguishes "salt-deficiency heat exhaustion" from "water-deficiency heat exhaustion" [28]. This distinction has persisted in the literature [83, 94]. Salt-deficiency heat exhaustion is considered to develop when fluid replace-

FIGURE 10.2
Rates of water, sodium, and carbohydrate absorption (secretion) from different solutions infused into the small bowel. Note that sodium and water absorption are greatest from the isotonic solution with modest sodium (25 mmol/liter) and carbohydrate (6%) content whereas carbohydrate absorption is greatest from the high (10%) carbohydrate solution; this solution causes net water secretion into the small bowel. Redrawn from data of Gisolfi, C.V., K.J. Spranger, R.W. Summers, H.P. Schedl, and T.L. Bleiler. Effects of cycle exercise on intestinal absorption in humans. J. Appl. Physiol. *71:2518–2527, 1991; and Gisolfi, C.V., R.W. Summers, H.P. Schedl, T.L. Bleiler, and R.A. Oppliger. Human intestinal water absorption: direct vs. indirect measurements.* Am. J. Physiol. *258:G216–G222, 1990.*



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ment is adequate but replacement of salt is inadequate; water-deficiency heat exhaustion is believed to result from the converse. But if body sodium content regulates the extracellular fluid volume [112, 129–131], it is difficult to understand how there could be these distinct conditions. Nor do the accepted descriptions of the two conditions provide robust guidelines for their differentiation on either clinical or biochemical ground [83, 94].

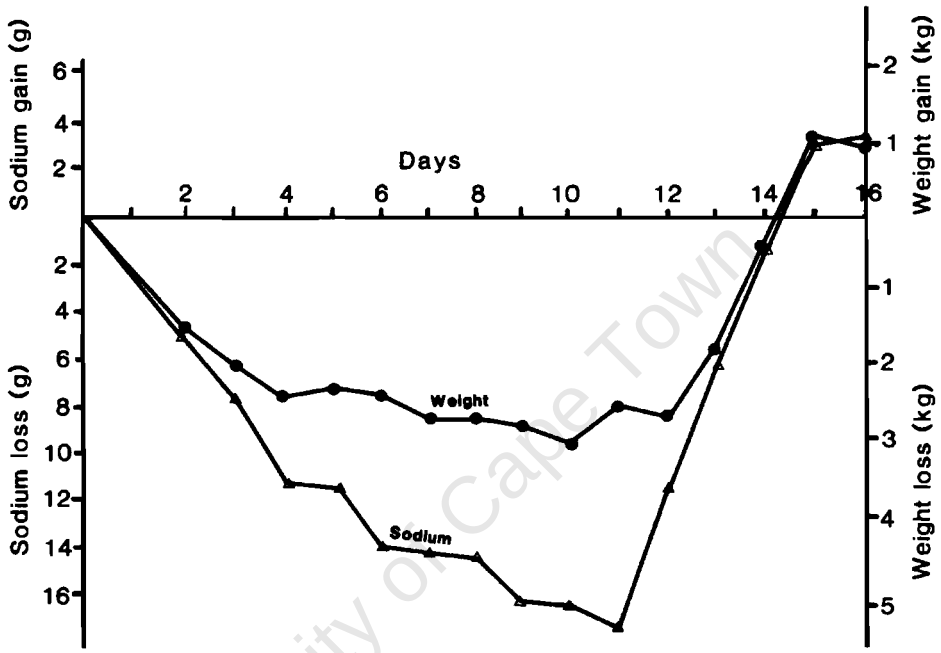
The original distinction was made on the basis of an experimental model developed to induce salt deficiency in animals. In this model [38, 54, 81, 111], true sodium chloride deficiency was induced by injecting a 5% glucose solution into the peritoneal cavity of experimental animals; the solution that was withdrawn 4–5 hr later had a high sodium chloride content but a low protein content. The characteristics of this salt-deficiency syndrome were the following: hypotonic hyponatremia; a large fluid shift from the extracellular to the intracellular fluid compartments causing intracellular overhydration; and extracellular dehydration with a disproportionate reduction in plasma volume. The fall in plasma volume was greater than that developing in pure water loss and was associated with a large reduction in the total circulating protein content. Circulatory changes were more severe in salt-deficiency than in water-deficiency dehydration; animals with salt depletion were incapacitated whereas animals with pure water deficiency remained "vigorous and healthy" with no evidence of peripheral vascular collapse.

Elkinton et al. [54] concluded that the greater loss of circulating plasma protein content probably explained the larger fall in plasma volume and the more severe circulatory collapse with salt depletion than with water depletion. They concluded that "whenever there is any salt loss to the external environment or temporary segregation of salt *by pooling in the gut* (author's emphasis), peritoneum, or in the traumatized region, shock will be produced with greater ease than would otherwise be the case." It is understandable why these original researchers considered that subjects with more severe heat injury must be suffering from salt-deficiency heat exhaustion whereas those with less severe circulatory abnormalities had water deficiency alone.

It is extremely difficult, however, perhaps impossible, for healthy humans to develop salt deficiency regardless of the environment in which they live and the amount of exercise they perform [47, 56, 170]. Indeed, their inability to discover a single case of salt deficiency either in the literature or in their personal experience of 20 yr work in environmental physiology led Epstein and Sohar [56] to suggest that the mythical condition of "salt deficiency heat exhaustion" is another example of "christening by conjecture." "Such a syndrome" they conclude "has never been proven to exist."

Rather, sodium chloride deficiency has only ever been induced in healthy humans by combining a salt-free diet with daily exercise or sauna

FIGURE 10.3
Changes in body weight and body sodium content of subjects eating a sodium-free diet for 11 days (days 1–11) and during 5 days (days 11–16) of sodium repletion. Note that the rate of sodium loss is greater than the rate of weight loss between days 2 and 11. Hyponatremia developed during this period. Redrawn from McCance, R.A. The changes in plasma and cells during experimentally human salt deficiency. Biochemistry *31:1278–1284, 1937.*



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exposure to increase sodium chloride losses [102–104]. A cardinal feature of the syndrome was severe physical incapacitation that prevented any desire or attempt to exercise.

Figure 10.3 from McCance [102] depicts mean water and sodium balance in subjects from one of their studies. It shows that for the first 2 and the last 4 days of the experiment, water balance follows sodium balance, but from days 3–12, relative water conservation occurred despite a continuing sodium deficit. Hyponatremia developed during this period and became progressively more severe despite a contraction of the extracellular fluid volume by up to 38% [104].

These findings can be explained if the initial response to human salt deficiency is a contraction of the extracellular fluid volume with maintenance of a normal or elevated serum sodium concentration (days 0–2 on Fig. 10.2); thereafter there is relative conservation of the extracellular fluid volume despite increasing sodium deficit. During this

period, hyponatremia develops. McCance [102] concluded: ". . . the human body comprised between (*a*) maintenance of its total osmotic pressure at the expense of anhydraemia, a reduction of blood volume, rise of haemoglobin, proteins and colloidal osmotic pressure in the serum, and (*b*) maintenance of its plasma and extracellular fluid volumes at the expense of a reduction in the concentrations of sodium and chloride in the serum, with a fall in its total osmotic pressure." The important point is that because the extracellular sodium content determines the extracellular fluid volume in health [112, 129, 130], any fall in serum sodium concentration can occur *only* if this interdependent relationship is lost so that the normal regulation of the extracellular fluid volume is disturbed.

The particular relevance of these studies is that they add important insights into the condition of the hyponatremia of exercise. This condition, which is reviewed in detail elsewhere [120], occurs typically in persons involved in very prolonged exercise during which they ingest large volumes of fluid, frequently containing 5–10% carbohydrate. Although it has been argued that large sodium chloride losses in sweat contribute to the pathogenesis of this condition [76–79], studies of runners with this condition have established that abnormal fluid retention, and not sodium deficiency, is the sine qua non for the development of the serious symptomatic form of this condition [85].

One proposal is that a third space effect similar to that produced in the experimental model of salt deficiency, may be operative. A large (± 2 liters) volume of unabsorbed fluid in the gut could, particularly if it has a high carbohydrate content, induce a sufficiently large sodium movement from the extracellular space into the unabsorbed fluid [66, 67, 139] to produce the changes found in experimental sodium chloride deficiency with hypotonic hyponatremia, intracellular overhydration, and a fall in plasma volume and in circulating protein content [120]. It is possible that sustained high rates of fluid intake (> 1 liter/hr), achieved uniquely only by some athletes during prolonged exercise [85] could exceed the fluid-absorbing capacity of the small bowel leading to this third space effect in the large bowel.

In summary, the hyponatremia of exercise appears to be due to the combination of at least three abnormalities: abnormal fluid retention, possibly on the basis of inappropriate ADH secretion; disturbed regulation of the extracellular fluid volume so that the normal relationship between its volume and sodium chloride content is lost, and possibly a third space effect with movement of sodium into unabsorbed fluid in the large bowel.

The sequence in which these abnormalities develops is not known. But the similarities between the hyponatremia of exercise and the experimental model of salt deficiency cannot be ignored [120]. This suggests that a third space effect may be crucial for the development of this condition.

Exercise-associated Collapse

After it had been found that rectal temperature rose as an apparently linear function of dehydration in marathon runners [169], it took only a small leap of faith to conclude that athletes who collapse after prolonged exercise must be suffering from a heat disorder caused by dehydration. As a result, it became fashionable to treat all athletes who collapsed during or after prolonged exercise with intravenous fluids [3, 51, 76–79, 93, 95, 132, 167].

But recent studies have shown that runners with this condition of exercise-associated collapse (EAC) [142] are not more likely to be hyperthermic than are control runners who do not collapse; indeed, a significant proportion may be hypothermic (Holtzhausen L.M., and Noakes, T.D. Unpublished observations). Nor is there any evidence that subjects with EAC are more dehydrated than are noncollapsed controls [118, 122]. In addition, intravenous fluid therapy retards rather than expedites the recovery of these subjects [55]; this form of therapy may also induce iatrogenic hyponatremia and hyperglycemia [122] and can be life-threatening in those with symptomatic hyponatremia due to fluid overload [85, 126].

On the basis of the evidence that: (*a*) the majority (> 85%) of subjects with EAC collapse after the cessation of exercise (Holtzhausen, L.M., and Noakes, T.D. Unpublished observations), and (*b*) that postural hypotension, often severe, is present in virtually all runners who complete ultramarathon races [80], we have proposed that postural hypotension probably caused by fluid displacement to the compliant veins of the lower limb, is the most likely cause of EAC [80, 118, 119]. This is not a novel proposal. For nearly 70 years it has been known that postural hypotension occurs frequently during exercise in the heat and is the principal abnormality in the condition incorrectly termed "heat exhaustion" [8, 49, 50, 155].

As the degree of postexercise postural hypotension is unrelated to the level of dehydration developed during exercise [80], it follows that intravenous fluid therapy is not the most rational form of therapy for EAC. Rather, therapy should aim to expedite return of blood from the peripheral pools in the lower limbs [19, 118]. This can be achieved by elevating the pelvis and legs; a form of therapy that has proven effective [68]. Failure to respond to this form of therapy may indicate the presence of dehydration.

Two additional points require emphasis. First, the most severe levels of exercise-induced dehydration yet reported [5] did not cause sudden collapse with circulatory failure, at least in the recumbent position. Rather, severely dehydrated subjects chose to lie down, possibly because they developed postural hypotension on standing. Hence, the development of postural hypotension could perhaps be the safety mechanism

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that prevents dehydrated subjects from continuing to exercise to levels of dehydration that would induce irreversible circulatory failure.

Second, Adolph [5] observed that blood biochemical markers were poor indicators of the level of dehydration, as also recently confirmed by us [80]. Adolph therefore proposed that the level of dehydration should be determined by conventional clinical parameters. In particular, intense thirst, a change in the timber of the voice, a dry mouth, and an inability to produce sputum indicated more severe dehydration.

In our experience, these are extremely uncommon findings in subjects whether or not they collapse after prolonged exercise. This observation is compatible with the finding that more severe levels of dehydration occur uncommonly in endurance athletes (Table 10.1).

SUMMARY

Current evidence indicates that adequate fluid ingestion during exercise enhances athletic performance, prevents a fall in plasma volume, stroke volume, cardiac output and skin blood flow, maintains serum sodium concentrations and serum osmolality, lowers rectal temperature and the perception of effort, and prevents a progressive rise in heart rate. Rates of sweating and urine flow are not influenced by fluid ingestion. The evidence suggests that the maintenance of serum osmolality and serum sodium concentrations at pre-exercise levels is the important determinant of these beneficial effects of fluid ingestion on cardiovascular function and thermoregulation. The provision of glucose in the ingested solution may be necessary to optimize performance; glucose ingestion that enhances fluid and sodium absorption in the small bowel may also prevent a progressive rise in oxygen consumption during exercise. Sweetened carbohydrate-containing drinks may also increase fluid intake during exercise, thereby minimizing voluntary dehydration.

Hence, the optimum solution for ingestion during exercise should provide carbohydrate, probably at rates of about 1 g/min and electrolytes in concentrations that, when drunk at the optimum rate, maintain serum osmolality and plasma volume at pre-exercise levels by replacing exactly the water and electrolyte losses from the extracellular space. At present, the composition of the fluid that will optimize electrolyte and fluid replacement of the extracellular space is not established. Neither are the optimum rates of fluid ingestion during exercise known. At low sweat rates (< 1 liter/hr), it is probable that all of the lost fluid can and should be replaced; rates of fluid ingestion needed to offset higher sweat rates may exceed the maximum intestinal absorptive capacity for water. Furthermore, high rates of fluid intake (> 1 liter/hr) are achieved with difficulty during exercise, especially when running, and are likely

to lead to feelings of abdominal discomfort, possibly due to the accumulation of unabsorbed fluid in the small bowel or colon. Practicing to drink regularly during training might reduce the severity and frequency of these symptoms, possibly by increasing intestinal absorptive capacity.

Most athletes are "reluctant" drinkers during exercise and do not ingest fluid at rates equal to their rates of fluid loss; hence, they develop progressive (voluntary) dehydration during prolonged exercise. Surprisingly, the level of voluntary dehydration that develops during exercise is relatively independent of the duration or intensity of the activity. The factors that explain these phenomena remain elusive. Fluid consumption during exercise is enhanced by the ingestion of cold, sweet fluids. Simultaneous food consumption also stimulates fluid ingestion.

Despite the modest sodium losses in sweat, the serum sodium concentration remains relatively unchanged during exercise. This results from a regulated contraction of the extracellular volume, which develops in proportion to the sodium deficit. As its sodium content regulates the volume of the extracellular space, correction of any fluid loss incurred during exercise requires that electrolyte losses, especially sodium, also be corrected.

Failure of adequate contraction of the extracellular volume in response to sweat sodium losses is characteristic of the hyponatremia of exercise in which there is also abnormal fluid retention in subjects who sustain very high rates of fluid intake (> 1.3 liters/hr) for prolonged periods (> 6 hr). These subjects exhibit the extreme of "avid" drinking behavior during exercise.

It is frequently assumed that severe dehydration is the critical factor explaining the development of both exercise-induced heatstroke and the apparently related condition of EAC. Yet there is no evidence that dehydration plays an essential role in either condition. EAC, in particular, is not a heat disorder and appears to be caused by the rapid onset of postural hypotension with the cessation of exercise. Elevation of the lower limbs, rather than intravenous fluid therapy, is the initial treatment of choice.

Future research needs to establish (*a*) techniques that will increase the fluid intakes of "reluctant" drinkers during exercise so that the extent of the voluntary dehydration can be reduced or prevented; and (*b*) the nature of the ingested solution that will optimize maintenance of serum osmolality and plasma volume during exercise under different exercise conditions and in different individuals whose sweat sodium and water losses, and rates of intestinal absorption of electrolytes and water may differ substantially as a result of individual variability and levels of training. Indeed, the complex interrelationship between all of these diverse variables remains to be clarified.

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Water intoxication: a possible complication during endurance exercise

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ABSTRACT

NOAKES, TIMOTHY D., NEIL GOODWIN, BRIAN L. RAYNER, TREVOR BRANKEN, and ROBERT K.N. TAYLOR. Water intoxication: a possible complication during endurance exercise. *Med. Sci. Sports Exerc.*, Vol. 17, No. 3, pp. 370–375, 1985. Four athletes developed water intoxication (hyponatremia) during endurance events lasting more than 7 h. The etiology of the condition appears to be voluntary hyperhydration with hypotonic solutions combined with moderate sweat sodium chloride losses. The reason why the fluid excess in these runners was not corrected by increased urinary losses is unknown. When advised to drink less during prolonged exercise, three of the athletes have subsequently completed prolonged endurance events uneventfully.

WATER INTOXICATION, HYPONATREMIA, ULTRA-MARATHON, TRIATHLON, HYPERHYDRATION

Sweat is a hypotonic solution which in heat-acclimatized distance runners has a low sodium chloride content (3,6). For this reason, it is generally held that sodium chloride losses during prolonged exercise are relatively minor (3,4,6) and do not pose as great a threat to health as does the dehydration that attends the sweat losses (20,21). Thus, Costill and Miller have stated that "during prolonged, heavy sweating the need to replace body water is greater than any immediate demands for electrolytes" (6, p. 10). The finding that muscle sodium levels are not reduced after 2 h of exercise and that blood sodium levels are either normal or elevated after prolonged exercise, such as 42-km standard marathon (2,15) or longer ultra-marathon races of 90 (11) or 160 km (12), further supports the belief that sodium chloride replacement during marathon or ultra-marathon racing is unnecessary. This argument is further strengthened by evidence that salt ingestion during prolonged exercise may either be detrimental or may be no better than water.

First, the addition of any electrolytes to water causes increased osmolality which may reduce the rate of gastric emptying (6), thereby increasing the likelihood that dehydration will occur during exercise. Second, exercising heart rates may be increased during prolonged exercise if salt is ingested (9,14), and serum sodium levels and osmolality are increased (9). Third, the ingestion of hypertonic saline solutions inhibits sweating and may impair heat-losing mechanisms, at least at rest (17). Finally, five separate studies have shown that the addition of sodium chloride to the optimum fluid replacement regimens fails to improve either work performance during exercise (5,9,14,18) or the rate of heat acclimatization (22).

For all these reasons, most authorities have advised that only hypotonic solutions with low or no sodium chloride content be ingested during prolonged exercise (1,2,6,16). It is therefore of interest to report four cases of hyponatremia, two severe, in athletes competing in prolonged endurance events. Their condition was almost certainly aggravated by the ingestion of excessive amounts of hypotonic fluids with low sodium chloride content during and after exercise.

CASE REPORTS

Case 1. A healthy 46-yr-old female (body weight, 49 kg) who had been running for 3½ yr (best ultra-marathon performance: 55 km in 4 h and 47 min; best standard 42-km marathon time: 3 h and 55 min) trained a total of 1700 km in the 5 months before the 1981 88 km Comrades Marathon (number of finishers, 3665) and was well at the start of the race. After she had run about 30 km of the race, she developed watery diarrhea. The diarrhea persisted and in the next 40 km, she passed a further four stools. During the race she drank an estimated 250 ml fluid at every aid station, which were situated approximately every 3 km. Her

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estimated fluid intake to that point was therefore approximately 6 l. The fluid she drank consisted of a mixture of Coca-Cola and water mixed in equal volumes (estimated total sodium chloride intake during the race equalled 20 mmol).

After 70 km, the athlete was removed from the race by her husband, whom she did not recognize. She was exhausted and mentally confused. She was taken to a hospital in Pietermaritzburg, where she received a 1-l intravenous electrolyte solution and was then discharged. However, during the 90-km drive to her hotel in Durban, she had a grand mal seizure and was rushed to the hospital.

On admission, she was comatose and responded nonpurposefully to painful stimuli. There was also random twitching of the limb muscles. The pulse was 60 bpm and regular, and the blood pressure was 110/70 mm Hg. With the upper body at 45°, the jugular venous pressure was raised to the angle of the jaw. The heart was clinically of normal size. On auscultation of the chest, the heart's sounds were normal, but there were crepitations at both lung bases. Palpation of the abdomen showed that the liver was palpable 2 cm below the costal margin.

Examination of the central nervous system showed marked neck stiffness and generalized muscular hypertonia. All limbs moved equally, the tendon reflexes were symetrically increased, and the plantar reflex was normal on both sides. Both pupils were deviated to the left, and the right pupil was dilated. Both responded sluggishly but equally to light. Opthalmoscopy showed bilateral papilledema.

The electrocardiogram showed sinus bradycardia only. The chest X-ray showed enlargement of the cardiac shadow (cardiothoracic ratio, 60%). There was bilateral perihilar shadowing with numerous septal lines, changes that are in keeping with acute pulmonary edema (Figure 1).

The striking finding on blood analysis was hyponatremia and hypochloremia, both of which normalized only after 3 d. Serum potassium, bicarbonate, urea, and creatinine levels remained within normal limits for the entire duration of hospitalization. Hemotological parameters measured on admission showed a normal hemoglobin level (14.2 $g \cdot dl^{-1}$) and hematocrit (43.1%) but with an elevated white cell count of 17,500/ml, in keeping with an acute exercise effect (18). Arterial blood gas levels and pH were normal.

The initial differential diagnosis was either water intoxication or subarachnoid hemorrhage. A central venous pressure line was inserted into the right axillary vein, and a pressure of 13 cm H_2O was recorded. An intravenous infusion of 0.9% saline was commenced and, after a lag phase of about 12 h, the patient's condition began to improve: she developed a dilute diuresis, passing about 4 l of urine per 24 h. After 48 h, her mental state was normal, and there were no abnormal neurological signs. The jugular venous pressure was normal, the chest X-ray showed that the heart size was reduced (cardiothoracic ratio, 53%), and the perihilar patchy shadowing had resolved (Figure 1). Her condition continued to improve, and she was discharged in good health after 6 d in the hospital. She has no apparent neurological or renal sequelae, and she has returned to work, is running again, and has completed

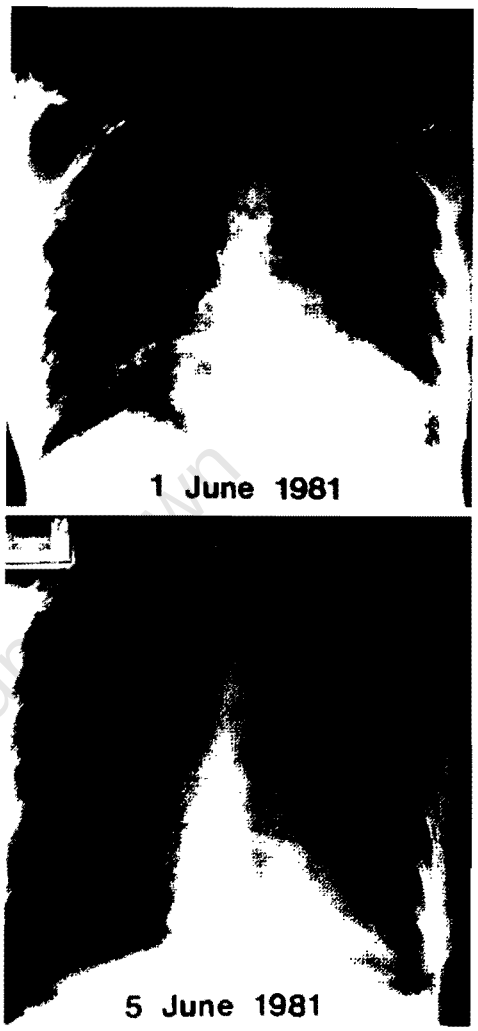

Figure 1—The chest X-ray taken on 1 June 1981 (*upper picture*) shows cardiomegaly (cardiothoracic ratio, 60%) and bilateral perihilar shadowing with numerous septal lines, changes that are in keeping with acute pulmonary edema. With the exception of the increased heart size which had nevertheless reduced somewhat (cardiothoracic ratio, 53%), all of these features had cleared in the chest X-ray taken 5 d later (*lower picture*).

subsequent standard 42-km and longer marathon races, including the Comrades Marathon, without incident.

Case 2. A 37-yr-old anesthetist (body weight, 75 kg) who had been running marathon and ultra-marathon races (best standard 42-km marathon time: 3 h and 48 min) for only 3 months and who trained between 60 and 80 km per wk completed the 1981 Comrades Marathon in 10 h and 10 min.

During the race, he had meticulously monitored his fluid intake by running with a 500-ml fluid container which he filled 2–3 times an h with the same fluid as that drunk by the female athlete (Case 1): Coca-Cola diluted with an equal volume of water. In this way, he was able to calculate that his fluid intake during the 10 h that he ran had been approximately 12 l (estimated total sodium chloride intake during the race equalled 41 mmol). He passed little urine during the race.

During the last 1½ h of the race, he developed mild muscle cramp which he considered might indicate an electrolyte imbalance. He therefore decided to drink electrolyte-containing fluids for the remainder of the race. He completed the race feeling well and immediately drank 500 ml of tea and about 70 ml of beer.

Five h later, he noted that he had persistent muscle twitching and that his consciousness was lapsing periodically. He admitted himself to the hospital for correction of what he considered to be an electrolyte imbalance.

On admission, examination of the cardiovascular system showed that the pulse rate was 80 bpm and regular, and the blood pressure was 120/90 mm Hg. The jugular venous pressure was not raised. On auscultation of the chest, the cardiac and respiratory sounds were normal. No other abnormalities were apparent on clinical examination.

Blood biochemical results, measured on hospital admission, showed an initial hyponatremia and hypochloremia. Serum levels of potassium, bicarbonate, and urea were normal. The patient was treated with a 0.9% saline/5% dextrose infusion. After 2½ l of fluid had been infused, he had passed 2.8 l of urine, and his serum sodium and chloride concentrations had increased. Overnight, the saline infusion was continued, and there was a marked net output of urine (exact figures not available). The following day, the patient's serum electrolyte levels had normalized and he was discharged. There have been no sequelae, the patient is well and, when told to drink less during races, he has since completed long-distance races without incident.

Case 3. A 20-yr-old university student (body weight, 73 kg) was admitted to the hospital after suffering a grand mal seizure approximately 1 h after completing the 1982 Comrades Marathon (number of race finishers equalled 4618). There was a history of encephalitis in childhood, but no previous seizures. He had been running for 6 months, during which time he had run about 60 km a week in training, and had completed a standard 42-km marathon without complication. He had not previously run more than 60 km in a single run.

As he had been warned of the danger of becoming dehydrated during the Comrades Marathon, he drank about 150 ml at each of the aid stations situated every 3 km along the route. He drank either an electrolyte-containing sport drink or the same Coca-Cola/water mixture ingested by Cases 1 and 2. His estimated fluid intake during the 9 h that he ran was 10 l (estimated total sodium chloride intake during the race equalled 34 mmol). He felt well immediately after completing the race, but while taking a bath 1 h after the race, he had a grand mal seizure and was rushed to the hospital.

On admission, his level of consciousness fluctuated from semi-conscious to restless and aggressive. He was sweating profusely, his neck was supple, and there was no gross neurologic deficit. On examination of the cardiovascular system, the pulse rate was 92 bpm. The jugular venous pressure was not raised, the heart sounds were normal, and the chest was clear. Blood analysis revealed hyponatremia and hypochloremia, normal potassium, bicarbonate, and urea levels, and elevated blood glucose (7.2 $mmol \cdot l^{-1}$), calcium, and inorganic phosphate (2.3 $mmol \cdot l^{-1}$) levels.

The patient was sedated with etomine and given an intravenous infusion of isotonic (0.9%) saline, receiving approximately 4 l (640 mmol NaCl) over the following 12 h. Within 2 h, his level of consciousness was normal. During the first 24 h after admission, his urine output exceeded his fluid intake by 2.2 l (3.8 vs 1.6 l); the urinary osmolality was 257 $mosmol \cdot l^{-1}$ and the sodium content was 115 $mmol \cdot l^{-1}$. On the second and third days, urinary osmolality fell to 87 and 141 $mosmol \cdot l^{-1}$ and urinary sodium content to 18 and 39 $mmol \cdot l^{-1}$, respectively. On the second day, the patient's urinary output exceeded his intake by 3.9 l. Thus, during the 4 d in the hospital, the patients urinary output exceeded his intake by 5030 ml.

The patient has since been lost to follow-up.

Case 4. A 29-yr-old female (body weight, 57 kg) with a best 42-km standard marathon time of 3 h 2 min, completed the 1983-km Comrades Marathon in 7 h, 29 min. At the finish she felt "bloated" and unwell but was not short of breath. Ten wk later, she competed in the Durban Triathlon, comprising a 6-km swim which she completed in 1 h, 29 min, a 100-km bicycle ride (3 h, 46 min), and a 42-km marathon run in 4 h, 41 min (total time = 9 h, 56 min). There were 54 finishers in the event.

On the last 14-km lap of the marathon run, she found that she was unable to run, as she became short of breath at any pace faster than a walk. She finished the race and was taken directly to the hospital.

Weight checks done during the race indicated that she had shown a progressive weight increase of 4½ kg from the end of the swim to the end of the run. She estimated that she had ingested approximately 8 l of fluid, mainly water, during the race and had urinated only once, early in the run. Her estimated total sodium chloride intake during the race was 27 mmol.

On admission to the hospital, she was fully conscious, her pulse rate was 80 bpm, and her blood pressure 100/70 mm Hg. The jugular venous pressure was not noted to be raised. On auscultation of the chest, crepitations were heard scattered throughout both lung fields.

The heart sounds were normal. The electrocardiogram showed ST-segment elevation in leads V_2 and V_3, and the chest X-ray showed pulmonary edema with bilateral effusions. Blood analysis revealed hyponatremia and hypochloremia, normal potassium and urea levels, and elevated blood glucose (8.4 mmol·l^{-1}) and serum creatine kinase levels (1119 U·l^{-1}; normal up to 110 U·l^{-1}).

A diagnosis of water intoxication was made, and the patient was treated with a diuretic and a slow intravenous infusion on 0.9% saline. Her condition rapidly improved, and she was discharged from the hospital 4 d later.

A week after discharge, she resumed training for the Hawaiian Iron Man Triathlon to be held in October. During training, she monitored her weight losses during swimming, cycling, and running and found that, on average, she lost about 100, 300, and 500 g·h^{-1} during these respective events. She was therefore advised to drink less (a maximum of 450 ml·h^{-1}), during the cycling and running stages of the Hawaiian Triathlon, and she completed the event in 12 h and 19 min in 30th place in the women's division. She did not experience any symptoms of water intoxication during the race, and her total fluid intake during the 12-h event was about 5½ l (compared to 8 l during the 10 h of the Durban Triathlon).

DISCUSSION

Hyponatremia is considered to occur when salt is lost from the body in excess of water or when water is retained in excess of salt (19). Conventional calculations (19) suggest that if the hyponatremia in these cases had been solely caused by sodium chloride losses, they would have had to lose between 445 (Case 4) and 1007 (Case 3) mmol of sodium chloride (Table 1). Alternatively, if the hyponatremia had been due solely to excessive fluid ingestion, the runners would have had to be overhydrated by between 3.6 (Case 4) and 8.8 (Case 3) l (Table 1).

Although exact data on fluid and electrolyte balance in all of these runners before and after the race are not available, information on Cases 3 and 4 clearly indicate which of these mechanisms was most likely. Case 3 excreted an extra 5 l during the 4 d following the race, suggesting that he had been overhydrated by the same amount during the race. Case 4's body weight increased 4½ kg during the Triathlon, indicating that she had been overhydrated by at least the same amount. If data on fluid intake are correct, this would indicate that Case 3's sweat loss was only 5 l during the Comrades Marathon, whereas Case 4 lost only 3 l during the Durban Triathlon (Table 1).

Assuming a sweat sodium content of 60 mmol·l^{-1} (3), the attendant sodium chloride losses would have been 300 and 210 mmol, respectively. Some of these

TABLE 1. Estimated water and sodium chloride balance in four athletes who developed water intoxication during prolonged exercise.

1 Case No.	2 Body Wt. (kg)	3 Exercise Duration (h:min)	4 Post-Race Serum Sodium Concentration (mmol·l^{-1})	5 Predicted Sodium Chloride Losses to Explain Degree of Hyponatremia (mmol)	6 Predicted Excess Fluid Intake to Explain Hyponatremia (l)	7 Estimated Fluid Intake (l)	8 Predicted Total Sweat Loss (l)	9 Estimated Excess Fluid Intake (l)*	10 Estimated Total Sodium Chloride Loss in Sweat** (mmol)	11 Estimated Sodium Chloride Intake Required to Correct the Hyponatremia*** (mmol)	12 Estimated Post-Race Serum Sodium Concentration (mmol·l^{-1})****
1 (E.S.)†	49	±7:00	115	676	5.4	6	4††	2	240	722	122
2 (R.G.)†	75	10:10	118	900	7.6	12	9††	3	540	960	118
3 (P.B.)†	73	±9:00	124	1007	8.8	10	5	5†††	300	683	118
4 (M.H.)	57	9:56	125	445	3.6	8	3½	4½†††	210	503	117

All calculations were made using conventional calculations (Ref. 19) and are subject to the many assumptions that were necessary for their computation.

† Although exact environmental data for the 1981 and 1982 Comrades Marathons (Cases 1–3) are not available, data from the 1983 and 1984 races indicate that the average WBGT during this race ranges between 15 and 23°C. Environmental conditions during the Durban Triathlon (Case 4) were similar.

†† Estimated on basis of 70-kg man losing 9 l of sweat during the 90-km Comrades Marathon and 50-kg woman losing 4 l in 70 km (Ref. 7).

††† Estimated on basis of excess fluid losses during period of hospitalization (Case 3) and body weight gain during exercise (Case 4). See text.

* Calculated as estimated fluid intake (Column 7) − predicted total sweat loss (Column 8).

** Calculated on the assumption that the average sweat sodium content is 60 mmol·l^{-1} (Ref. 3)

*** Calculated on the basis of estimated total body water at the end of the race (0.6 × body weight in kg (Column 2) + estimated excess fluid intake (Column 9) and the measured post-race serum sodium chloride concentration (Column 4).

**** Calculated on the basis of estimated excess fluid intake (Column 9) and estimated sweat sodium (chloride) losses (Column 10).

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losses would have been corrected by sodium chloride intake during the race. Analysis of a Coca-Cola/water mixture similar to that ingested by the runners revealed a sodium content of 3.4 mmol·l^{-1}. When drunk in the amounts estimated by these runners, they would have ingested only about one-tenth those drinks required to correct their sweat sodium chloride losses (Table 1). However, their total predicted sodium chloride losses in sweat of 300 and 210 mmol would be less than one-half those necessary to cause hyponatremia by sodium chloride losses alone (Table 1, Column 5). But when combined with the estimated fluid intake excesses of 5 and 4½ l in Cases 3 and 4, respectively, this degree of sodium loss would have dropped their serum sodium chloride levels to 118 and 117 mmol·l^{-1}, respectively (Table 1, Column 12)—a figure not greatly different from the values actually measured.

However, if account is taken of the additional fluid load caused by the approximate 1.5 l of metabolic water released by the breakdown of glycogen, the predicted post-race serum sodium levels for Cases 3 and 4 would be 115 mmol·l^{-1}. The discrepancy in Case 4's predicted post-race vs her actually measured value (115 vs 125 mmol·l^{-1}) could be explained by her actually overestimating her weight gain during the race. If her weight gain had been only 2 kg, her predicted post-race serum sodium level would have been 125 mmol·l^{-1}, identical to the value actually measured. Possibly Case 3 also overestimated his fluid intake during the race. It should also be noted that higher (or lower) sweat sodium contents would produce hyponatremia at lower (or higher) levels of overhydration.

Nevertheless, the general accuracy of the estimations in Table 1 suggests that the overall assumptions are correct. The postulate that these two athletes were overhydrated raises the question of whether it is possible to drink too much during ultra-marathon racing, as it is usually held that dehydration is universal among marathon runners (20,21) and other endurance athletes. However, a weight gain of 2.5 kg in one Comrades Marathon runner has been measured (10), indicating voluntary hyperhydration during the race. A previous study has shown that total sweat loss during the Comrades Marathon is independent of the runner's age or time taken to complete the race, but is related to his or her weight (7). Runners over 72 kg were found to lose an average of 9 l, whereas those below 60 kg lost less than 6 l. Cases 1–3, therefore, all drank more than required, although for Cases 1 and 3 the excess was not great. One must presume that, for whatever reasons, these two had either lower-than-predicted sweat rates or they drank more than they estimated or, less likely, they were salt-deficient before they started the race. On the other hand, the fact that Case 2's predicted and measured post-race serum sodium levels were the same suggests that his total sweat loss was probably 9 l, as predicted by the data of Dancaster and Whereat (7).

Thus, it would seem that a very strong case can be made that the etiology of the hyponatremia in these runners was due to overhydration. The reason why this excess fluid was not excreted in urine is not clear, but may relate to the sodium- and water-conserving mechanisms which are activated by prolonged exercise (3) and which probably last for at least 48 h after exercise (8). The high urine osmolality measured in Case 3 for the first 24 h after the race is compatible with this interpretation.

PRACTICAL IMPLICATIONS

On the basis of this evidence, we would suggest that, while the advice that sodium chloride intake should be restricted during marathon and ultra-marathon races is basically sound, this advice should be tempered with the proviso that the intake of hypotonic fluids in excess of that required to balance sweat and urine losses may be hazardous in some individuals.

It would appear that slower runners are the more likely to develop hyponatremia. As these athletes run at lower intensities than the top competitive runners, they (i) produce less heat and therefore sweat less and (ii) may experience less nausea and less inhibition of gastric emptying (3) and therefore may be more likely to drink and absorb larger volumes of fluid during the race. They are also running for a much longer time. But, as total sweat losses during an ultra-marathon like the Comrades Marathon may relate to body weight, not to running time (7), a runner of the same weight as the race winner but who took 11 rather than 5½ h to complete the race could be overhydrated by as much as 5½ l at the end of the race if encouraged to drink at the same rate of 1 l per h as the race winner, whose body weight is usually less than 60 kg. In combination with the normal sweat sodium chloride losses, this degree of overhydration is sufficient to cause marked hyponatremia (Case 2). Similarly, the much lower sweat rates in events like swimming and cycling (Case 4) and canoeing (13) must be appreciated, as a fluid intake appropriate for running may be greatly excessive for these events (20).

Thus, advice on the fluid and sodium chloride requirements of endurance athletes should probably be specific to the event and to the different classes of athletes and should stress the importance of *weight*, not speed, as the determinant of fluid losses during the race.

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Physiological and biochemical measurements during a 4-day surf-ski marathon

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Summary

We studied competitors in the 1983 Texan Challenge surf-ski paddle marathon to determine the effects of 4 days' prolonged paddling on sweat rates, rectal temperatures, renal function, serum glucose, free fatty acid, porphyrin and C-reactive protein levels and serum creatine kinase activity. Sweat rates during the race varied from 0,5 to 1,0 l/h, and peak rectal temperatures did not exceed 38°C, even in the most dehydrated subjects. Renal function was unchanged during the race. Plasma renin activity remained low during the race but C-reactive protein levels and serum creatine kinase activity were elevated. Seventy per cent of the subjects had immediate post-exercise blood glucose levels below 3,9 mmol/l after the 1st and 4th days, and 27% had values below 3,0 mmol/l, one competitor requiring intravenous glucose therapy on the beach.

Surf-ski paddling is therefore associated with low sweat rates, low levels of dehydration, low body temperature and unchanged renal function. The low post-exercise blood glucose levels indicate that competitors must eat high-carbohydrate diets for the duration of the event and must either eat carbohydrate-containing foods or drink concentrated carbohydrate solutions while paddling.

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The Texan Challenge, a 244 km surf-ski paddle marathon, is contested biennially in four stages between Port Elizabeth and East London, South Africa (Fig. 1). The race, which originated as a challenge to see whether a surf-ski paddler could reach East London before a runner, has now been held four times. It is open only to registered lifesavers, and in 1983 102 paddlers competed in the race, including the first-ever female entrant.

As little is known of the physiological and biochemical demands that the race places on the competitors, we decided to study a group of participants during the 1983 race. Particular attention was paid to fluid and energy requirements, and to the effects of the race on serum enzyme and fuel levels and renal function.

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Subjects and methods

At the briefing held the day before the race, the competitors were informed of the project and a request for volunteers was made. A total of 30 subjects agreed to participate in the project, and they were divided into five different study groups.

The race was scheduled to be paddled in four stages of 80, 46, 68 and 50 km. However, conditions on the 3rd day were so atrocious that that day's stage was abandoned after the competitors had been afloat for about 2 hours and had covered about 10 km. The actual race distance was therefore 186 km.

Fluid balance

A group of 6 subjects (group 1) were weighed each morning between 04h00 and 04h30 on a digital-reading Seca 77 electronic scale (Vogel and Halke, Hamburg, West Germany) accurate to 100 g and again immediately after they had completed the day's paddling. During each day's paddling they were asked to calculate the amount of fluid they had drunk, and they were encouraged not to pass urine during the race. This information, together with their paddling time, was collected immediately after each day's paddling. For the purpose of calculating sweat rates it was assumed that those subjects who had passed urine had passed 200 ml with each micturition, although in reality few subjects passed urine while paddling.

These data were used to calculate sweat rates (ml/h) according to the following formula:

$$\frac{\text{weight loss (g)} + \text{urine loss (ml)} + \text{fluid intake (ml)}}{\text{paddling time (h)}}$$

Dehydration (%) was calculated as:

$$\frac{\text{early morning (pre-exercise) wt} - \text{post-exercise wt}}{\text{pre-exercise wt}} \times 100$$

Rectal temperatures

On the 4th (final) day, 6 of the better paddlers (group 2) were weighed before and after the race, as for group 1, and their post-race rectal temperatures were measured with a rectal thermometer.

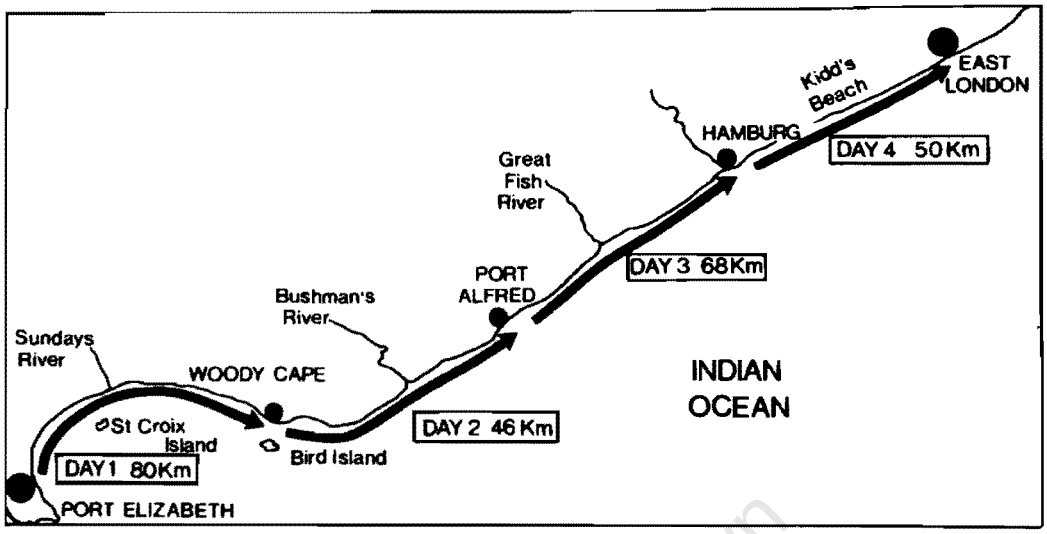

Fig. 1. Map of the coast along which the biennial 244 km, 4-day Texan Challenge race is held.

Renal function

Five subjects (group 3) participated in a study of changes in renal function during the race. They were each given two 1-litre plastic flasks protected from the light by a covering of silver foil and were asked to collect 24-hour urine samples for the duration of the race, ending 24 hours after the completion of the last stage. As it was impossible to collect urine samples while at sea, these subjects were asked not to micturate while paddling. Should this prove impossible, they were asked to note very accurately the time of the last micturition, and the timing of their urine sample collection was adjusted accordingly.

Immediately after each day's paddling, a venous blood specimen was drawn from each of these subjects and allowed to clot before being spun, separated, and stored deep-frozen for later analysis. Each morning the volume of the 24-hour urine samples was measured, and two separate aliquots were placed in 80 ml bottles, wrapped in tin foil, and stored deep-frozen for subsequent analysis.

The blood specimens were analysed for serum sodium, potassium, creatinine, urea and C-reactive protein levels, serum osmolality, plasma renin activity and plasma porphyrin levels by conventional methods. The urine specimens were analysed for sodium, potassium, protein, creatinine, porphyrin, porphyrin precursor and urea levels and osmolality, also by conventional methods. Porphyrin levels were measured because these have been related to renal function.[1]

Serum creatine kinase activity

Blood samples were drawn on the day before the start of the race and after each day's paddling from another group of 13 subjects (group 4). These samples were analysed for total serum creatine kinase (CK) and iso-enzyme activity by methods previously described.[2]

Blood glucose and free fatty acid levels

At the end of the first and last stages, blood was drawn from 15 of the subjects participating in the various studies (groups 1 - 4) for estimation of blood glucose levels by the glucose oxidase method as previously described.[3] There was usually a delay of between 2 and 10 minutes before blood could be drawn. Nine of these group 5 subjects paddled in double surf-ski's and 6 in single ones. Additional samples from 7 double and 5 single paddlers were analysed for serum free fatty acid (FFA) levels by thin-layer chromatography as previously described.[4]

Statistical methods

Only paired data were evaluated. A P value of $< 0,05$ using the Student's paired t-test was considered to be statistically significant.

Results

Fluid balance

There was a significant fall in early-morning body weight on the 2nd and 3rd days, but by the 4th day the early-morning weight had returned to control levels (Table I). This can probably be explained by the short distance paddled on the 3rd day.

Paddling speeds varied quite considerably on the 3 days for which they were calculated and were highest during the first and longest stage, when there was a strong following wind (Table I). Mean weight losses of about 1 kg and dehydration of about 1% were recorded on all 3 days; mean fluid intakes varied from 400 to 540 ml/h and mean sweat rates were between 520 and 750 ml/h. The highest sweat rate was 960 ml/h and the lowest 490 ml/h. Sweat rates were highest on the last day, which was also the hottest day, with dry-bulb temperatures of 22 - 26°C.

Rectal temperatures

Rectal temperatures at the end of the last stage in the group 2 subjects ranged between 37,5°C and 38°C, with a mean of 37,7°C (± 0,1°C). These 6 subjects had paddled considerably

TABLE I. FLUID BALANCE

	Day 1	Day 2	Day 3	Day 4
Early-morning weight (kg)*	84,1 ± 3,4	83,1 ± 3,6†	83,7 ± 3,5	84,7 ± 3,5
Distance paddled (km)	60	46	± 10‡	50
Paddling speed (km/h)*	10,2 ± 1,0	7,9 ± 0,6	—	8,8 ± 1,0
Weight loss (g)*	950 ± 44	1 000 ± 31	—	920 ± 38
Dehydration (%)*	1,1 ± 1,3	1,2 ± 0,8	—	1,1 ± 1,0
Fluid intake (ml/h)*	400 ± 14	520 ± 7	—	540 ± 21
Sweat rate (ml/h)*	520 ± 23	700 ± 11	—	750 ± 15

*Values expressed as mean ± SD for 8 subjects
†$P < 0,05$ v. day 1.
‡The third stage of the event (68 km) was cancelled after about 2 hours' paddling (see text).

faster than the group 1 subjects (10,8 ± 0,3 km/h v. 8,8 ± 1,0 km/h) and were also considerably more dehydrated (3,0 ± 0,3% v. 1,1 ± 1,0%). The highest degree of dehydration was 4,1%, measured in the winner of the race, who lost his drinking bottles at the start of the day's paddling and sweated at a rate of 0,96 l/h. Despite this quite marked level of dehydration, his rectal temperature reached only 38°C.

Renal function

Biochemical values measured in the serum and urine of the 5 group 3 subjects are listed in Tables II and III. Urine flow and creatinine clearance rates and electrolyte excretion remained within normal limits and urine osmolality did not diminish. Plasma and urinary porphyrin and urinary porphyrin precursor levels remained normal. The serum urea concentration and urinary urea and protein excretion were all in the high-normal range for the duration of the competition.

It should be noted that the first blood sample was drawn after the paddlers had completed the first stage of the race and that no urine collections were made in the resting state. Although these biochemical values did not change during the course of the event, they may therefore have been different from those measured at rest. However, as all values were within the normal range, any changes must have been small and of no physiological significance.

TABLE II. SERUM BIOCHEMICAL CHANGES*

	Day 1	Day 2	Day 3	Day 4
Sodium (mmol/l)	140 ± 1,4	139 ± 1,1	140 ± 1,5	141 ± 1,1
Potassium (mmol/l)	4,6 ± 0,2	4,5 ± 0,2	4,8 ± 0,2	4,7 ± 0,1
Creatinine (μmol/l)	97 ± 5,8	93 ± 4,7	92 ± 7,1	89 ± 5,9
Urea (mmol/l)	7,2 ± 0,7	6,6 ± 0,5	6,0 ± 0,9	7,0 ± 0,7
Osmolality (mmol/kg)	287 ± 3,1	291 ± 7,2	290 ± 2,9	289 ± 1,8
C-reactive protein (mg/l)	8 ± 4	11 ± 3	9 ± 6	5 ± 5
Total plasma porphyrins (g/dl)	0,06 ± 0,02	0,12 ± 0,05	0,09 ± 0,05	0,08 ± 0,04

*Values expressed as mean ± SE for 5 subjects for the duration of the competition. Note that blood was first drawn on day 1 *after* the subjects had exercised, so that no control (inactive) data are available (see text).

TABLE III. RENAL FUNCTION*

	Day 1	Day 2	Day 3	Day 4
Urine flow (ml/min)	1,2 ± 0,2	0,9 ± 0,2	0,8 ± 0,2	0,8 ± 0,1
Sodium excretion (mmol/d)	163 ± 35,5	122 ± 26,4	155 ± 42,5	127 ± 33,7
Potassium excretion (mmol/d)	69 ± 14,8	53 ± 13,6	50 ± 11,2	60 ± 19,4
Protein excretion (g/d)	0,2 ± 0,1	0,2 ± 0,1	0,1 ± 0,1	0,1 ± 0,1
Creatinine excretion (mmol/d)	13,9 ± 2,2	12,9 ± 1,7	16,3 ± 3,2	14,7 ± 2,2
Urea excretion (mmol/d)	594 ± 91,2	446 ± 61,5	415 ± 80,6	481 ± 76,7
Osmolality (mmol/kg)	766 ± 88,2	783 ± 100,7	819 ± 86,5	850 ± 59,9
Creatinine clearance (ml/min)	102,8 ± 11,9	99,3 ± 16,0	120 ± 18,4	121 ± 12,3
Urinary porphyrin precursor excretion (mg/d)	6,4 ± 2,8	5,77 ± 3,3	4,6 ± 1,1	3,9 ± 0,9
Urinary porphyrin excretion (μg/d)	56,2 ± 16,9	52,1 ± 17,7	44,1 ± 15,8	36,0 ± 13,4

*Values expressed as mean ± SE for 5 subjects for the duration of the competition (see footnote to Table II).

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CK activity, glucose, FFA and C-reactive protein levels and plasma renin activity

Fig. 2 shows that serum CK activity rose markedly after the 1st day's paddling and then fell progressively but was still significantly elevated after the 4th day. Electrophoresis showed that only the MM iso-enzyme fraction of CK was present. Plasma renin activity was significantly elevated when measured after the second and fourth stages (but nevertheless low). Serum C-reactive protein levels were slightly elevated above normal resting levels of 3 mg/l.[5]

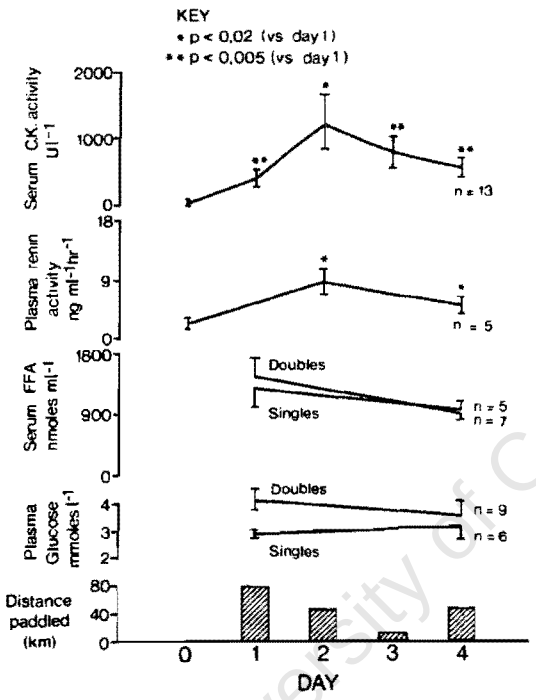

Fig. 2. Changes in serum CK and plasma renin activities and in serum FFA and blood glucose levels during the 4 days of the competition. Note the marked elevation in serum CK and plasma renin activities.

After the 80 km first stage, 11 of the 15 subjects (73%) had blood glucose levels below 3,9 mmol/l; the lowest value was 2,4 mmol/l in a competitor who collapsed on the beach and required resuscitation with intravenous glucose. After the last stage, 10 of the 15 subjects (67%) had blood glucose levels below 3,9 mmol/l. Blood glucose levels were lower in single than in double paddlers after the first stage but not after the last stage (Fig. 2).

Discussion

The significant findings of this study were that: (*i*) the subjects developed trivial levels of dehydration and hyperthermia, their sweat rates were low, and their renal function was essentially unchanged; and (*ii*) the majority had low to very low post-exercise blood glucose levels. In view of the dangers that hypoglycaemia could pose to paddlers in the open sea, this latter finding is cause for concern.

The relatively low sweat rates of between 490 and 960 ml/h and the fact that the highest rectal temperature was only 38°C contrast with sweat rates of up to 2000 ml/h and rectal temperatures in excess of 40°C measured in marathon runners.[6] It must be concluded that the ski-paddlers investigated in this study were exposed to less thermoregulatory strain than are most marathon runners. Possible reasons for this are the lower intensity of effort and smaller muscle mass used in paddling than in running and the more favourable environmental conditions, particularly when paddling in the open sea early in the morning. It seems likely that the low levels of dehydration explain why renal function was essentially unchanged, although this cannot explain the elevated plasma renin activity.

The persistently elevated serum CK activity and C-reactive protein levels suggest low-grade muscle damage.[7,8] In contrast to findings in marathon runners,[2,9] the CK activity and C-reactive protein levels were lower and only the CK MM iso-enzyme was present. In runners, CK BB and MB iso-enzyme fractions are present,[2] total CK levels may reach 3000 IU/l 24 hours after races of 88 km, and C-reactive protein levels of up to 62 mg/l have been reported.[9] The reasons for these differences are not known, but they probably indicate less severe muscle damage in ski-paddling, in which the active muscles do not also bear the weight of the body.

Probably the most important finding was the very high incidence of low blood glucose levels, including a case of clinical hypoglycaemia in a competitor who collapsed shortly after landing on the beach. Of the sampled blood glucose values 70% were below 3,9 mmol/l and 27% below 3,0 mmol/l. Values in this range are sufficiently low to produce symptoms of hypoglycaemia, including impaired performance and judgement, in marathon runners.[10] Furthermore, we have subsequently found that blood glucose levels can rise by as much as 1,5 mmol/l within minutes of the termination of prolonged exercise (data in preparation). As these blood samples were usually drawn 2 - 10 minutes after the subjects had finished exercising, it is possible that their blood glucose levels may have been even lower while they were actively paddling. In this situation hypoglycaemia poses the particular danger that, after a hard day's paddling, competitors frequently have to negotiate heavy surf on returning to the beach. Impaired judgement or physical weakness places them at risk should they capsize and be forced to swim.

The low blood glucose levels in our subjects probably relate to inappropriate dietary practices both before and during the competition and to the relatively small muscle mass used in paddling. Our observation was that the diet provided for the competitors had a low carbohydrate content, and that most paddlers drank fluids with a low carbohydrate content during the competition.

As glycogen resynthesis on a low-carbohydrate diet occurs first in the muscles and only later in the liver,[11,12] the risk of liver glycogen depletion during subsequent exercise is high. Furthermore, the small muscle mass used in paddling could also predispose to hypoglycaemia. Recent studies have shown that the rate of glucose uptake by muscles during exercise is inversely proportional to their glycogen content.[13] As muscles become progressively glycogen-depleted during prolonged exercise, their uptake of glucose from blood increases. The likelihood of hypoglycaemia increases during exercise utilizing small muscle groups because these muscles will become glycogen-depleted more rapidly and therefore have a greater need for exogenous glucose than would occur if exercise was performed utilizing a larger muscle mass.

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Synopsis and recommendations

This study emphasizes that the avoidance of hyperthermia, a critical factor determining the choice of fluid replacement in marathon running, is not a factor in surf-ski paddling, at least under the mild environmental conditions experienced in this study. The avoidance of hypoglycaemia during paddling would seem to be far more important. Ski-paddlers must be encouraged to eat a high-carbohydrate diet for the duration of the race and to ingest carbohydrate-containing drinks and foods while paddling. The optimal concentration of the carbohydrate-containing drink is not known but should probably be as high as can be tolerated without producing nausea during paddling.

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Dehydration During Exercise: What Are the Real Dangers?

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Abstract: The belief that dehydration poses significant health risks for endurance athletes, especially marathon and ultramarathon runners, stems from the classical 1969 study of Wyndham and Strydom entitled "The Danger of an Inadequate Water Intake During Marathon Running." The subsequent influence of the paper relates more to its incorrect title than to its scientific content. For the authors did not study nor did they identify any dangers resulting from an inadequate water intake during marathon running. In fact, the most dehydrated runners in their studies were also the most successful, as they won the competitive races that were studied. The positive result of the study was to influence international rule changes to allow increased fluid intake during competitive running races. The less desirable effect was to induce a dogmatic zeal among sports medicine practitioners who began to extol the dangers of dehydration during exercise. The (il)logic spurring this zeal seems to have been the conclusion that progressive dehydration during exercise will cause heatstroke, which is the most important cause of collapse during exercise. Hence, (i) heatstroke during running can only be avoided if dehydration is prevented, and (ii) all persons who collapse in association with exercise will have a heat disorder, which must be treated with intravenous fluid therapy. This article reviews the evidence which shows (i) that the levels of dehydration commonly measured in endurance athletes (1–4% of body weight) cause measurable physiological change and impair exercise performance in the heat but are not associated with health risks such as heatstroke or acute renal failure; (ii) that most athletes collapse after exercise and have rectal temperatures that are no higher than values measured in control runners; and (iii) that no study has yet shown that collapsed runners are more dehydrated than controls. It is proposed that postural hypotension, unrelated to levels of dehydration, is the most common cause of the exercise-associated collapse that occurs *after* the athlete stops exercising. Clinicians treating athletes with exercise-associated collapse should initiate treatment only after a thorough clinical evaluation has produced rationale differential diagnoses. Intravenous fluid therapy should be reserved only for those patients with clear clinical evidence for dehydration which contributes to their clinical presentation. **Key Words:** Exercise-associated collapse—Postural hypotension—Dehydration—Marathon running. *Clin J Sport Med* 1995;5(2):123–8.

Historically, athletes and their coaches have promoted the value of fluid *restriction* during both athletic training and competition. For example, the Oxford University rowing crew of 1860 were restricted to a maximum of 2 pints of fluid each day during training. But "outraged human nature rebelled against it; and although they did not admit it in public, there were very few men who did not rush to their waterbottles for relief, more or less often, according to the development of their conscientiousness and their obstinacy" (26).

A popular book on marathon running published in 1909 advised that prospective competitors in that race should be careful to avoid eating or drinking

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during the race: "Don't get in the habit of drinking and eating in a Marathon race; some prominent runners do, but it is not beneficial" (45).

Although some famous athletes of that era, most especially multiple Boston marathon winner, Clarence de Mar, drank fluids more freely during competition (12), the general practice was to restrict fluid ingestion during competition to an absolute minimum. Arthur Newton, who in the 1920s and 1930s held world records for running distances of 80–221 km and who competed in the Professional Trans America races of 1928 and 1929, wrote: "Even in the warmest English weather, a twenty-six mile run ought to be manageable with no more than a single drink, or at most two" (32).

Similarly, English marathoner, Jim Peters, who lowered the world record in the standard 42-km marathon by more than 9½ min between 1952 and 1954 and who is arguably the greatest marathoner of all time (35), believed: "There is no need to take any solid food at all (during a marathon race) and every effort should be made to do without liquid, as the moment food or drink is taken, the body has to start dealing with its digestion and in so doing some discomfort will almost invariably be felt" (43).

Peters is also remembered as the athlete who collapsed with heatstroke within 200 m of the finish of the 1954 Empire Games Marathon in Vancouver, British Columbia, thereby ending his competitive athletic career. The race was run in the early afternoon in stifling heat. Unacclimatized to such conditions and unwilling to reduce his speed to suit the environmental conditions, Peters raced at a suicidal pace (30,43). Hence, many factors contributed to this tragedy, and speculation that dehydration was an important factor must also acknowledge that all his world marathon records were set in races in which Peters drank little if anything.

Another world record holder at ultramarathon distances and who, because of his greater experience in hot weather marathons, had successfully completed the 1954 Empire Games Marathon in second place, would later reflect: "In those days, it was quite fashionable not to drink, until one absolutely had to. After a race runners would recount with pride, 'I only had a drink after 30 or 40 kilometres'. To run a complete marathon without any fluid replacement was regarded as the ultimate aim of most runners, and a test of their fitness" (30).

This conventional wisdom was enshrined in the rules of the International Amateur Athletic Federation (IAAF) governing the conduct of long distance races at that time. Thus the rules in force at that time (1953) stated that "refreshments shall (only) be provided by the organizers of a race after 15 km or 10 miles, and thereafter every 5 km or 3 miles. No refreshment may be carried or taken by a competitor other than that provided by the organizers" (22). Water was the only drink available to runners at the official refreshment stations despite evidence that carbohydrate ingested during exercise could aid performance (9,16).

This historical introduction is relevant because it establishes that at least until 1969, competitors in endurance events, most especially marathon running, were actively discouraged from drinking during exercise. Indeed the first text which actively promoted fluid ingestion during exercise was published as recently as 1979 (10). Despite universally inadequate fluid replacement during exercise, there is no evidence that the endurance athletes of the first 70 years of this century were at noticeably greater *health* risk during exercise than are modern runners.

It was into this intellectual vacuum that one of the most influential studies in the modern exercise sciences exploded (48). The study was completed as an adjunct, perhaps as an afterthought, to a larger study funded by the sugar industry and which was designed to measure the effects of a high carbohydrate, specifically a sucrose supplemented, diet on running performance in 30-km footraces (29). The authors were unable to measure any ergogenic effect of the high sucrose diet. But their efforts were not completely in vain. For they had also measured the rates of fluid ingestion and the levels of dehydration that developed in the runners during those races. It was those findings that would become so influential.

Their principal findings were that the athletes drank less than they sweated; hence, all lost weight. More specifically, there was a linear relationship between levels of dehydration of >3% and the athletes' postexercise rectal temperatures. Hence, the authors concluded that the level of dehydration that develops during exercise is the principal determinant of the rectal temperature during exercise so that avoidance of weight loss (dehydration) must be the most important factor preventing heat injury during exercise.

But to reach this conclusion, the authors had to ignore their own published findings (49), which established that the metabolic rate is (also) a major determinant of the rectal temperature during exercise (36).

But the real influence of the study came not so much from its findings but from its provocative title: "The Danger of an Inadequate Water Intake During Marathon Running." This title delights in a capacious degree of artistic license.

For the research neither studied nor did it identify any *dangers* of an inadequate fluid intake during marathon running. Rather the most dehydrated runners won the races. Given this unexpected finding and the low rate of reported cases of heatstroke and other health disorders in marathon runners at that time despite their hopelessly inadequate fluid intakes, a more appropriate title might perhaps have been: "Remarkable Resistance of Marathon Runners to the Detrimental Effects of Dehydration."

The immediately beneficial effect of this study was to cause a review of the IAAF rules governing the conduct of international distance races. As a direct result, rule changes were introduced in 1977 that allowed fluid ingestion every 2.5 km after the first 5 km of long distance races. In 1990 the rule was again modified to allow the ingestion of water *and* carbohydrate every 3 km after the first 2.5 km of long distance races. The origin of all these rule changes is unquestionably the stimulus provided by Wyndham and Strydom's classic study (48).

But the less desirable effect of this study was to induce a dogmatic zeal amongst sports medicine practitioners who began to extol the dangers of dehydration in endurance athletes. Attempts to question this dogma (34,37–39) have not been universally popular (11,19). Those who were influenced by the article's title without digesting its contents seem to have adopted the following (incorrect) logic (38): Progressive dehydration during exercise causes heatstroke (48,50); hence, the most important method to prevent heatstroke during exercise is to ensure that athletes ingest as much fluid as possible (6,48,50). But heatstroke is also the most important cause of collapse during exercise. Hence, all persons who collapse after exercise have a heat disorder and must necessarily be dehydrated. Therefore, intravenous fluid therapy is the logical treatment of choice for "all" athletes who collapse during or after exercise (1,19,23,24). The illogic in this argument should be apparent, but is not always appreciated. Hence, it is appropriate to look more carefully at the (lack of) evidence for each of the steps leading to these conclusions.

First, no study has yet shown that dehydration of the levels present in endurance athletes (1–4% of body weight) (41) exercising under more moderate environmental conditions poses any major *health* risks or that it even predisposes to heatstroke. Given the historical evidence it would seem unlikely.

Indeed the classic studies of exercise dehydration performed during the Second World War (2–5) found that military personnel forced to exercise without fluid replacement would continue to exercise in hot, desert conditions until levels of dehydration of >7–10% were reached. "Dehydration exhaustion" (8), characterized by circulatory instability with, in particular, tachycardia and postural hypotension and psychological alterations, including heightened aggression and a loss of discipline, terminated exercise. Subjects were neither markedly hyperthermic nor did they show significant alterations in renal function. All recovered quickly when they lay down and ingested fluid. Recovery occurred even before any physiological effects could have resulted from the fluid ingestion. Brown (8) concluded that dehydration posed significant health risks only at levels of dehydration of 15–20%. These levels of dehydration are two to three times greater than those normally measured in endurance athletes (41). Perhaps "dehydration exhaustion" acts to prevent athletes continuing to exercise to levels of dehydration that cause medical complications.

Second, no study has yet shown that the majority of persons who collapse during or after exercise are "hotter" than noncollapsed runners and hence are suffering from a diagnosable heat disorder. For example, Holtzhausen et al. (25) have shown (i) that the rectal temperatures of athletes who collapse in ultramarathon footraces are not abnormally elevated, nor are they higher than the temperatures of control runners who do not collapse after exercise and (ii) that 85% of these athletes collapse *after* they have completed the race. Paradoxically a proportion of subjects who collapse after prolonged exercise may be hypothermic (25,44). It is difficult to imagine how a heat disorder should cause an athlete to collapse immediately *after* exercise, when the metabolic rate is beginning to fall.

Third, no study has yet shown that collapsed runners are more dehydrated than are control runners who do not collapse after completing the same races. As already argued, levels of dehydration in endurance athletes are not in the range known to induce pathophysiological changes. Furthermore, it is again difficult to explain how dehydration *alone* can cause collapse *after* the athlete has already stopped exercising, when heart rate, stroke volume and cardiac output are all falling from the higher levels sustained during exercise. Logic demands that dehydration should induce collapse *during* exercise when the stroke volume is highest and therefore most likely to be affected by a reduced *circulating* blood volume.

More likely, perhaps, is that the sudden cessation of exercise is an important aetiological factor explaining this collapse, which is probably due to the sudden onset of postural hypotension. This would be due to a fall in *central* (rather than circulating) blood volume and hence, atrial filling pressure, due to pooling of blood in the dilated, capacitance veins in the lower limbs. Indeed the historical studies of collapse in persons exposed to exercise in hot environmental conditions, so-called "heat exhaustion," emphasized that all had postural hypotension (2,4,17,46) but that rectal temperatures were not abnormally elevated. The cardiovascular instability and associated symptoms disappeared as soon as the subjects lay prone and without the need for intravenous fluid therapy.

Adolph (2) noted that patients with "heat exhaustion" were "still producing sweat and keeping cool" but that they showed evidence of postural hypotension. Adolph and Fulton (4) concluded: "The peripheral blood vessels are greatly dilated during exposure to high temperatures, and this dilation continues indefinitely. The lack of a high resistance in the peripheral blood vessels prevents blood from returning to the heart. The heart rate

increases steadily and rapidly, and is even able to increase the systolic blood pressure. In spite of this compensating activity on the part of the heart, the blood flow back to the heart finally becomes inadequate. At this point circulatory collapse or shock is complete, with faintness." Adolph (2) also noted that patients with this condition usually needed "merely to lie down to feel better. The shock-like circulatory failure appears to be the crucial element in this condition."

Talbott et al. (46) also concluded that "heat prostration is associated with vasomotor collapse. It is known that peripheral dilation of blood vessels and tachycardia accompany exposure to high temperature. During muscle activity in high environmental temperatures, the peripheral dilatation with vasomotor collapse may approach pathological proportions."

Similarly Eichna et al. (17) showed that 58% of subjects developed syncope on their first exposure to "exhausting" exercise in the heat. Despite the finding that the rectal temperatures were not greatly elevated (<38°C) and were similar to those measured in our subjects with EAC, those authors labelled the condition "heat exhaustion." Others had also noted that the rectal temperature was either "submaximal or slightly elevated" in heat exhaustion (13). In common with the other early workers, Eichna et al. (18) proposed that postural hypotension explains the syncope present in their subjects with "heat exhaustion." The concluded that this postural drop in blood pressure resulted from pooling of blood in the lower extremities on cessation of exercise due to a work-induced venodilatation in the lower limb muscles and inactivation of the muscle pump that aids venous return during exercise.

Thus the conclusion from these early studies must be that, historically, the terms "heat exhaustion," "heat prostration," or "heat syncope" were used only to describe a condition of collapse due to postural hypotension that develops in persons exercising in the heat. The terminology should not be misinterpreted to indicate that the collapse is caused by an elevated body temperature and is therefore a mild form of heatstroke. But ever since these early studies the possibility that postural hypotension could explain EAC has been overlooked (33).

These same features, in particular, hypotension and tachycardia, which are rapidly reversed on lying supine, are seen in athletes with exercise-associated collapse (25). Hence, we (38) have proposed that most athletes who collapse *after* exercise have postural hypotension and should be managed by lying supine with legs and pelvis elevated above the level of the heart. This treatment has proved particularly effective and, in our hands, has essentially removed the need for intravenous fluid therapy from the management of the vast majority of athletes who collapse *after* completing marathon and ultramarathon races.

What then is the current state of knowledge about the dehydration that develops during exercise? First, there is no doubt that dehydration causes important and mostly detrimental physiological changes during exercise. For example, heart rate and rectal temperature are higher and stroke volume and skin blood flow lower in proportion to the level of dehydration that develops during exercise (31). These changes are reduced by adequate fluid ingestion (31). Furthermore, performance during more prolonged exercise in the heat may be impaired even at quite low levels of dehydration (47).

Hence, it is entirely appropriate that competitive athletes should be encouraged to drink fluid during exercise, especially in the heat, in order to optimize performance and to reduce the detrimental physiological changes that develop with increasing levels of dehydration. Hence, fluid ingestion during exercise can be safely promoted to aid performance. But for reasons described below, it may not always be possible to replace all fluid lost during exercise and some degree of dehydration may be inevitable when sweat rates are sustained in excess of 1 l/h.

But whether optimum fluid ingestion will necessarily prevent some of the more important medical complications of prolonged exercise, including heatstroke, acute renal failure, or postexercise collapse is not established. Indeed there is growing evidence that both heatstroke and acute renal failure may occur in persons who are genetically predisposed, perhaps by the presence of a muscle disorder, to the development of malignant hyperthermia and rhabdomyolysis in response to a variety of stresses including prolonged exercise (15). This would perhaps explain why true heatstroke (i) occurs so infrequently even when large numbers of subjects compete in endurance events held in unfavorable environmental conditions and conversely (ii) why heatstroke frequently occurs during exercise in mild environmental conditions (7).

Second, there is no good evidence that dehydration is either an important or a necessary component of the common form of exercise-associated collapse (25) that occurs on the cessation of exercise. Hence, treatment with intravenous fluids is not necessarily the most appropriate form of therapy for this condition (39).

Rather, we have proposed that the first step in the management of persons who collapse especially during, or after prolonged exercise, is to establish a reasonable working clinical diagnosis. This will include an assessment of the patient's level of dehydration. From his classic studies of military personnel exercising in desert heat in the Second World War, Adolph (3) suggested that symptoms characteristic of more severe (>8%) dehydration included severe thirst, a dry mouth, and an inability to spit because of absent salivary flow. To this we would add measures of cardiovascular function, including heart rate, blood pressure, and peripheral color

measured with the patient in the supine position with legs and pelvis elevated to exclude any contribution of peripheral blood pooling to cardiovascular instability. If the cardiovascular system is stable and if the symptoms of marked dehydration are not present, then it is difficult to justify intravenous fluid therapy if no additional indications are present.

Indeed, because intravenous fluids can induce iatrogenic hyponatraemia (37,39) with potentially fatal results, it behooves physicians treating collapsed runners to be absolutely certain of the defensibility of their choice either to use or restrict the use of intravenous fluid therapy in collapsed athletes.

Third, it is apparent that athletes can drink too much during exercise causing the hyponatraemia of exercise (40). This condition occurs more frequently than classical heatstroke in endurance athletes (37,41) and is potentially more dangerous as the diagnosis is made only if there is a high degree of clinical suspicion, and the treatment is more complex. As this is purely an iatrogenic condition, its prevention should be relatively simple.

We have proposed that the ultimate cause of the hyponatraemia of exercise is a limited rate of fluid absorption by the intestine during exercise (40,41). This hypothesis is compatible with the belief that intestinal function is not infinite, but is limited—"enough, but no more" (14). We estimate that the maximum rate of intestinal water absorption especially during exercise, is of the order of 750–1,000 ml/h (41,42). The hypothesis predicts that when fluid is ingested at rates faster than 1,000 ml/h, the unabsorbed fluid accumulates in the intestinal lumen; sodium would then move from the extracellular fluid into the intestinal fluid to a concentration of 40–100 mmol/l (21,27). In a 50-kg woman runner—the condition is more common in women, perhaps because of their smaller size—the movement of ~180 mmoles of sodium from the ECF into 2 l of unabsorbed intestinal fluid would cause the serum sodium concentration to fall from 140 to 125 mmol/l.

Studies performed during both exercise (20) and at rest (42) show that hyponatraemia can be induced by high rates of fluid intake and that the hyponatremia develops in proportion to the fluid retention (20,42) and can be explained if the sodium "lost" from the ECF moves into the unabsorbed intestinal fluid to a concentration of approximately 45 mmol/l (42).

An alternate argument is that the peak rate of urine production is <1,000 ml/h (28) so that ingestion of fluid at higher rates causes fluid retention in all the body fluid compartments and hence a dilutional hyponatraemia.

Regardless of the mechanism causing the hyponatraemia, the conclusion is that fluid intake cannot always equal the rate of weight loss during exercise as the rate of weight loss is determined principally by the sweat rate [which is proportional to the metabolic rate (36)] whereas the rate of fluid replacement is probably limited by the rate of intestinal fluid absorption. Attempts to ingest fluid at rates higher than ~1,000 ml/h are unlikely to be beneficial if they lead only to fluid retention either in the intestine (if the rate of intestinal fluid absorption is limiting) or in the body fluids (if the rate of urine formation is limiting).

In summary, the assumption that dehydration is the underlying cause of heatstroke and all cases of collapse in endurance athletes is not supported by firm scientific evidence. This review has traced the evolution of the (il)logic that led to the widespread propagation of this belief. However, there is good evidence that quite mild levels of dehydration impair exercise performance; but levels of dehydration much greater than have ever been measured in endurance athletes are necessary to produce acute renal failure and death. Hence, athletes can safely be encouraged to maintain low levels of dehydration by drinking "enough but not too much" during exercise. But they should be warned that very high rates of fluid ingestion (>1.5 l/h) sustained for many hours can lead to hyponatraemia with a potentially fatal outcome (40).

Finally, clinicians must be discouraged from assuming that all complications found in endurance athletes are heat-related and are due to a severe dehydration that should be corrected immediately by intravenous fluid therapy even before a reasonable working diagnosis has been made. Rather, like all patients, the collapsed athlete first deserves a rational diagnosis before initiation of the most appropriate therapy for the specific diagnosis (33). There is no evidence that, if the diagnosis is not readily apparent, withholding therapy for a few minutes, will have any detrimental consequences.

We also propose that the majority of athletes who collapse *after* the cessation of exercise will recover rapidly if treated for postural hypotension by elevating the pelvis and lower limbs.

In contrast, those who collapse *before* completing these events and who show significant alterations in their level of consciousness, are likely to have one or more significant medical problems (25) that will require expert medical treatment. The differential diagnosis for such patients should include: heatstroke or alternatively hypothermia, hyponatraemia, hypoglycaemia, or other major cardiovascular or medical conditions.

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Evaluation of renal function and fluid homeostasis during recovery from exercise-induced hyponatremia

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IRVING, R. A., T. D. NOAKES, R. BUCK, R. VAN ZYL SMIT, E. RAINE, J. GODLONTON, AND R. J. NORMAN. *Evaluation of renal function and fluid homeostasis during recovery from exercise-induced hyponatremia.* J. Appl. Physiol. 70(1): 342–348, 1991.— Renal function including fluid and electrolyte balance was studied during recovery in eight subjects who developed symptomatic hyponatremia (HN; plasma sodium concentration <130 mM) during an 88-km ultramarathon footrace and compared with results for normonatremic runners [NN; $n = 18$, mean postrace plasma sodium concentration, 138.2 ± 1.2 (SE) mM]. Estimated fluid intake during the race for HN was 12.5 ± 1.6 (SE) liters over 9 h 41 min (±28 min). HN excreted a net fluid excess of 2.95 ± 0.56 (range 1.2–5.9) liters compared with a fluid deficit of 2.7 ± 0.3% body weight in NN. The sodium deficit was 153 ± 35 mmol in HN and 187 ± 37 mmol in NN. Despite the fluid overload, plasma volume was decreased by 24.1 ± 5.0% in HN compared with 8.2 ± 2.6% in NN. Serum renin activity (5.1 ± 2.0 $ng \cdot ml^{-1} \cdot h^{-1}$), aldosterone concentrations (410 ± 34 ng/l), creatinine clearances (174.8 ± 28.2 ml/min), and urine output (6.4 ± 1.0 ml/min) were markedly elevated in HN during recovery. Thus the hyponatremia of exercise results from fluid retention in subjects who ingest abnormally large fluid volumes during prolonged exercise.

prolonged exercise; plasma volume; fluid compartments; arginine vasopressin

RECENT REPORTS have described the development of hyponatremia in participants in ultradistance running and triathlon events lasting ≥8 h (5, 8–11, 14, 17, 24–27). The condition, which has also been reported after a shorter 42-km marathon footrace (21, 34), has been associated with life-threatening complications including grand mal seizures resulting from increased intracranial pressure, pulmonary edema, and respiratory arrest (21, 24).

Because the pathogenesis of this condition is not established, its treatment and prevention remain largely empirical. One postulate is that the hyponatremia of exercise is caused by large sweat sodium chloride losses, which are not replaced by athletes who ingest only sodium-free hypotonic solutions during exercise (8–11, 14, 17, 27). Accordingly, this form of hyponatremia would be associated with either a reduced or a normal extracellular fluid volume. Others (5, 21, 24, 34) have proposed that the condition results from fluid retention in athletes who ingest excessive fluid volumes during prolonged exercise. Elevated antidiuretic hormone (ADH) secretion induced by exercise has been suggested to lead to excessive free water retention in these athletes, resulting in hyponatremia and hypotonicity (21). This proposal does not explain why counterregulatory mechanisms fail to prevent the development of hyponatremia.

The most accurate method of determining the pathogenesis of this condition would be to study renal function and fluid and electrolyte balance in athletes as they develop hyponatremia during prolonged exercise. However, the extreme infrequency of the condition [<0.03% of 20,000 ultramarathon runners in 1 study (25)] negates this approach.

Accordingly, we chose the more practical approach in which renal function and fluid and electrolyte balance were studied during recovery in eight runners who developed hyponatremia during and after the 1988 88-km Comrades Marathon footrace, the event in which the condition was first described (24). We reasoned that a study of these parameters during recovery would establish which hypothesis was correct. For comparison, we studied the same variables in a group of normonatremic runners over a similar time period after their ultramarathons.

MATERIAL AND METHODS

All runners who collapsed during or after the 1988 Comrades Marathon (run annually between Durban and Pietermaritzburg, South Africa) had blood drawn for the estimation of serum electrolyte levels and hematocrit by a Novastat Profile 1 analyzer (Nova Biomedical, Waltham, MA). Five of ~300 collapsed runners were found to be hyponatremic (serum sodium levels <130 mM) and were referred, according to a prearranged protocol, to a local hospital for evaluation and treatment. One runner's plasma sodium concentration was initially 132 mM. Her condition deteriorated, and a repeat measurement showed a serum sodium concentration of 128 mM. Accordingly, she was included in the study. Sera

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from these runners were stored frozen at −20°C for subsequent analysis of osmolality and serum creatinine, urea, chloride, total protein, and albumin concentrations by conventional methods. Renin activity was measured by use of a radioenzyme assay (Biodata, Serono, Switzerland) and serum aldosterone concentration by radioimmunoassay (Biodata). Three additional runners admitted themselves directly to the hospital later the same day and were found also to be hyponatremic. They were included in the study and treated according to the predetermined protocol.

The protocol required that the nature and volumes of all fluids administered to the patients intravenously or orally were recorded and that all urine passed was collected and measured. Urine aliquots were retained and stored frozen for subsequent analysis. Blood samples were drawn at regular intervals with minimal stasis while the patients were supine and were analyzed immediately for hematocrit with a model ZF Coulter counter. Plasma and urine electrolytes were determined by use of a flame photometer (Instrumentation Laboratory model 543). Osmolality was measured by depression of freezing point with an automatic osmometer (Gonotec Osmomat 030). Creatinine was determined by the Jaffee reaction measured on an Instrumentation Laboratory model 919 spectrophotometer and chloride by use of CMT10 chloride titrator. Serum albumin and total protein were measured by a Technicon SMAC Auto Analyzer.

During the period of the sodium balance study, the patients received only intravenous fluids of which the sodium content was known. Patients received food by mouth only when their serum sodium concentrations had normalized, at which time their participation in the sodium balance component of the study was terminated.

During hospitalization, a detailed medical and athletic history was taken from each subject. Particular care was taken to determine the volumes of fluid the subjects ingested and urinated during the study as accurately as possible.

As a comparison, and to assist in understanding the similarities and differences between these subjects and runners who did not develop hyponatremia, we include selected data from 18 experienced runners who took part in three ultramarathons, one of which was a previous Comrades Ultramarathon (12, 13). In these runners we measured the same variables over a similar time period.

Calculations. Fluid excess was estimated as the difference between urine output and fluid intake (mainly by intravenous fluid). No account was taken of respiratory and sweat water losses during recovery, even though they can be as high as 50 ml/h (6). Our estimations of fluid excesses, therefore, are conservative. Sodium deficit was estimated as the difference between intravenous sodium intake and urine sodium excretion. The sodium deficit in the normonatremic runners was taken as the difference between the mean 24-h urine sodium excretion during five prerace days and the urine sodium excretion during the 24 h including the race. Although the runners' diets were not controlled during this period, it was assumed that their sodium intakes had not altered.

Percent changes in plasma volume, serum total protein content, and serum albumin content for both hyponatremic and normonatremic runners were calculated according to the formulas of van Beaumont et al. (32).

Free water clearance was calculated as the difference between the osmolal clearance and urine output.

Statistical analyses. Statistical analysis was performed by use of Student's t test for paired data and analysis of variance with Dunnett's post hoc test for unpaired data. Significance was determined at the 0.05 level.

RESULTS

Subject descriptive data. The subjects were four males of mean height 1.80 (range 1.74–1.83) m and mean body weight 78 (range 73–84) kg and four females of mean height 1.58 m (range 1.52–1.64 m) and mean body weight 53.5 (range 50–59) kg. The average age of all the runners was 41 yr (range 35–56 yr). All were experienced long-distance runners who had run 15 ± 7 (SE) marathons and 6 + 2 ultramarathons. Only *subject 4* (Table 1) had not previously run an ultramarathon. Six runners completed the full 88-km distance; *subjects 4* and *7* ran 68 and 61 km, respectively (Table 1). The runners conservatively estimated their fluid intakes at between 0.8 and 1.85 l/h (mean 1.3 ± 0.1 l/h) of a cola-water mixture (sodium concentration 3.4 mM) (24) or a total of 12.5 ± 1.6 liters of fluid and 42.5 ± 5.6 mmol of sodium. The subjects urinated between one and eight times during the race (mean 5 ± 1).

Three of the runners (*subjects 3*, *4*, and *6*) took nonsteroidal anti-inflammatory agents during the race; *subject 7* was on 0.1 mg L-thyroxine sodium salt (Eltroxin) daily for hypothyroidism, and *subject 1* was taking one tablet of Adelphane-Esidrex (reserpine 0.1 mg, dihydralazine SO_4 10 mg, hydrochorothiazide 10 mg; Ciba) daily. None of the subjects consumed caffeine during the study period.

Clinical presentation. Subjects 1–3 developed grand mal convulsions and coma. Symptoms in the remainder of the subjects included weakness, confusion, incoordination, and nausea.

Subject 1 was the most severely affected. He remained in the Intensive Care Unit for 24 h and suffered one episode of respiratory arrest. Pulmonary edema was confirmed radiographically.

All subjects were discharged from the hospital fully recovered within 9–68 h.

Renal function and fluid and electrolyte balance during recovery. During recovery, the results shown by *subjects 1–8*, whose mean plasma sodium concentration at the end of the race was 122.4 ± 2.2 mM, were significantly different from those of runners who were normonatremic at the end of their ultramarathons (n = 18; mean plasma sodium concentration 138.2 ± 1.2 mM).

Table 1 shows that *subjects 1–8* excreted a fluid excess of 2.95 ± 0.56 (range 1.22–5.92) liters during the 15.6 ± 2.1 h of study, and their sodium deficit was 153 ± 35 (range 24–307) mmol. This can be compared with the normonatremic runners, who completed their races in a

TABLE 1. *Fluid and electrolyte balance during recovery from exercise-related hyponatremia*

Subject No.	Duration of Study, h	Total Fluid Intake, ml	Total Urine Output, ml	Fluid Excess, ml	Total Sodium Intake, mmol	Total Sodium Urine Losses, mmol	Total Sodium Deficit, mmol	Postrace Plasma Sodium Concentration, mM
1	27	6,000	10,105	4,105	780	579	201	113
2	19.5 (13.5)	4,100	7,430	3,330	630	323	307	122
3	16 (10)	3,450	9,370	5,920	390	145	245	113
4	9	2,000	3,520	1,520	260	62	198	124
5	12	2,000	3,460	1,460	260	162	98	127
6	11	1,000	3,760	2,760	130	58	72	124
7	18 (12)	1,300	4,610	3,310	130	106	24	128
8	12	1,000	2,220	1,220	130	52	78	128
Mean ± SE	15.6±2.1 (13.1±2.0)	2,606±628	5,559±1057	2,953±563	339±87	186±64	153±35	122.4±2.2

n = 8 runners. *Subjects 1-4* are males and *5-8* are females. Values in parentheses are durations of sodium study when different from fluid study durations.

state of mild dehydration (with a weight loss of 2.08 ± 0.25 kg or 2.7 ± 0.3%) and with a sodium deficit of 187 ± 37 mmol.

Figure 1 compares urine output and creatinine, osmolal, and free water clearance as well as urine osmolality in the two groups during the recovery period (15.6 ± 2.1 h for the hyponatremic runners, 17.7 ± 0.5 h for the normonatremic runners). There are significant differences in all these parameters, with *subjects 1-8* showing greatly increased urine output and creatinine, osmolal, and free water clearances and a decreased osmolality compared with the normonatremic runners.

Figure 2 shows the mean serum sodium, chloride, and potassium concentrations and serum osmolality in the eight subjects when they were first examined (in the medical tent or, in 3 patients, on admission to the hospital) and again on completion of the study (recovery). These results are compared with those from normonatremic runners at the beginning and end of a similar time period. The data from the subjects show that serum sodium and chloride concentrations increase during recovery (from 122.4 ± 2.2 and 85.6 ± 3.2 to 138 ± 0.7 and 104.4 ± 1.8 mM, respectively), whereas serum potassium concentration falls (from 4.0 ± 0.15 to 3.55 ± 0.1 mM). There were no significant differences between the race end and the recovery serum chloride and potassium concentrations in the normonatremic runners. In contrast to the finding in the hyponatremic runners, serum sodium concentrations fell during recovery in normonatremic runners.

Figure 3 shows the mean hematocrit, serum creatinine, and urea concentrations. The hyponatremic subjects were the five runners who were first examined at the finish of their races. The subjects' mean hematocrit decreased from 48.2 ± 0.8 to 41.2 ± 1.6% on recovery, whereas the mean hematocrit of the normonatremic runners decreased from 41.7 ± 1.3 to 39.6 ± 1.0%. The subjects' mean serum creatinine concentration at the end of the race was 89.8 ± 8.3 μM, compared with 104.2 ± 5.6 μM in the normonatremic runners. However, the subjects' serum urea concentration of 5.7 ± 0.8 mM did not differ from the value of 5.7 ± 0.3 mM measured in the normonatremic runners.

Serum renin activity and aldosterone concentrations were measured in the five runners seen immediately after the race. All the runners had elevated serum aldosterone concentrations. The mean serum aldosterone concentration was 410 ± 34 (range 303-507) ng/l. However, only two of the subjects had increased serum renin activities (11.1 and 8.7 $ng \cdot ml^{-1} \cdot h^{-1}$, respectively; mean 5.1 ± 2.0 $ng \cdot ml^{-1} \cdot h^{-1}$).

Figure 4 shows calculated percent changes in plasma volume serum total protein and serum albumin contents in the five subjects who were examined immediately after the race and can be compared with changes in eight runners who remained normonatremic after an ultramarathon.

When data collected during recovery were compared with those collected immediately after the race, the subjects' plasma volumes had decreased by 24.1 ± 5.0% at the end of the race compared with an 8.2 ± 2.6% decrease in the normonatremic runners. Serum total protein and albumin contents were decreased by 11.2 ± 4.5 and 9.6 ± 3.4%, respectively, in the hyponatremic runners compared with 2.8 ± 3.8 and 2.4 ± 3.9%, respectively, in the normonatremic runners.

DISCUSSION

The hyponatremia of exercise is a life-threatening condition (21, 24) the etiology of which has yet to be established. Two conflicting theories are in vogue. Some authors have postulated that this condition is caused by large sweat sodium chloride losses (8-11, 14, 17, 27) often associated with dehydration (9, 11); others have proposed that the condition results from fluid retention after the ingestion of excessively large fluid volumes during prolonged exercise (5, 21, 24, 34).

This study conclusively resolves this issue. It shows that each of eight subjects who collapsed with the hyponatremia of exercise (mean plasma sodium concentration 122.4 ± 2.2 mM) were fluid overloaded by an amount ranging from 1.22 to 5.92 liters (Table 1). These fluid volumes are conservative because no allowance was made for insensible water losses during recovery (6). The subjects conservatively estimated that their fluid intakes during exercise ranged from 0.8 to 1.3 l/h,

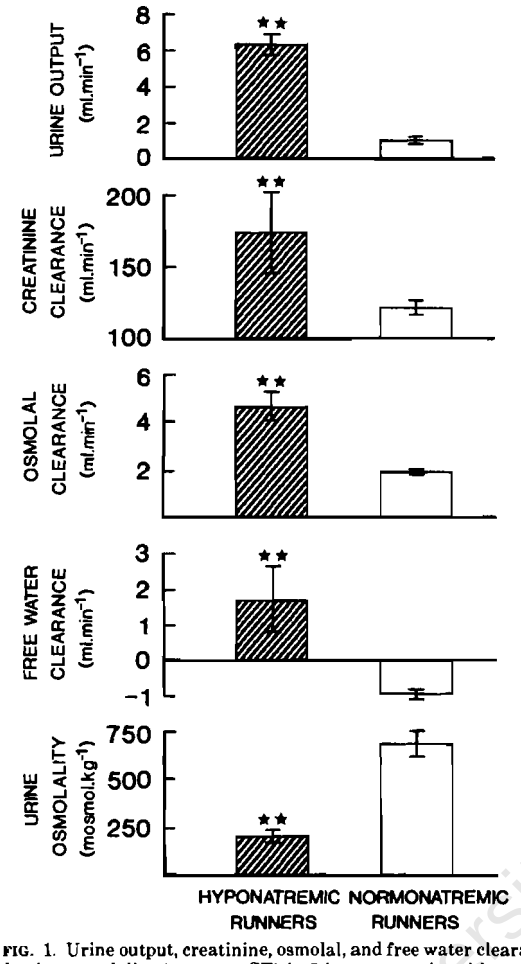

FIG. 1. Urine output, creatinine, osmolal, and free water clearance, and urine osmolality (means ± SE) in 8 hyponatremic subjects over study period. Results are compared with 18 normonatremic runners who were studied over a similar period. $^{**}P < 0.01$ between hyponatremic and normonatremic runners.

compared with maximum values of 0.6 l/h in normonatremic runners (22, 23).

We also found that the subjects' sodium losses (153 ± 35 mmol, Table 1) were not larger than those of runners who maintained normonatremia during exercise. The normonatremic ultramarathon runners lost 183 ± 37 mmol of sodium, whereas other subjects undergoing prolonged exercise in the laboratory have lost 154.8 mmol of sodium in 4.11 liters of sweat (3). Even higher sweat losses (7.7 ± 0.4 liters) have been recorded in normonatremic Comrades Marathon runners (4), suggesting that sodium losses equal to or greater than those measured in the hyponatremic runners in this study may occur commonly in ultramarathon runners without the development of hyponatremia. Thus sodium chloride losses alone cannot explain the hyponatremia of exercise.

Our third finding was that the renal response during the recovery phase in the hyponatremic runners was normal as indicated by the elevated urine output and creatinine clearance. Therefore it would seem unlikely that exercise-induced renal damage prevented the excretion of the excess fluid during the race.

Finally, hyponatremic runners initially showed a large postexercise reduction of up to 24% in plasma volume, compared with normonatremic runners who either maintain (12) or show only a modest reduction in plasma volume (18, 19, 33) during prolonged exercise. Associated with the marked reduction in plasma volume were large reductions in total plasma protein and albumin contents (Fig. 4) and increased serum aldosterone concentration in all runners and increased serum renin activity in two runners; these latter findings provide additional evidence for a reduced plasma volume in these subjects.

Thus we conclude that the hyponatremia found in marathon runners results from excessive fluid retention with only mild sodium chloride losses and with no evidence of exercise-induced renal damage. Renal function during the race was, however, clearly inappropriate, as indicated by the volume of retained fluid. The retained fluid appears to be distributed mainly into the intracellular volume while there is a reduction in plasma volume. Others have also measured elevated hematocrits in

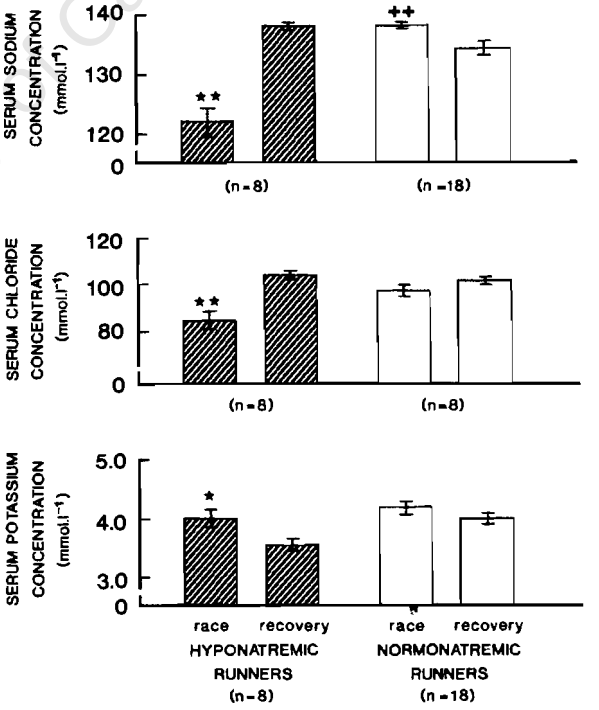

FIG. 2. Serum sodium, chloride, and potassium concentrations (means ± SE) of hyponatremic and normonatremic runners measured at the end of the race in 5 runners, on admission to hospital in another 3, and in all again on recovery. Significantly different between race and recovery in hyponatremic runners: $^{*}P < 0.05$; $^{**}P < 0.01$. $^{\dagger\dagger}P < 0.01$ between race and recovery in normonatremic runners.

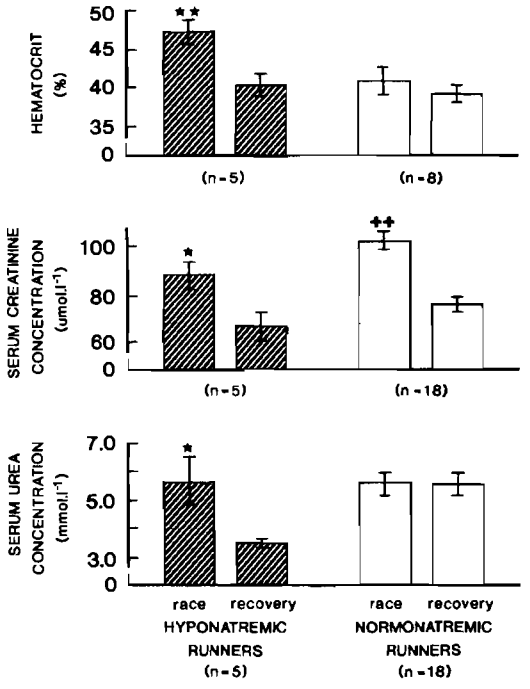

FIG. 3. Hematocrit and serum creatinine and urea concentrations (means ± SE) in hyponatremic subjects examined at the end of the race and again on recovery compared with normonatremic runners over a similar period. Significantly different between race and recovery in hyponatremic runners: $^{*}P < 0.05$; $^{**}P < 0.01$. $\dagger\dagger P < 0.01$ between race and recovery in normonatremic runners.

hyponatremic athletes (27), indicating a reduction in plasma volume.

However, it is unclear why the subjects were unable to excrete the excess water consumed during the race. There are several possibilities.

First, although creatinine clearance was elevated during the recovery stage, during the race glomerular filtration rate (GFR) may have been unusually decreased. Marathon running does not necessarily reduce GFR when this is measured over the duration of a marathon (13), but the renal response of these subjects may have been different. However, the serum creatinine and urea concentrations measured in the subjects after the race were not greater than those in normonatremic runners in this study (Fig. 3) or in other studies (4, 12, 13, 29). A reduced GFR during the race is therefore unlikely.

Second, three of the subjects took nonsteroidal anti-inflammatory agents. These can cause a decrease in renal prostaglandin production, which can lead to a decline in GFR and accentuate the effects of ADH (2). However, there were no significant differences in renal function or fluid balance between this subgroup and the remainder of the hyponatremic subjects.

Third, in normonatremic runners plasma volume usually decreases moderately (18, 19, 33) or not at all (12). Despite gross fluid overload, the subjects in this study failed to maintain a normal plasma volume (Fig. 4). The reduced plasma volume would act as a nonosmotic cause for both increased fluid intake and arginine-vasopressin (ADH) release; the latter would prevent free water clearance, thereby compounding fluid retention in athletes stimulated to ingest hypotonic fluids in excess. That ADH secretion was appropriately suppressed in these subjects during recovery is shown by the positive free water clearance and reduced urine osmolality during recovery (Fig. 1), which is the opposite of the response in normonatremic runners. The time course of this response followed the rapid normalization of hematocrit and therefore presumably of plasma volume within the first few hours of collapse (Fig. 3). It is of interest to speculate why hyponatremic runners were unable to maintain plasma volume during exercise.

The most important variable besides extracellular sodium content that influences plasma fluid shifts during exercise is probably transcapillary colloid osmotic pressure (20, 30, 31). Ingress of protein into the plasma space during exercise acts to maintain plasma volume; thus the reduced plasma volume of hyponatremic runners may have resulted from an inability to mobilize interstitial protein into the vascular space (Fig. 4). Under these conditions the excess volume of ingested fluid would be redistributed mainly into the intracellular but also partially into the interstitial space. An expanded interstitial volume would lead to a further reduction in the protein concentration in this space and in the lymph;

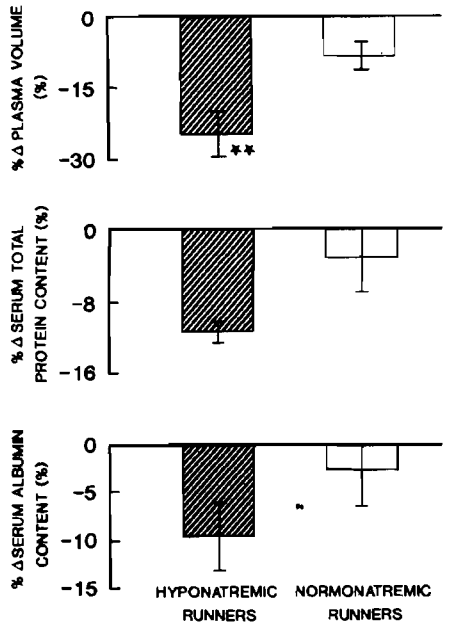

FIG. 4. Calculated percent changes in plasma volume, serum total protein content, and serum albumin content (means ± SE) in 5 hyponatremic and 8 normonatremic runners measured immediately post-trace and during recovery. $^{**}P < 0.01$ between hyponatremic and normonatremic runners.

the latter is believed to be a major source of the intravascular protein influx during exercise (30).

Nonsteroidal anti-inflammatory agents have been shown to increase protein loss from the vascular compartments of exercising subjects (28), and this may have been a factor in the three runners who ingested these drugs during the race. The protein losses in these subjects were, however, no greater than in the other hyponatremic runners.

Atrial natriuretic peptide (ANP) increases during exercise (1) and may be associated with increased urine sodium losses in normal subjects (15). Whether ANP is a factor in the genesis of the hyponatremia of exercise is unknown but would not seem to be of importance in view of the increased serum aldosterone concentrations in the five subjects. The sodium deficits in these subjects would also not seem to have been excessive. ANP may also increase capillary membrane permeability to plasma proteins (16) and may have been a factor in these subjects either because of increased rates of ANP secretion or an increased sensitivity to its actions. Further work is necessary to establish levels of both ADH and ANP in hyponatremic subjects.

The final question that needs to be addressed is why the subjects drank to excess. We suggest that there are both physiological and behavioral reasons for this. On questioning, all the subjects expressed surprise that they had collapsed because they had drunk so much and could therefore not be dehydrated. Paradoxically, the three subjects who developed grand mal convulsions and coma (*subjects 1–3*) reported the highest fluid intakes during the race.

This would seem to confirm that the potential dangers of severe dehydration and the need to drink adequately during prolonged exercise have been so well publicized (23) that, as a result, some individuals may choose to ingest dangerously large fluid volumes during prolonged exercise. In addition, it is possible that, during the later stages of the race, a reduced plasma volume would induce volume-dependent dypsogenic drive, thereby sustaining the high rates of fluid intake.

Finally, despite the moderately low sodium losses in these runners, we would include the hyponatremia of exercise as a form of hyponatremia caused by a low total body sodium content according to the Goldberg classification (7) but would emphasize that, without the excess fluid intake, hyponatremia would not have developed. Empirical evidence suggests that a reasonable intake of fluid while exercising prevents the recurrence of hyponatremia in predisposed subjects (24). Further work is required to determine whether sodium replacement during endurance events will, in addition, assist in the prevention of this condition as has been suggested (9).

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Figure 11

Note that 40oz. of fluid every hour equals a rate of fluid intake of 1200ml/hour.

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Figure 12

Ideas to which runners in the Houston Marathon were exposed prior to January 2003. These statements promote the idea that runners must drink "as much as possible" during exercise. The Houston Marathon has had the highest reported number of cases of hyponatraemic encephalopathy in any athletic event in the world.

2002 Compaq Houston Marathon Medical Report

Research

Research was conducted on a group of approximately 40 runners. The runners were divided into two groups, those that consumed fluids on the course as per usual and those that were given an additional electrolyte supplement to boost their sodium levels. Runners were weighed and had their vital signs check. A small sample of blood was taken from each runner prior to the start of the race. Those receiving the additional fluids were given their first 5-oz. sample at the medical area. Subsequently they were given samples at mile 7, mile 13 and mile 20 for a total of 20 ounces. Afterwards all research subjects reported to the Brown where weight, vital signs and a blood sample were drawn. A two-sided medical questionnaire was filled out regarding their hydration habits on the course. Preliminary inspection of this data reveals that there were no significant differences between the electrolyte levels of those that used typical hydration and those that used the supplemental beverage. Additionally, equal numbers in both groups became clinically hyponatremic. Both groups had several runners that had lower sodiums at the finish than they did at the start indicative of over-hydration.

Based on the data that was collected this year and previous years, it has become very clear to the Medical Committee that hyponatremia is a behavioral phenomena that is almost certainly caused by over-hydration. Climatic conditions will influence the severity of those cases of hyponatremia. Based on our findings, it is recommended that a significant educational effort be utilized to inform runners to hydrate less aggressively while on the course, particularly those that are slower. Additionally, it will be recommended to the Board of Directors of the Marathon that fewer water stations be supplied on the course. One possibility for enactment of this recommendation would be to alternate water stations with power aid stations. This would probably have the effect of reducing the amount of water and/or Power Aid consumed by any one runner during the race. It is thought that this would significantly reduce the incidence of hyponatremia, as has been demonstrated in research done in other races.

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RECOMMENDATIONS

1. **It is recommended that serious consideration be made towards reducing the amount of water and/or Power Aid available on the course. This could significantly improve the safety for runners, particularly in hot weather who have been shown to be regularly over-hydrating. The implementation of this recommendation should be subject to further review and discussion. One possibility would be to alternate water stations with Power Aid stations every other mile.**

2. Consideration be given to the purchase of canopies for every aid station on the course. These ideally would be red and would allow greater visibility for each aid station. Additionally, the use of red t-shirts might be advantageous for all medical volunteers. This would improve visibility of every volunteer and diminish any confusion on the part of runners with respect to medical care.

3. Continue the current layout for the medical area in subsequent years. The flow and setup of this year's medical area was deemed to be optimal. The setup should be accomplished Saturday afternoon after Buildings B and C are set up. The medical area will be contained entirely in the A Building. The use of tables and chairs as well as fencing and drapes will remain as has been in the past years. The use of a larger ICU area should be employed next year to allow for more room in taking care of such patients. Additionally, the purchase of vacutainers to make blood draws and IV starts more efficient.

4. Maintain the current level of security provided by the Houston Police Department. This year's police staff was much improved over the past with respect to vigilance and execution.

5. Medical supplies needed for next year will include additional Mylar blankets and IV fluids. A full review will be done later in 2002 to make complete updates for the 2003 race.

6. Increase the amount of data entry personnel and/or computers utilized within the medical area. If more race casualties are seen, additional staff will need to be utilized to keep up with the input of data to allow adequate tracking of ill runners. This might be best accomplished with the use of additional laptops in the major medical area or with the use of wireless IPAQ-type devices for practitioners in the medical area.

7. Continue using the passes employed this year for the family waiting area. These proved to be a significant improvement over past methods of credentialing for family members.

Hydration 101

brought to you by Gatorade Sports Science Institute®

IMPORTANT FLUID GUIDELINES FROM THE GATORADE SPORTS SCIENCE INSTITUTE®

1. **Drink early and often.** Two hours before a run, drink 16 to 20 ounces of water or sports drink. Take in between 7 and 10 ounces every 10-20 minutes during the run.

2. **Always drink sports drinks on long runs.** Performance is significantly improved when sports drinks are consumed during hour or longer workouts. Easily absorbed carbohydrates provide fuel, while the electrolytes help reduce the risk of muscle cramps, fatigue, and hyponatremia.

3. **Don't wait until you feel thirsty.** You don't often feel thirsty early in a run, but that's exactly when you need to start drinking. Proper hydration helps maintain muscle and skin blood flow, promotes body cooling, and aids in the delivery of carbohydrates and electrolytes.

4. **Rehydrate after the run.** Drink between 20 and 24 ounces of sports drink for every pound of body weight lost during exercise. Calculate your weight loss by weighing yourself before and after exercise.

5. **Beware of hyponatremia.** Hyponatremia, or "water intoxication," could happen during long, hot runs, when a runner loses a lot of sodium through sweat and consumes a great deal of water. This can dilute sodium levels in the blood, causing an electrolyte imbalance.

   Warning signs mimic those of dehydration, including confusion, disorientation, muscle weakness, and vomiting. To help maintain blood sodium levels, consume sports drinks, rather than plain water, on runs over an hour.

BASIC RULES of HYDRATION:

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Figure 14

Advert placed in the June 2002 issue of Runners' World by the Gatorade Sports Science Institute (GSSI). The inference of this advert is that the ingestion of an electrolyte-containing sports drink during exercise can prevent the development of hyponatraemic encephalopathy (in those who overdrink). This inference is not evidence-based.

Figure 15

Advert placed in the July 2002 issue of Runners'World (USA) by the Gatorade Sports Science Institute (GSSI). The advice presented here – ("learn to adjust fluid intake to minimise weight loss") – contradicts the dogmatic advice in Figure 11.

COMMENTARY

Hyponatremia in Distance Athletes

Pulling the IV on the 'Dehydration Myth'

Timothy D. Noakes, MB ChB, MD

The strength of modern medicine is its relentless quest for an elusive perfection. That quest requires that we examine our errors even more closely than our successes. It is for this reason that the case report of Flinn and Sherer ("Seizure After Exercise in the Heat: Recognizing Life-Threatening Hyponatremia," page 61) is so important. For it records a potential tragedy that was prevented by expeditious and appropriate medical care[1]—care that conflicted with popular dogma. The timeworn understanding is that collapse during or after prolonged exercise is caused by heat exhaustion; heat exhaustion is caused by dehydration; both are prevented by inordinate fluid ingestion; and immediate treatment should be intravenous fluids. I have termed this traditional litany the "dehydration myth."[2,3] It has been relentlessly perpetuated, always in the guise of good science.

Drinking (Water) to Death

Flinn and Sherer conclude that their recruit developed the complications of hyponatremia as a result of drinking too much plain water during a series of exercises that included a 10-km hike with an 18-kg pack. He had been actively encouraged by his military leadership to drink water, presumably in copious amounts, to prevent exertional heat injury.

The debate of whether exercisers drink too little, too much, or the correct amount during endurance exercise—and whether such fluid ingestion actually

continued

Photo: © 2000. ALLSPORT

influences the risk of heat injury—has been contested with vigor in the pages of this journal for more than a decade.[3-9] In addition, the journal has previously reported a case of water intoxication in a marathon runner.[10] Despite drinking copiously during and after the race, that runner (whose case was also described in the *American Review of Respiratory Disease*) received 1.5 L of intravenous fluids because "the emergency room physicians assumed that the patient was suffering from volume depletion, as they had observed repeatedly that day in other marathon runners."[11] The illogic in such assumptions has been repeatedly argued.[1-3,9,12-15]

A characteristic of this debate has been the inability of some to comprehend the obvious. Whereas there are no case reports or clinical trials that unambiguously link exercise-induced dehydration with specific, life-threatening, exercise-related disorders,[2,3,13] the evidence that iatrogenic fluid overload can have very serious consequences is absolute and irrefutable. Indeed, there are now at least 21 publications describing the life-threatening consequences of fluid overload in runners,[10,11,16-24] triathletes,[16,25-27] army personnel,[28-30] and even recreational hikers.[31-33] How is it possible that this evidence can be so long ignored and that athletes can continue to be encouraged to "consume the maximum amount that can be tolerated" during exercise,[34] without any cautionary reference whatsoever to the dangers of drinking too much? It is a scientific paradox, for which any logical explanation continues to elude me.

Moderate Dehydration Not Hazardous

Compared with this irresistible proof, the evidence is nonexistent that the modest levels of dehydration in endurance athletes—body mass losses of 2% to 8%[12]—have any health consequences during exercise.[2]

Consider first the definitive series of studies undertaken in the Nevada desert during World War II.[35] There, in one study,[36] groups of army conscripts exercised during the day in desert heat for as long as they could, usually up to 8 hours, without any fluid ingestion whatsoever. During this time they would cover up to 34 km. At the point of fatigue, caused by "dehydration exhaustion," subjects exhibited the following symptoms and signs: They "grew peevish and intractable; others walked in silence and were unresponsive." All developed marked physical fatigue and ultimately became "incapable of even mild physical effort." Yet "there were no obvious aftereffects of dehydration. . . . We do know that man can suffer a water deficit so incapacitating that he can neither walk nor stand; yet he recovers his walking ability within a few minutes of water ingestion, and his feelings of well-being within half an hour or less after he begins drinking. With a meal or two intervening, his recovery is practically complete in 6 to 12 hours."

If these army subjects, who developed levels of dehydration twice as great as those usually measured in modern endurance athletes, were able to recover within minutes of drinking fluids orally, where did the idea arise that much lesser degrees of dehydration are (1) life-threatening and (2) must be treated immediately with intravenous fluids?[8]

The second body of evidence—also conveniently ignored—is that up to 1969, endurance athletes were encouraged *not* to drink during exercise.[2,12] Yet there are almost no documented case reports of complications experienced by these athletes. Thus, the impressively titled review article "Heat Stroke and Hyperthermia in Marathon Runners"[37] mentions only one case of heatstroke in a competitive marathon runner, that of Jim Peters in the 1954 Empire Games Marathon in Vancouver. The reasons other than dehydration that explained Peters' only collapse in a remarkable competitive career have been described.[38] Generations of competitive distance runners were, like Peters, able to set world records at a wide range of running distances without ever consuming anything (let alone maximal quantities) and without apparently suffering life-threatening complications (as is now frequently reported in those who drink too much).

Perpetuated Error

The first error identified by the case reported in this issue may well be the perpetration and perpetuation of the dehydration myth within the United States Army[28,29] (and among other groups) despite an ava-

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lanche of contradictory evidence. So ingrained is this myth that attempts by a local Chicago columnist[39] to warn runners about the dangers of overhydration following the death of a runner in the 1998 Chicago Marathon were met with howls of indignant protests from runners, doctors, and exercise scientists (Eric Zorn, personal communication, October 1999).

I suggest that the resulting desire to administer intravenous fluids to collapsed exercisers, commendably avoided by Flinn and Sherer, has developed because the physiologic term *dehydration* has become established as a specific medical diagnosis encompassing almost any form of collapse in endurance athletes.[2,3] But dehydration is not a diagnosis of a specific medical condition, and there is no proven relationship between dehydration and any condition associated with collapse in distance athletes.[2,3] In my view, intravenous fluids are almost never required in the management of postexercise collapse, for the simple reason that they have no effect on the physiologic abnormality that is most usually present: postural hypotension secondary to peripheral blood pooling and inadequate peripheral vasoconstriction immediately on the cessation of exercise.[3,14,15,40]

Diagnose, Then Treat

To return to the specifics of this case report, two points are of note regarding overall management. First, definitive treatment was not begun until diagnosis was complete. An intravenous line was placed at the field aid station only to provide intravenous access (not to treat a presumed dehydration with rapid infusion of a large volume of fluids), and the blood sodium concentration was measured as an immediate priority. Second, an appropriate treatment algorithm, presented in their figure 1, page 66, was followed.

Diagnosis first. Diagnosis before treatment, in my view, identifies the kernel of solution. These authors avoided the usually uncontrollable urge to treat with intravenous fluids any exerciser admitted to a medical facility regardless of symptoms and clinical signs. Rather, they followed good medical practice, which is to establish a reasonable working diagnosis before initiating any therapy. This practice is especially important if that (unnecessary) therapy can also cause a fatal outcome in an otherwise healthy person.[14]

My colleagues and I have shown that two factors predict the likely diagnosis in exercisers who are admitted to the medical facilities at endurance events.[15,41] The first is whether collapse occurs before the finish of the race or after the athlete completes the event; the second is whether or not the athlete is fully conscious or has an altered level of consciousness, however subtle. Athletes who collapse after finishing the race are almost always fully conscious and are suffering from the sudden onset of postural hypotension, so-called exercise-associated collapse. Formerly, this condition was called heat exhaustion, but that term is inappropriate for reasons previously described.[3,13] The patient described here did not finish the exercise bout; hence, the differential diagnosis excludes exercise-associated collapse,

continued

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Although athletes are often encouraged to consume as much fluid as they can tolerate during exercise, evidence has shown that fluid overload can be life-threatening.

which should be diagnosed only in persons who collapse after finishing the race. As the patient had been exercising in the heat, the moment he lost consciousness, the initial differential diagnosis included hyponatremia, a cerebrovascular accident, and heatstroke, probably in that order. The initial distinction is made by measuring the rectal temperature,[15] as was done in this case. As it was in the normal range of 37°C to 40°C, a diagnosis of heatstroke was excluded. The next most probable diagnosis then becomes the hyponatremia of exercise,[1,15,19] confirmed by prompt measurement of the serum sodium concentration.

Although the authors report that the recruit was alert and oriented when first seen, the mental changes in hyponatremia are subtle. It is improbable that his very low serum sodium concentration (113 mmol/L) did not cause an altered level of consciousness, however elusive. Subtle mental changes without other clinical evidence of a defined medical condition, and with a normal body temperature, must always alert the clinician to a probable diagnosis of hyponatremia[1,15] in anyone who has exercised for a prolonged period with ready access to fluid—especially if the patient has been encouraged to "force fluids" to prevent heat injury.

Rational treatment. For the majority of collapsed athletes, then—ie, those with exercise-associated collapse—the sole treatment required is nursing in the head-down, Trendelenburg position.[15] (See also "A Guide to Treating Ironman Triathletes at the Finish Line," August, page 35.) Since adopting this technique, we have essentially removed the need ever to give intravenous fluids to these athletes, regardless of the intensity or duration of the effort they had sustained. For example, in the recent 226-km Cape Town 2000 Ironman Triathlon, we intensively evaluated in the medical tent at the race finish all the athletes who completed the race. This included 290 triathletes and approximately 100 athletes who had either run the 42-km marathon or who had cycled the 180-km course as individual members of relay teams also participating in the race. It was not necessary to treat any athlete with intravenous fluids, despite the fact that the race was held in midsummer temperatures that approached 30°C at midday, the time the marathon race began. Treatment in the other exercise-related conditions, hyponatremia and heatstroke, is described ably by Flinn and Sherer and elsewhere.[1,3,15,20,24,25,32]

Hyponatremia vs Heat Illness

Regarding the classification of exercise-related collapse, the only very minor quibble I have with Flinn and Sherer is their (albeit updated) definition of heat exhaustion. These authors suggest that heat exhaustion is a form of heatstroke in which there are only minor changes in mental status and function. As this distinction can only be made retrospectively, I would prefer that all patients with an elevated rectal temperature and mental changes at the time of collapse be diagnosed with heatstroke and the severity assigned only when the patient has recovered.

The danger in the novel definition proposed is that subjects with the subtle mental changes characteristic of hyponatremia—which, as this case report shows, can progress to convulsions and coma with frightening rapidity—may be diagnosed as cases of heat exhaustion and treated inappropriately, perhaps with intravenous fluids. Rather, I argue that, if the rectal temperature is not elevated to 40°C *at the time of collapse*, the patient does not have a heat illness, and another cause for collapse must be sought.[3,13,15]

We have found that athletes who are fully conscious, and whose rectal temperatures are below 40°C, do not require active cooling because their body temperatures will normalize without intervention. Nor are their symptoms of collapse caused by their (normally) elevated body temperatures. Rather, they are likely to be suffering from postural hypotension and will recover rapidly when treated in the head-down position.

Introducing a new definition for heat exhaustion can only lead to more confusion and further hamper the general acceptance of a concise and logical approach to the assessment and management of the collapsed exerciser. Mental changes in an exerciser whose rectal temperature is less than 40°C should only be ascribed to a heat injury if hyponatremia and hypoglycemia have been excluded by appropriate blood testing.

Too Much Fluid Can Hurt

To summarize, once the recruit convulsed and lapsed into coma, the most likely diagnosis was the hyponatremia of exercise. Heatstroke was excluded by the expeditious measurement of the rectal temperature, and the correct diagnosis of this case was immediately established by the equally rapid measurement of the serum sodium concentration. The condition

continued

was caused by a fluid intake that was, at the very least, 6.5 L in excess of requirement during 9 hours of moderate military exercises. Such inappropriate fluid replacement was caused by the promotion of the twin dogmas that hold that heatstroke is caused by dehydration,[2,34] and that it is prevented by copious fluid ingestion during exercise.[42] There is no scientific evidence whatsoever for either belief.[2,3,13] Rather, as this recruit and these authors discovered, "Too much fluid can hurt."

It is not a novel observation.[1,16] PSM

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Editor's Notes

The Journal's Role in Helping Change Medical Practice

THE PHYSICIAN AND SPORTSMEDICINE - VOL 29 - NO. 7 - JULY 2001

We place a great deal of faith in the results of experimentation, for it is from research data that medical innovations are born and medical practice is changed. As the volume of biomedical publications continues to increase, it is important to recognize that somewhere, buried in all that information, are studies that represent the seedbeds of change. Filtering through the data requires an understanding of the nature of research and its ability to change practice, but it also requires that we understand what produces resistance to change. New information may be unexpected and alarming. Dogma is a fact of life and of medicine.

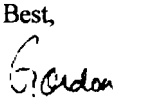
Thomas Kuhn is widely regarded as coining the term "paradigm shift." Kuhn (l) described "revolution" as the abandonment of one theoretical structure and its replacement by another incompatible one. In this way "normal" science (a paradigm) inevitably produces crisis and revolution that leads to "new" normal science (a paradigm shift) and, ultimately, a new crisis. Puzzles that resist solution are seen as anomalies, and failure to solve the puzzle is seen as an inadequacy of the scientist rather than the paradigm. "Normal" scientists must be uncritical of the paradigm so as to concentrate on its detailed articulation and to perform the esoteric work of probing nature in great depth.

One reality is that during the crisis/revolution phase, professional insecurity sets in, followed by a change in professional allegiance. There is then no single reason to abandon a paradigm. Change occurs through persuasion rather than compulsion. A scientific revolution corresponds to the abandonment of one paradigm and the adaptation of a new one, not by an individual scientist but by the relevant scientific community as a whole. Thus, the revolution is only successful if the majority shifts allegiance.

A current sports medicine discussion relevant to science and medicine as a whole concerns fluid balance, dehydration, and hyponatremia during exercise. Last September, Senior Associate Editor Tim Noakes, MBChB, MD, wrote a commentary questioning what he calls the "dehydration myth." His observations elicited a heated response. We present both sides of the issue in our Letters to the Editor department. The emotion that characterizes this debate is complicated by the influence of research supported by the sports drink industry. When an entire industry is based on a single paradigm, additional resistance is encountered. If the medical profession purporting to uphold the virtue of science and its processes benefits substantially from a commercial interest whose desire is to maintain the status quo, then medical science misses its higher calling.

Our role at this stage is not to take sides but to give the debate a forum, which we are in a unique position to do as an independent journal. Many previous dogmas have since been refuted. An example is the change in ideas about gastric ulceration and the effects of bacterial infection (2). Let's not have it said of us in the history books that our reluctance to embrace new information or points of view prevented the advancement of the science of sports medicine, particularly as we go about protecting our beliefs in the very same name of that science. We should embrace discussion in the fullest sense of the word and in the spirit of science in much the same way that Francis Bacon described new knowledge: "Read not to contradict and confute, nor to believe and take for granted, nor to find talk and discourse, but to weigh and consider."

Best,



Gordon O. Matheson, MD, PhD
Editor-in-Chief

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University of Cape Town

LETTERS TO THE EDITOR

Letters to the Editor gives readers a chance to comment on articles we publish and on other issues important to sports medicine practitioners. Illustrative figures are welcome. Send letters to Editor, THE PHYSICIAN AND SPORTSMEDICINE, 4530 W 77th St, Minneapolis, MN 55435; e-mail to psmletters@mcgraw-hill.com.

Hyponatremia or Hype?

We have spent months correcting damage among physicians, athletic trainers, coaches, and athletes done by the article published last year by Dr Noakes on hyponatremia[1] and similar comments by him in the October 2000 *Runner's World*.[2] While the article in THE PHYSICIAN AND SPORTSMEDICINE contains useful information about the potentially serious medical condition of hyponatremia, it contains this inaccurate statement on page 72: "...the evidence is nonexistent that the modest levels of dehydration in endurance athletes—body mass losses of 2% to 8%—have any health consequences during exercise."

It may be true that endurance athletes and other athletes who participate at very low exercise intensities (eg, most of the athletes competing in ultra events) would be at a low risk (but not no risk) of adverse medical effects associated with the stated degrees of dehydration. However, this statement is not true for endurance athletes and other athletes who participate in shorter events where the intensity is great enough to overwhelm the thermoregulatory system, especially in the presence of extreme environmental conditions. Further, 8% dehydration should never be deemed "a modest level of dehydration." When a 200-lb athlete loses 16 lb of sweat, that is a significant or severe level of dehydration.

Noakes' observations of ultramarathoners may exist because dehydration does not affect heat storage and rectal temperature (T_{re}) if the exercise intensity is low. A study by Montain et al[3] demonstrated this fact in healthy males who exercised at 25%, 45%, and 65% of $\dot{V}O_2max$. However, the following physiologic and clinical facts provide strong evidence that the risk and likelihood of serious hyperthermia (above the 39° to 40°C threshold for heatstroke) increases when athletes are dehydrated:

- A high exercise intensity increases heat production and storage in the deep tissues of the body. Thus, runners who run fastest are at greatest risk of hyperthermia.[4-6]
- Exercise in a hot (35°C) versus moderate (22°C) environment can result in a spiraling increase in T_{re} at a running pace of 6.3 min/mile.[4]
- When a small level of dehydration (1% to 1.5%) exists in someone running at moderate-to-strenuous speeds in a very hot (41°C) environment, obvious signs and symptoms of heat exhaustion may occur. These include the presence of flushed skin on the athlete's head and chest, chills, abdominal cramps, piloerection, vomiting, dizziness, and hyperirritability.[7] When more severe dehydration (6% to 8%) exists in someone who runs or cycles in the heat, dizziness, faintness, fatigue, dyspnea, tingling, indistinct speech, headache, and spasticity have been reported.[8]
- During 90 minutes of brisk walking in the heat (33°C), each 1% loss of body weight as sweat may result in a T_{re} increase of 0.4°C versus a similar test with normal body water. At this rate, 8% dehydration would increase T_{re} by 3.2°C and result in frank hyperthermia.[9]
- When 7% dehydration exists, the rate of sweating decreases 25%, and the onset of sweating is delayed.[10,11] Skin blood flow, another avenue of heat dissipation, decreases by more than 50% when 3% dehydration exists during exercise-related heat stress.[12]

Therefore, we conclude that athletes who exercise at high intensities and wear uniforms in hot environments are at great risk for dangerous hyperthermia, especially when dehydrated to 8%. The average person reading Noakes' article, however, could easily conclude that dehydration has no influence on heat storage during any exercise-related heat stress. In fact, one of us (D.J.C.) answered numerous telephone calls from athletic trainers who, after reading this article, questioned time-honored teachings regarding the need for adequate fluid intake.

We believe that the recent position statements by the American College of Sports Medicine[13] and the National Athletic Trainers' Association[14]—which stress the importance of minimizing fluid losses by encouraging fluid replacement that is equal to fluid losses—are better approaches to the issue of dehydration. (We were closely involved with both statements.) If the medical staff advocates individualized rehydration protocols, based on sweat rates, that properly maintain a normal hydration status, the problems associated with improper fluid replacement—such as dehydration and hyponatremia—will be eliminated, or at least dramatically diminished.

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continued

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I am incensed by the article on hyponatremia by Flinn and Sherer[1] and the commentary by Dr Noakes,[2] both of which fail to address the consensus opinions of hyperthermia as relating to dehydration and vascular shifts as outlined by Dr Carl Gisolfi and Dr David Costill. Their extensive and thorough evaluations refute Noakes' hypothesis. Noakes refers to his articles extensively without one reference to opposing views. For Noakes to ignore this literature implies that people treating hyperthermic athletes should ignore the words of Gisolfi and Costill, which is most inappropriate. Also, to state that hypothermia can exist at 102°F but possibly not at 106°F and above is a misstatement of facts.

I am the medical director of one of the top 25 races in the country, the Crim 10-mile Road Race. The race has been run in Flint, Michigan, in August heat and humidity for 24 years without one death from hyperthermic effect. Each year we treat 60 to 150 cases of mild or moderate-to- severe hyperthermia. We have done this on the basis of hydration, and we will continue to do so despite Noakes' comments. In theory, I am familiar with hyponatremia, but hyperthermia should be largely addressed as fluid-volume depletion.

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The articles on hyponatremia by Flinn and Sherer and Noakes bring up a very good clinical reminder not to treat a collapsed athlete automatically with intravenous (IV) fluids. The mechanism for hyponatremia during endurance events has been suggested by these authors and others to be related to overhydration with hypotonic fluids, increasing the loss of sodium through sweating or inappropriate ingestion of sodium during a long distance event.

In my experience and in some brief studies done on ultramarathoners, I have the suspicion that inappropriate ADH (vasopressin) syndrome may be a significant factor to add to the causes of hyponatremia in some of these athletes. It is my feeling that certain susceptible individuals, when subjected to the stress of long distance events, may develop inappropriate ADH clinical syndrome stimulated by the hemodynamics of long endurance activities. We know this can happen in other clinical "stress" situations in susceptible individuals, and I believe it might be associated with some of the case reports we have seen in the literature.

It is not easy to get levels of antidiuretic hormone done inexpensively by a laboratory, but it may be worthwhile in athletes who experience this syndrome to get more data and information regarding this hormonal possibility.

BARRY D. MINK, MD
ASPEN, COLORADO

continued

The recent articles on hyponatremia in THE PHYSICIAN AND SPORTSMEDICINE underscore the attention this topic is receiving—for good reasons.

Overhydration, both orally and IV, with hypotonic (relative to sweat) solutions is being nailed as the culprit in most of these cases, with some individuals reported to have been overhydrated by as much as 6 to 7 L of free water. I am in full agreement with the opinions of Dr Noakes, and others, outlining the absolute importance of confirming the diagnosis prior to treatment. The injudicious use of IV fluids, especially hypotonic (relative to serum) fluids, can only lead to worsening of hyponatremia, if present, with all of its potential consequences.

However, from an initial prevention standpoint, I believe that overhydration with hypotonic (relative to sweat) fluids is not the primary problem. The primary problem is underreplacement of relevant electrolyte at the rate at which they are lost.

Renal physiology is certainly complex, but the human kidney is more than able to excrete plenty of free water, up to 15 L/day, according to most renal physiology texts. Certainly the rate of free water accumulation during endurance events may overwhelm the kidney's ability to excrete it. However, we must also ask what process in the kidneys might lead to water accumulation. The same renal physiology texts tell us that:

- Dehydration triggers ADH release, and this stimulates free water resorption from the kidneys. Dehydration is still the No. 1 concern with exercising in the heat, and much evidence supports the fact that dehydration alters one's ability to manage "internal heat."
- Free water clearance requires adequate serum electrolyte levels, especially sodium. The farther serum sodium levels fall, the more difficult it is for the kidneys to excrete water.
- Dehydration reduces renal perfusion, which drops the glomerular filtration rate.
- In the face of all these physiologic challenges, ingesting hypotonic fluids, typical of many sports drinks and certainly typical of water, results in eventual hyponatremia.

Sodium and fluid are two independently regulated processes. Therefore, if I am losing 1 L/hr of water via sweating, I must replace it *at this rate* for optimal performance (and survival!). If I am losing sweat sodium at 1,000 mg/L of sweat, I must replace it *at this rate*.

Increasing the ingestion of relevant electrolytes includes sodium and potassium, and possibly others like calcium, magnesium, and zinc. The problem of "overhydration" and hyponatremia will certainly be reduced, if not eliminated, if we advise athletes about the importance of electrolyte replacement at the rate at which it is lost.

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I found both articles on hyponatremia of high standard, thought-provoking, and prideworthy. No expert, I have the following observations:

Heat exhaustion (not heat hyperpyrexia) is prevalent in nonacclimatized persons. Acclimatization is a graduated exposure to increasing loads of exertion over a period (typically 3 weeks) under "hot" conditions expected to be encountered at a scheduled event. I believe this allows sweat glands to conserve sodium, thus precluding hyponatremia from drinking water, the most commonly available source.

Further, convulsions are known to occur in the hyponatremic. Trans-urethral removal of the prostate associated with concurrent fluid overload has in fact resulted in just such incidents.

SHYAM M. PATHAK, MD
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DR NOAKES RESPONDS: It is a pleasure to respond to this series of letters, as it allows an opportunity to clarify some important issues. Perhaps there are three reasons for this unnecessary confusion of the relationships between dehydration, fluid replacement, and exercise-related heat illness.

Confounder #1. The first reason is that popular concepts on this topic have changed incrementally over the past 25 years independent, in my view, of sufficient new scientific information to justify some of those changes. For example, during that time, the American College of Sports Medicine (ACSM) has produced four different position stands pertaining to fluid ingestion and the prevention of heat injury during exercise.[1-4] Each is somewhat different, particularly concerning the nature of the claims made for the benefits of such fluid replacement and the volumes of fluid that should be ingested during exercise.

In 1975, the simple advice was that athletes should "be encouraged to frequently ingest fluids during competition."[1] Frequently was considered to be every 3 to 4 km in races

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of 16 km or longer, suggesting that fluid ingestion was of lesser importance in races less than 16 km. This advice was entirely appropriate in 1975 since, for the previous 100 years, athletes had been advised to avoid fluid ingestion during exercise.[1] The rationale for fluid ingestion was to "reduce rectal temperature and prevent dehydration." No specific reference was made to the possibility that fluid ingestion alone would influence the risk of, much less prevent, heat illness during exercise.

The subsequent position stand of 1987[2] introduced two additional statements of relevance to this debate: First, "Fluid consumption before and during the race will reduce the risk of heat injury, *particularly in longer runs such as the marathon* [emphasis added]." [3-8] The three references cited, however, do not support that conclusion because all of them studied only the effects of fluid ingestion on rectal temperature during exercise. None studied the incidence of heat injury in marathon runners, nor the influence of different rates of fluid ingestion on that incidence. So none could conclude that fluid ingestion reduces the risk of heat injury, however defined, in marathon runners. Hence, this position stand, which introduced a fundamentally novel concept not present in the 1975 position statement, was not based on new evidence.

The second statement was: "Such dehydration will subsequently reduce sweating and predispose the runner to hyperthermia, heat stroke, heat exhaustion, and muscle cramps."[9] Nor is this statement evidence-based since the cited reference did not study the incidence of hyperthermia, heatstroke, heat exhaustion, or muscle cramps in marathon runners or the effects of different rates of fluid ingestion on those incidences. Rather, the study reported a relationship between the postexercise rectal temperature and the extent of weight loss in competitors in 32-km running races. The conclusions that have been applied to that study have been criticized in detail elsewhere, including argument that any apparent relationship between weight loss and the postexercise rectal temperature may have been spurious.[3,9] Of interest was the finding that the winners of those races were also the most dehydrated and hyperthermic, a finding at variance with the theory that dehydration impairs athletic performance and increases the risk of heat illness.

The position dtand of 1996[3] proposed that dehydration can "predispose the runner to heat exhaustion or the more dangerous hyperthermia and exertional heatstroke."[10,11] However, this statement is not evidence-based since the two referenced articles are literature that which do not provide any new findings available since the 1987 position stand, which supports the conclusion that dehydrated runners are at increased risk of "dangerous hyperthermia" or heatstroke. Indeed, the 1996 position stand appears to be contradictory since it later states that "excessive hyperthermia may occur in the absence of significant dehydration" especially in short distance races when the rate of heat production is high. That statement *is* evidence-based.

The 1996 position stand also includes the statement, "Adequate fluid consumption before and during the race can reduce the risk of heat illness, including disorientation and irrational behavior, *particularly in longer events such as a marathon* [emphasis added]." [8,9] But the statement is not evidence-based since the same three references from the 1987 position stand are again cited, and none measured the effects of different rates of fluid ingestion on the incidence of heat illness, disorientation, or irrational behavior in any running races, including marathon races. The statement also proposes that athletes should be encouraged to "replace their sweat losses or consume 150 to 300 mL every 15 minutes (600 to 1,200 mL per hour)". No scientific rationale for that proposal is provided.

The position stand also includes the statement, "Intravenous (IV) fluid therapy facilitates rapid recovery [in runners with heat exhaustion]."[12,13] But that statement is also not evidence-based since it cites two review articles that do not contain evidence from controlled clinical trials proving that novel claim.

The related 1996 position stand on exercise and fluid replacement[4] extends these new claims by stating that the "most serious effect of dehydration resulting from the failure to replace fluids during exercise is impaired heat dissipation, which can elevate core temperature to dangerously high levels (ie, >40°C)." Later the statement is made that dehydration during exercise "presents the potential for the development of heat-related disorders ... including the potentially life-threatening heatstroke."[14,15] It is therefore reasonable to surmise that fluid replacement that offsets dehydration and excessive elevation in body heat during

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exercise may be instrumental in reducing the risk of thermal injury."[16]

Once again, these conclusions are not evidence-based, as all the material cited to support these new ideas are review articles that represent the individual beliefs of the authors. Furthermore none, provides specific data showing either that athletes who are dehydrated are at greater risk of heatstroke during exercise or that fluid ingestion during exercise can reduce that risk. My criticisms of the flaws in the paper of Wyndham[15] and the related paper on which it is based,[8] are detailed elsewhere.[5,9]

The position stand on exercise and fluid replacement confirms the belief that the rate of fluid ingestion during exercise should equal the sweat rate and that "fluid and carbohydrate requirements can be met simultaneously by ingesting 600 to 1,200 mL/hr of solutions containing 4% to 8% carbohydrate." In addition, runners are encouraged to "consume the maximal amount that can be tolerated." Although there is substantial evidence supporting the proposal that ingesting carbohydrate at rates of about 60 g/hr can enhance performance during prolonged exercise by preventing hypoglycemia, there is no published evidence to prove that fluid should be ingested at rates equal to sweat rates in order to prevent heat injury.

To summarize, over the course of four revisions, the ACSM position stands have become progressively more strident in promoting the belief that high rates of fluid ingestion during exercise are necessary to prevent heatstroke and other heat illnesses. But this advice is not evidence-based, since none of the Position stands refers to specific prospective studies from which such definite conclusions can be drawn. Furthermore, not even one published cross-sectional study shows that runners with heat illnesses are more dehydrated than are those who do not develop heat injury during exercise.

Hence, the conclusions of the four ACSM position stands are based on a "reasonable-to-surmise" doctrine. Furthermore, they promote high rates of fluid replacement during exercise, sufficient to replace sweat losses (without ever referring to urine losses), but without providing a scientific validation for that conclusion. Again, the doctrine of "potential for prevention" is invoked. The position stands acknowledge that high exercise intensities are more likely to produce heatstroke regardless of the levels of dehydration that develop.

Confounder #2. The second factor that, in my personal view, has increased the confusion of the role of fluid ingestion during exercise, has been the growing academic influence of certain sports-related industries. For the reality is that nothing will convey a message more powerfully than commercial advertising, which is more likely both to reach the athletes and to have a more lasting impression than are the more cautious and less widely distributed statements of the scientists.

For example, Gatorade's Web site repeats one of the key ACSM guidelines: "The goal of fluid replacement during exercise should be to fully replace sweat losses. The physiological and performance benefits of doing so are well documented."[16] Another publication from the Gatorade Institute states, "Dehydration can imperil health by increasing the risk of heat illnesses such as heat exhaustion and heatstroke."[17] The former document[16] also includes a statement that implies that the ACSM guidelines, which specifically promote the ingestion of sports drinks, are the reason why heat injuries have become less common: "Although athletes and others continue to fall prey to exertional heatstroke, the frequency of such deaths has been dramatically reduced over the years,[18] in large part because the necessity of adequate fluid replacement has become well recognized."

This statement can have no factual basis since neither the historical nor the current incidence of heatstroke in "athletes" is known. Nor is this conclusion supported by any specific data in the reference cited.[18] This apparently informed opinion can only entrench the belief—among a much broader audience of athletes and coaches without access to the ACSM position stands—that complete replacement of sweat losses during exercise is essential to avoiding heat injury.

Indeed, as I have argued in the disputed article,[19] the hyponatremia of exercise is always either a self-inflicted, or, less commonly, an iatrogenic condition, that occurs when affected athletes and the physicians who treat them follow this informed opinion to its literal conclusion. I have been unable to understand why the guidelines for fluid replacement during exercise[4] fail to include the warning that drinking too much is dangerous. This is particularly surprising since the most recent position stand[3] includes the statement that: "Excessive consumption of pure water or dilute fluid during ex-

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ercise may lead to a harmful dilutional hyponatremia," but the message is distorted in the position stand on exercise and fluid replacement,[4] which concludes only that "One major rationale for inclusion of sodium in rehydration drinks is to avoid hyponatremia."

A probable result of this subtle distortion is to promote the unproven concept that the ingestion of sports drinks during exercise is more beneficial than water because, unlike water, any sodium-containing fluid ingested during exercise will prevent the development of hyponatremia. In contrast, these position stands should really warn that it is the gross overconsumption of any fluid—even those containing sodium in the relatively low concentrations found in popular sports drinks—that causes hyponatremia.[19-21]

Confounder #3. The final possible reason for confusion is that the diagnostic features of the different exercise-related heat illnesses include just about anything anyone ever wants to include.[22,23] In particular, those with special expertise in laboratory research but who may not treat athletes with heat illnesses describe diagnostic criteria that, in my clinical experience, are not particularly helpful for managing collapsed athletes. For example, in their letter, Drs Casa and Armstrong list what they consider the "obvious signs and symptoms of heat exhaustion." But their "obvious" signs and symptoms are so nonspecific that they are without any clinical value whatsoever. If one were to diagnose heat exhaustion on the basis of their extensive list of nonspecific signs and symptoms, the condition would be overdiagnosed, and conclusions of the effects of fluid ingestion on the incidence of heat exhaustion, so defined, would be quite meaningless. Later in their letter, Casa and Armstrong extend their definition by suggesting that any degree of "heat storage" during exercise should be considered a heat illness.

In contrast, the view of a clinician treating collapsed runners might be that a rise in body temperature to above 40°C during exercise is, by itself, not abnormal since such values are frequently measured in the top finishers.[6,24-26] Furthermore, rectal temperatures in excess of 40oC can be induced quite readily by vigorous running in hot conditions for short durations[26] so that dehydration cannot be a factor.

Thus, unless the core temperature is raised above 40.5 °C and is associated with specific symptoms, most particularly a change in cerebral function that persists when the patient is lying prone with the legs elevated, I would caution that a diagnosis of heat illness, specifically heatstroke, is not appropriate.[22,23] Nor would many who measure rectal temperatures frequently in healthy athletes completing short distance races agree with Casa and Armstrong's suggestion that the threshold for heatstroke is 39° to 40°C. My personal impression is that rectal temperatures become a concern only when they are above 41°C in athletes who exhibit the other diagnostic features of heatstroke.

Because the classically defined symptoms of the so-called heat illnesses are, with the clear exception of heatstroke, nonspecific and are not associated with rectal temperatures even close to those measured in patients with heatstroke,[26] I have proposed that patients with these nonspecific symptoms should not be diagnosed as suffering from "heat" illnesses.[22,23] Rather, any definition should consider that postural hypotension may be the important pathophysiologic abnormality common to all these so-called "heat" illnesses.[23,28,30]

The definition of what exactly constitutes the heat illnesses has been further confused because some physicians who provide medical care at endurance events have not been exposed to the more subtle complexities of the research findings in this field. Rather, they assume that the opinions of the laboratory-based experts are directly applicable to the clinical conditions that they treat, as does Dr Schriner in his letter. As a result, the diagnostic classification of the heat illnesses and the related treatment protocols are seldom challenged by those clinicians who provide medical care at endurance events.

I have been fortunate to experience the three sides of this debate, first as an endurance athlete, next as a clinician, and finally as a laboratory-trained scientist. I began marathon running in 1972 in the era when runners were still being advised *not* to drink during exercise.[5] At that time, watering stations were provided at one or occasionally two points during marathon races, and there were usually no medical facilities to treat collapsed athletes. My first published articles[31-33] emphasized the need to provide more fluid during such races. By 1976, I was involved in the medical care of athletes after marathons and ultramarathons in South Africa. This led, over the next two decades, to a series of stud-

ies[29,31,34-36] of the etiology of postexercise collapse in endurance athletes. These studies have, at least in my biased opinion, helped to develop a rational, more scientifically based approach for the management of collapsed endurance athletes.[23,30,37]

These management principles are followed at the 226-km South African Ironman Triathlon, of which I am currently the medical director. In the inaugural (2000) race, the weights of all competitors were recorded before and after the race, as were their blood sodium concentrations and their postrace rectal temperatures. In addition, all competitors were examined medically after the race to evaluate the efficacy of the preventive measures introduced to safeguard the health of the athletes.

The results suggest that, perhaps because the triathletes were advised to drink no more than between 500 to 800 mL per hour during exercise, the race was one of the safest ironman triathlons on record. The percentage of finishers requiring medical care, all for trivial conditions, was 7%, compared with a more common frequency of 20% to 30% in the Hawaiian[38] and New Zealand[39] ironman triathlons. Furthermore, only 3 triathletes (1%) finished the race with serum sodium concentrations below 135 mmol/L, diagnosed as asymptomatic hyponatremia. This is the lowest reported incidence in any ironman triathlon of which we are aware and compares with values of 29% and 18% in the Hawaiian[40] and New Zealand[39] ironman races, respectively.

I emphasize these points to indicate that I have at least some practical experience about the scientific issues about which I write. I return now to the exact issues raised in the different letters.

What is particularly remarkable about the letter from **Casa and Armstrong** is that, from my entire article, they select just one sentence that they consider inaccurate and have apparently spent months trying to correct. Yet they actually agree with what I have written. To quote: "It may be true that endurance athletes who participate at very low exercise intensities (most of the athletes competing in ultra events) would be at low risk (but not no risk) of adverse medical effects associated with the stated degrees of dehydration".

Their acceptance of the truth of my statement is especially important because Armstrong is listed as one of the principal authors of two ACSM position stands.[3,4] My understanding is that the ACSM position stands focus principally on endurance events, especially races of 10 to 42 km in which the exercise intensity will be lower than in short distance races that last less than 30 minutes, in which significant dehydration is also unlikely so that dehydration cannot be a factor influencing the risk of heat illness. If my arguments are accepted, then future ACSM position statements should acknowledge that dehydration of up to 8% (at least) may have no medical consequences during more prolonged exercise when the exercise intensity is appropriate for the duration of the exercise and the environmental conditions are within those prescribed as of either low or moderate risk according to the ACSM guidelines.[3]

Indeed, I offer data (table 1) that strongly support the correctness of this new interpretation of Drs Casa and Armstrong. These data are from all athletes whose rectal temperatures and body weight changes were measured in the 2000 South African Ironman Triathlon. Table 1 includes data from individual athletes who completed either the running or the cycling legs as part of relay teams, which competed at the same time as individual triathlon competitors.

A total of 201 athletes, to our knowledge the largest such group yet reported, in the different disciplines (triathletes, cyclists, runners) are grouped according to the percentage of weight lost during the race, a surrogate measure of dehydration. Thus, athletes in group 1 lost between 12% and 8% of their starting body weight during the race (mean, -8.4%); group 2 lost from 8% to 4% - (means, -5.0% to -5.6%); and group 3 lost from 4% to 1% (means, -2.8% to -2.6%). Seven triathletes but no cyclists or runners (group 1) reached levels of dehydration in excess of 8%. Yet regardless of their sporting discipline or the level of dehydration during the race, there were no differences in the rectal temperatures measured within 2 to 3 minutes of the athletes' crossing the finish line between group 1, 2, and 3. Indeed, mean rectal temperatures were low in all groups of athletes; the highest value of 40.5°C was measured in the athlete who finished second in the individual triathlon after he had led the race until the last kilometer. That athlete developed profound postural hypotension (85/50 mm Hg) at the finish line but was discharged fully recovered, within 20 minutes of lying supine in the head-down position with appropriate cooling. His data are not included in table 1 as he chose not to participate in the

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TABLE 1. Percentage Weight Change and Postrace Rectal Temperatures in Athletes Competing in the 2000 South African Ironman Triathlon (226 km)

	Dehydration (% of Body Weight)		
	Group 1 (12% - 8%)	Group 2 (8% - 4%)	Group 3 (4% - 1%)
Triathletes			
Mean ± SD	8.4% ± 0.4	5.6% ± 1.1	2.8% ± 0.8
Range	9.0% - 8.1%*	8.0% - 4.0%*	4.0% - 0.2%*
No. of subjects	7	86	55
Cyclists			
Mean ± SD	–	5.4% ± 0.1	2.9% ± 1.1
Range	–	5.5% - 5.2%	3.9% - 1.1%
No. of subjects	–	4	31
Runners			
Mean ± SD	–	5.2% ± 0.9	2.6% ± 1.0
Range	–	6.8% - 4.5%	3.4% - 0.1%
No. of subjects	–	6	12
	Rectal Temperature (°C)		
	Group 1	Group 2	Group 3
Triathletes			
Mean ± SD	37.9° ± 0.3	37.7° ± 1.3	37.9° ± 0.5
Range	37.5° - 38.4°	37.6° - 38.8°	37.0° - 39.9°
No. of subjects	7	86	55
Cyclists			
Mean ± SD	–	37.4° ± 1.0	37.9° ± 0.3
Range	–	35.5° - 38.0°	37.4° - 38.5°
No. of subjects	–	4	31
Runners			
Mean ± SD	–	37.5° ± 0.7	38.1° ± 0.4
Range	–	36.3° - 38.1°	37.5° - 38.8°
No. of subjects	–	6	12

*Group 2 different from group 3; group 1 different from group 3 ($P<0.0001$). SD=standard deviation

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weighing section of the trial.

Hence, whatever the findings in the laboratory, in cross-sectional studies in actual competition, there is no relationship between the level of dehydration reached during the race and postrace rectal temperature. This confirms our previous conclusion from earlier field studies[25,26] involving many fewer athletes. In fact, the rectal temperatures reached by even the most dehydrated triathletes, runners, and cyclists were no higher than those of the least dehydrated athletes despite the fact that, in each sporting discipline, the most dehydrated group finished the race faster than those who were less dehydrated (data not shown). The finding that the more dehydrated athletes are also the faster finishers is frequently observed. Nor were postexercise rectal temperatures anywhere near the range that might suggest risk of heatstroke as also found, but not recognized, in the study of Wyndham and Strydom.[8,15]

Thus, these data do not support the conclusion, now also included in

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the recent position statement of the National Athletic Trainers' Association, that all athletes involved in prolonged exercise should, or need to, "minimize fluid losses by encouraging fluid replacement equal to fluid losses." This may indeed by a "time-honored" dogma, but it has no scientific basis—at least if it is advocated on the grounds that this practice is necessary to prevent hyperthermia, heatstroke, or exercise-associated collapse during prolonged exercise, including marathons and ironman triathlons, run at usual intensities and in the environmental conditions considered safe according to the ACSM guidelines. I submit that, if we wish to ensure that ACSM position stands do no harm, then the authors of future position stands should, at the outset, ensure that their conclusions are first evidence-based. Then, if they become time-honored, they are at least more likely also to be correct.

The gist of Casa and Armstrong's criticism is that my conclusions, here confirmed (see table 1), are not relevant to higher exercise intensities or when the exercise is undertaken in severe environmental conditions, "where the intensity is great enough to overwhelm the thermoregulatory system," especially if the efficiency of that system is impaired by what they consider are the detrimental effects of dehydration. These specified conditions—high-intensity exercise of short duration in extremely hot environmental conditions—are, of course, precisely opposite to those favoring the development of hyponatremia, which was the focus of the original article.[1]

But to "prove" that my conclusions are "damaging" if applied to events of short distance and high intensity, they are forced to introduce two variables that have no relevance in the real sporting world and that destroy their argument, thereby nullifying their criticisms.

First, they argue that laboratory-based studies prove that high levels of dehydration are dangerous during exercise in extreme environmental conditions. The specific environmental temperatures needed to prove this effect in two separate studies were 35°C and 42°C. But the ACSM guidelines do not condone competitive exercise under such conditions. Rather, the guidelines indicate that the risk of heat injury would be "very high"[1] at a dry-bulb temperature of 42oC, even when the relative humidity is only 15%. Similarly at any humidity greater than 50%, a dry-bulb temperature of 35°C would also constitute "very high" risk.

Hence, Casa and Armstrong are guilty of trailing a red herring by quoting those laboratory studies as their "proof" that dehydration increases the risk of heatstroke during exercise—for the simple reason that athletes should never be allowed to compete under those extreme environmental conditions without the potential risk of legal consequences. I assume that Casa and Armstrong do not wish to promote participation in exercise under conditions that are unacceptable to the guidelines established by a committee of which Armstrong was a member. What their diversionary argument effectively confirms is that it is the environmental conditions, not the level of dehydration, that determine the risk of heat injury during exercise.

The second reason why the criticism of Casa and Armstrong has no practical validity is because, although they now acknowledge that levels of dehydration of up to 8% are not associated with documented medical risks during prolonged exercise, they argue that those levels of dehydration would be of dire consequence during exercise when the exercise intensity is "great." But the practical relevance of that claim completely escapes me. For example, a 70-kg athlete could only become 8% dehydrated if he were to exercise in usual environmental conditions at a sufficiently high intensity to sustain a sweat rate of 1.6 L/hr while ingesting no fluid for at least 3.5 hours. None of the runners or cyclists in the South African Ironman Triathlon was able to reach levels of dehydration of 8%, for example, despite exercising for up to 6 hours, although some of the faster triathletes achieved that level (see table 1).

I doubt that there is any athlete in the world able to sustain a "great" exercise intensity for 3.5 hours (and without drinking) in order to reach the point where his or her level of dehydration would be sufficient to place the athlete at theoretical risk of heatstroke. Surely after the 3.5 hours of exercise necessary to introduce a "significant" or "severe" level of dehydration, his or her previously "great" exercise intensity would have dropped to approximate that of the athletes reported in table 1 and in whom no "dangerous" effects of severe levels of dehydration were apparent, since postrace rectal temperatures were independent of the level of dehydration. ▪

Their additional statement that "athletes who exercise at high intensities and wear uniforms in hot environments are at great risk for dan-

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gerous hyperthermia" is obvious. Whether being dehydrated to "-8%" alters that risk is not established but is irrelevant for the very reasons detailed above. The danger in those circumstances is posed by the environmental conditions and the clothing that is worn, not by the extent of any dehydration. Prevention of risk requires that the exercise and the clothing, not the dehydration, be avoided until more usual environmental conditions again prevail.

Casa and Armstrong are also guilty of incorrect and selective quotation from the classic studies of Adolph, cited in Brown.[41] They use that reference to support their argument that "someone who runs or cycles in the heat" at "a larger dehydration level" will develop the nonspecific symptoms of heat illness that they list. However, Adolph did not study cyclists and runners but army personnel who walked for 8 or more hours in desert heat while they were denied access to fluid.[8] Furthermore, there were two important features of that study that are never quoted because they are so detrimental to the argument that dehydration is especially dangerous because it increases the risk specifically of heatstroke during prolonged exercise.

First, the common physiologic abnormality that the subjects developed was not hyperthermia, but postural hypotension. Rectal temperatures at exhaustion were seldom higher than those we measured in our healthy triathletes at the completion of the Ironman (see table 1). The other signs and symptoms listed by Casa and Armstrong are nonspecific and by themselves would not explain the physical incapacitation of the military personnel when they became dehydrated by more than 8%.

Second, the really telling conclusion from that study and one that can never be quoted because it makes a mockery of the entire argument that "significant" dehydration carries grave health risks, was that "there were no obvious after effects of dehydration.... We do know that man can suffer a water deficit so incapacitating that he can neither walk nor stand; yet he recovers quickly within a few minutes of water ingestion, and his feelings of well-being within half an hour or less after he begins drinking. With a meal or two intervening, his recovery is practically complete in 6 to 12 hours."[42]

A final comment regarding that letter is appropriate. I have considered why carefully conducted laboratory studies by expert scientists consistently show that the rectal temperature rises in proportion to the degree of dehydration[7,43-45] during exercise in the heat, yet as shown in our other studies[25,28] and confirmed in the data presented in table 1, no such relation is found in field studies.

One key difference is that rates of body cooling by convection may be different in laboratory studies and field trials performed out of doors. In addition, most of those laboratory studies were performed in environmental conditions that would be rated "high risk" by the ACSM guidelines.

For example, the facing wind speed, the main determinant of convective heat loss, in those four laboratory studies was either 0.3 km/hr,[7] 3.6 km/hr,[45] 5.7 km/hr,[43] or 9 km/hr,[44] and it is not clear whether such cooling affected the whole body. All of these are well below the wind speeds generated by athletes, especially cyclists, exercising at the "great" intensities necessary to cause heat injury according to the theory of Casa and Armstrong. Furthermore it is known that convective heat loss increases with increasing wind speed.[46] Thus, the convective cooling provided in those laboratory studies was less than that found in usual exercise conditions and would have substantially affected the athlete's ability to lose heat normally.

Furthermore, the environmental conditions present in the two studies that most clearly establish a proportional effect of dehydration on the elevation of rectal temperature were performed in environmental conditions (33°C, humidity 50%[44] and 33°C, humidity 64%[45]) that constitute "borderline very high" and "very high" risk, respectively, of heat injury, according to the ACSM guidelines.[3] Exercise physiologists are welcome to study physiologic phenomena under environmental conditions in the laboratory that have little practical application to competitive sport. But they should exhibit sufficient clinical judgment not to extrapolate their data to the quite different environmental conditions under which competitive sport can be safely conducted.[3]

Hence, it makes no sense to quote these studies as proof of the "dangers" of dehydration when they were performed under the very environmental conditions that the ACSM guidelines describe as unsafe for competitive sport. Surely there should be a consistency of logic in the pronouncements of the ACSM?

Perhaps these criticisms explain why, when exercise is performed

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under more usual, competitively safe environmental conditions in the laboratory (25°C, relative humidity 55%, and facing wind speed 13 to 15 km/hr in a properly constructed wind tunnel so that the athlete's entire body was subject to rapidly moving air), drinking fluid according to the ACSM guidelines did not offer any performance advantages over ad libitum ingestion.[47] Rectal temperatures were not measured because the emphasis in that trial was on athletic performance. Indeed, two other studies[48,49] have failed to show that high rates of fluid ingestion during exercise are better than "ad libitum" intakes or those that either replace sweat rates or are "as much as can be tolerated."[4]

Dr Schriner is quite at liberty to be incensed by my article, but he should be wary lest his hostility affect his scientific and clinical judgment. Points that might assuage his anger include the following:

First, I suspect that Drs Costill and Gisolfi seldom ventured near medical tents at the finish of sporting events and most certainly were not qualified to treat patients with heatstroke in those medical tents. I am unaware of any of their "consensus opinions of hyperthermia as relating to dehydration and vascular shifts," nor of any of their articles referring to the management of heatstroke. It is for this reason that I was unable to quote their (nonexistent) studies.

As indicated earlier in this article, the scientific contributions of Costill and Gisolfi that are quoted in the ACSM position stands were laboratory-based and showed only that ingesting fluid during prolonged exercise in hot conditions in which convective cooling was inadequate caused the rectal temperature to be reduced by about 0.7oC during 2 hours of exercise.[7,43] Mean rectal temperatures at the termination of exercise were below 40 °C in both studies; no athletes developed any medical complaints during exercise regardless of whether or not they ingested fluids. I was unable to find reference to the words "heat injury, heat cramps, or heatstroke" in either article. Therefore it is not clear to me exactly how these studies relate to the prevention or management of heatstroke in competitive athletes racing out of doors. Nor were the studies ever designed to measure the effects of fluid ingestion on the incidence of heat injury.

Had I been able to find any studies that established that connection, I am sure I would have quoted those studies and any others that contest my previous conclusion.[3] However, as detailed above, there are no such studies, so the ACSM guidelines—at least as they relate to fluid ingestion and the prevention of heat injury in runners competing in usual environmental conditions—are not evidence-based.

Second, Schriner is at liberty to treat heatstroke as a "fluid volume depletion" condition, but he must do so at both his own risk and that of his patients. The work of Costill and Gisolfi—however certain he may be of their findings—will provide him no legal comfort should he require it because their work has no bearing whatsoever on the treatment of heatstroke. Perhaps he would be better advised to follow the ACSM guidelines[1] and others[22] that advocate rapid whole-body cooling as the treatment of choice in heatstoke. Interestingly, the ACSM guidelines are silent on the role of IV fluids in the management of heatstroke, which is particularly surprising if dehydration is considered to be such an important cause of heatstroke.

Dr Mink is correct that the physiologic abnormality causing the hyponatremia of exercise is an inadequate renal response to high rates of fluid ingestion during very prolonged exercise, leading to fluid retention.[1,20,39] Indeed, the remarkable finding is the inability of affected athletes to excrete what in some is a massive fluid overload of up to 6 L (8% of body weight).[50] Their inability to excrete this fluid excess continues for some hours after exercise. The logical conclusion is that there must be an inappropriate secretion of hormones that prevents the normal renal response to fluid overload.

We suspect that this is indeed due to a circulating factor, the blood concentrations of which must decay quite slowly after exercise. Our clinical experience is that patients with this condition pass urine relatively slowly for the first few hours after exercise, and even their peak rates of diuresis during recovery are likely to be less than 600 mL/hr. In contrast, when tested under resting conditions, athletes with a history of exercise-related hyponatremia can reach peak rates of diuresis of up to 900 mL/hr in response to lesser degrees of fluid overload.[51] But plasma ADH concentrations have not been shown to be elevated in athletes with the hyponatremia of exercise.[44,52] Hence, we propose that the most likely explanation is that another hormone or hormones—perhaps as yet unidentified or when acting in concert—cause the abnormal renal response that leads to the

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abnormal fluid retention that causes the hyponatremia of exercise.

Perhaps the important clinical point is that, whereas at rest athletes can maintain normal fluid balance provided that their fluid intake is less than 900 mL/hr,[51] during exercise the peak rates of urine production fall in some individuals. If they then ingest fluid at rates that exceed their combined rates of sweat and urine production, they will develop symptomatic hyponatremia if their total fluid excess exceeds about 4% of body weight.

Dr Stoddard argues the popular belief that it is the failure to replace sodium losses, rather than fluid overload, that causes the hyponatremia of exercise. The ambiguity in the ACSM position stand,[4] described above, contributes to that incorrect conclusion.

In fact, all the scientific evidence suggests that sodium losses are not increased in athletes who develop symptomatic hyponatremia during exercise.[50,52] With regard to sodium replacement during exercise, there appears to be little benefit if only half of the fluid loss is replaced,[53] as is the usual practice. If there is full fluid replacement during exercise, partial sodium replacement reduces the extent, but does not completely prevent a fall, in the serum sodium concentration during exercise.[54] Furthermore in that study, the extent of the diuresis produced by high rates of fluid ingestion during exercise was the best (inverse) predictor of the extent to which the serum sodium concentration fell during exercise, and not the relatively small amounts of sodium ingested from the sports drink. Unfortunately, this important distinction was not reflected in the title of that article,[54] which continues to reflect the bias of the ACSM position stand.[4] Hence, it is the ability to mount an appropriate diuretic response in the face of a high rate of fluid intake that protects against hyponatremia.

But if there is full replacement of both sodium and water losses during exercise, the serum sodium concentration increases and the plasma volume expands.[55] As yet there are no studies of full sodium replacement with excessive fluid replacement; therefore, the possible role of full sodium replacement in the prevention of hyponatremia due to fluid overload is not established, despite the misleading inference in the ACSM position stand on exercise and fluid replacement, described earlier.

However, subjects in the South African Ironman Triathlon who ingested sodium in quantities approximating their losses generally reported positive effects. Thus, the ingestion of higher doses of sodium, especially during very prolonged exercise, may yet prove to be of some benefit even if not through purely physiologic effects on fluid and sodium balance. We are actively studying this possibility.

Stoddard repeats the popular belief that dehydration is still the "No. 1" concern during exercise in the heat and that dehydration alters the body's ability to maintain heat balance. The contrary evidence has been presented at the beginning of this response, including the data reported in table 1. Rather, the clear evidence is that fluid overload is the real potential killer in modern endurance sports.[20,21] For example, Speedy et al[21] have reviewed 57 cases of exercise-associated hyponatremia reported in the medical literature since 1985. These do not include at least 3 more recent fatal cases.[56-60] I have been unable to locate, anywhere in the published scientific literature, a similar body of evidence showing a greater number of equally serious cases resulting solely from "dehydration" during the same period of observation.

On behalf of all the authors, I thank **Dr Pathak** for his complimentary comments. Certainly, lack of preacclimatization to heat is recognized as an important risk factor for heatstroke and is so identified in the ACSM position statements.[2,3] Such preacclimatization does indeed reduce sodium losses in sweat and would therefore theoretically influence the risk of developing hyponatremia during exercise. However, the evidence is that the hyponatremia of exercise is due to fluid overload rather than sodium losses, so that any effect of acclimatization on sodium losses during exercise would not likely prevent hyponatremia in athletes who chose to follow inappropriate guidelines and to drink to excess during prolonged exercise.

Pathak's point that hyponatremic convulsions are well recognized in medical conditions associated with fluid overload is well taken. Two points are relevant. First, that high rates of IV fluid therapy are sometimes given to patients undergoing certain surgical conditions in the belief that such fluid assists in the maintenance of cardiac function and systolic blood pressure. The same logic explains why IV fluids were introduced early as the treatment of choice for the management of postexercise collapse.[61] Yet it is the

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reduced peripheral vascular resistance, rather than an impaired cardiac filling secondary to fluid loss, that more probably explains the hypotension in both conditions. Hence, the more logical medical intervention in both conditions should be to offset the cardiovascular effects of reduced peripheral vascular resistance.

Second, perhaps if urologists had been involved in the early management of cases of postexercise collapse, including those due to symptomatic hyponatremia, they would have alerted sports physicians earlier to the dangers[19] of giving IV fluids to collapsed or unconscious patients whose serum sodium concentrations are not known. RBM

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EDITORIAL

EDITORIAL

RUNNING, THE KIDNEYS AND DRINKING TOO MUCH — THE HYPONATRAEMIA OF EXERCISE

Dehydration, you will have been taught, is the single greatest danger to the health of the exercising athlete[1-4] — except for the minor intellectual inconvenience that there is no scientific basis whatsoever to support this universally pervasive dogma.[5,6] Rather, the unambiguous evidence is that drinking too much during exercise, leading to self-induced water intoxication (the symptomatic hyponatraemia of exercise), has become the greater threat to the health of modern athletes during prolonged exercise.[7]

In the past 15 years at least 70 cases[8-11] of significant illness including disorientation, grand mal epileptic seizures, coma, respiratory arrest and even deaths[12-14] have been described in ultra-distance triathletes and runners, army recruits and even desert hikers who drank too much during or after prolonged exercise. This includes perhaps as many as four deaths, some of which may have been iatrogenic since the usual history of this condition is spontaneous recovery if the existing fluid overload is not compounded by the administration of large volumes of intravenous fluids. Such deaths are especially sad since they involve physically fit individuals who not only began exercise without significant illness, but who often epitomised consummate 21st-century good health.

In contrast to the hyponatraemia of exercise, other complications of exercise including heatstroke and acute renal failure are reported far less frequently, and then usually in persons with other predisposing medical conditions or traits.[15,16] Nor is there any reputable scientific evidence to even suggest that fluid imbalance, specifically dehydration, contributes meaningfully to the cause of these latter conditions.[5,6,17]

The first reported modern case of the hyponatraemia of exercise occurred in a 46-year-old 49 kg woman competing in the 1981 90 km Comrades Marathon.[18] After running 70 km, she was removed from the race by her husband on the grounds that she had not recognised him! It was the correct decision, for on their return drive to Durban she suffered a grand mal seizure. On hospital admission this lady, who less than 10 hours earlier had been fit enough to start one of the most challenging ultra-distance footraces in the world, a right she had earned because she was appropriately trained and in perfect health, was close to death. She was in a coma, with marked pulmonary oedema, radiographic evidence of cardiomegaly, and a serum sodium concentration of 115 mmol/l. Treated appropriately with fluid restriction, promotion of diuresis and sodium supplementation, she recovered fully and was released from hospital 6 days later.

The earliest reports of the hyponatraemia of exercise speculated that it occurred in athletes who sustained inappropriately high rates of fluid ingestion for many (< 7) hours during prolonged exercise.[18,19] But a contemporary and unfortunately titled article suggested the reverse — that the hyponatraemia of exercise was caused by dehydration[20] and hence occurred in those who drank too little during exercise. This speculation was published in a peer-reviewed journal even though the article did not include measurements of changes in whole-body fluid balance during exercise in athletes who developed the hyponatraemia of exercise. More than a decade later, review articles published even as recently as this year continue to quote that article as evidence that the hyponatraemia of exercise can occur in those who drink too little during prolonged exercise.[21]

This particular controversy should have been laid to rest 10 years ago when another South African study[22] established that eight comatose and desperately ill Comrades Marathon runners with symptomatic hyponatraemia were all suffering from profound fluid overload. In addition, there was no evidence that abnormal losses of sodium in their sweat and urine had contributed significantly to their hyponatraemia. Since then, a series of additional studies[8,10] confirm that patients with the symptomatic hyponatraemia of exercise, and whose serum sodium concentrations are less than 129 mmol/l, all have a whole-body fluid excess of at least 2 - 3 litres and sometimes up to 6 litres. The suspicion exists that the main reason why this now incontrovertible conclusion has yet to be enthusiastically embraced, especially in the USA, is because it conflicts with commercial interests based on the deceptive paradigm that the unrestricted consumption of sports drinks under all circumstances is uniquely beneficial and scientifically proven.[23]

Importantly, these studies of the hyponatraemia of exercise also show that it takes a fluid excess of as little as 2 - 3 litres to produce significant illness, including the risk of mortality, whereas we frequently measure body weight losses of up to 8 kg in top finishers in the South African Ironman Triathlon who are outwardly completely asymptomatic and without any clinical evidence that such high levels of dehydration carry any risks whatsoever (K Sharwood *et al.* — manuscript in preparation).

However, if whole-body fluid content can rise dangerously during prolonged exercise, then the physiological question requiring attention is how this occurs. The logical assumption is that inappropriate secretion of the water-conserving hormone, antidiuretic hormone (ADH), must be involved. But why should the secretion of ADH, the hormone of water lack, be increased when the body has fluid in abundance? In fact there is no evidence that increased serum ADH activity plays

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any role in this condition.[10] Yet the clear clinical observation is that the return of adequate diuresis in patients who are profoundly fluid-overloaded occurs only many hours after the termination of exercise, suggesting the presence of a circulating antidiuretic factor other than ADH.

The other possibility is that the healthy kidneys have a limited capacity to excrete fluid that accumulates in the body at a rapid rate. Textbooks of renal physiology state that the maximum daily rate of urine production is about 24 l/day (1 l/h),[24] but this conclusion appears to be rooted in theoretical, albeit probably correct, calculations based on the known maximum rates of glomerular filtration and renal tubular function, and not on directly measured values.

As reported in this issue of the *Journal* (p. 852), we have established a model of fluid overload at rest specifically to determine the most likely mechanism by which such fluid overload induces hyponatraemia. The study establishes that the human capacity for intestinal fluid absorption may exceed a maximal capacity for renal free water clearance that appears to be about 900 ml/h. Hence when fluid is ingested at rates higher than about 900 ml/h, the total body water must expand and tissue osmolality must fall, leading to a generalised whole-body oedema, the most dangerous component of which is a potentially fatal cerebral oedema.

Hence this study provides the physiological explanation as to why it is never safe to consume fluid without restriction or 'the maximum amount that can be tolerated' according to the American College of Sports Medicine fluid replacement guidelines for exercise.[3,4] The simple reason is that the kidneys do not have an infinite capacity to prevent a fluid excess when exogenous fluid enters the body at high rates (in excess of 1 l/h) through either the gut or the veins.

This study will have been even more helpful if it draws attention to the widespread ignorance of the potentially mortal complications of the condition of water intoxication that is neither benign nor uncommon during prolonged exercise.[9,10] It exists because of: (*i*) a fallacious dogma which holds that even mild dehydration during exercise will have potentially catastrophic consequences — what has been termed the 'dehydration myth';[5,6] (*ii*) the resulting hysteria that dehydration must therefore be prevented at all costs;[4] and (*iii*) our confirmation that the kidney, like the gut, has an 'enough but not too much' capacity.[25]

Often it is only when humans adopt bizarre behaviour patterns, in this case aided and abetted by a science gone mad,[7,8] that these apparent limitations in human design become apparent.

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Hyponatremia in Distance Runners: Fluid and Sodium Balance During Exercise

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Since its first description in 1985, two opposing theories have evolved to explain the etiology of symptomatic hyponatremia of exercise. The first holds that the condition occurs only in athletes who lose both water and sodium during exercise, and fail to fully replace their sodium losses. The second theory holds that the symptomatic form of this condition occurs in athletes who generate a whole body fluid overload as a result of an excessive fluid intake during prolonged exercise. It is argued that the promotion of the idea that athletes should drink as much as possible during exercise has produced, rather than prevented, the recent increase in the incidence of this condition. A series of case reports and laboratory studies reported in the past 2 years have established that it is a whole body fluid overload, resulting from sustained high rates of fluid intake, that causes the symptomatic hyponatremia of exercise. There is no evidence that, in the absence of fluid overload, the usual sodium deficits generated during exercise can cause this condition. These findings confirm that the potentially fatal condition of symptomatic hyponatremia would be eliminated from sport immediately if all athletes were advised of the dangers of ingesting as much fluid as possible during any exercise that lasts more than 4 hours.

Introduction

The symptomatic hyponatremia of exercise

The symptomatic hyponatremia of exercise, described as a clinical condition in which altered cerebral function is associated with very low serum sodium concentrations, usually below 127 $mmol.L^{-1}$, was first reported in the modern literature in a 46-year-old woman of 49 kg who developed the condition during the 1981 90-km Comrades Marathon foot race between Pietermaritzburg and Durban, South Africa [1]. The condition became more prevalent in the 1980s, especially in those ultra distance (> 42 km) running and 226-km Ironman Triathlon events, which usually require more than 9 to 11 hours to complete [2]. But in the past 10 years, almost exclusively in the United States, there has been a dramatic increase in the prevalence of this condition in the military [3,4,5•,6], in runners who take 5 or more hours to complete standard 42-km marathon races because they run at speeds slower than 9 km/h [7••,8••], and in recreational hikers, often when walking in the desert [9,10]. Despite nearly two decades of research, consensus has yet to be reached on three questions that must be satisfactorily answered if the further progression of this epidemic is to be halted and further deaths are to be avoided [3,4,7••,11,12]. These core questions are as follows: 1) What causes this condition? In particular, what are the relative roles of abnormalities in either sodium or fluid balance, or both? 2) What is the optimum form of treatment for this condition? 3) Why has the hyponatremia of exercise become more common, especially in standard 42-km marathon races run in the United States in the past 5 years [7••,8••], as well as in the US Military between 1989 and 1999 [3–6], but apparently nowhere else?

A number of publications have now established, beyond any doubt in my view, the exact etiology of this condition: that it had already been correctly deduced in the very first case reports in 1985 [1] and 1986 [13], and subsequently confirmed more than a decade ago in a fluid balance study performed on ultra-marathon runners as they recovered from symptomatic hyponatremia [14]. Until recently, these findings had been ignored. Scientific evidence now exists which supports the appropriate answers to core questions 1 and 3.

What Physiologic Changes Cause the Hyponatremia of Exercise?

Much of the confusion concerning the etiology of the hyponatremia of exercise may arise from uncertainties about the precise condition being described.

The original reports of the hyponatremia of exercise described a clinical condition readily recognizable by

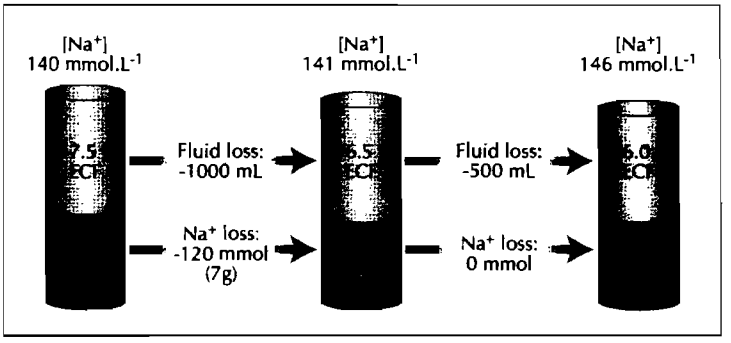

Figure 1. Hypernatremia develops when both sodium and fluid are lost in sweat; the loss of 120 mmol of sodium and 1 L of fluid from the extracellular fluid (ECF), corresponding to a fluid loss of 3 L from the total body water, will cause the serum sodium concentration to rise to 141 $mmol.l^{-1}$. If the ECF volume decreases by 1.5 liters rather than 1 L, the serum sodium concentration will rise to 146 $mmol.L^{-1}$.

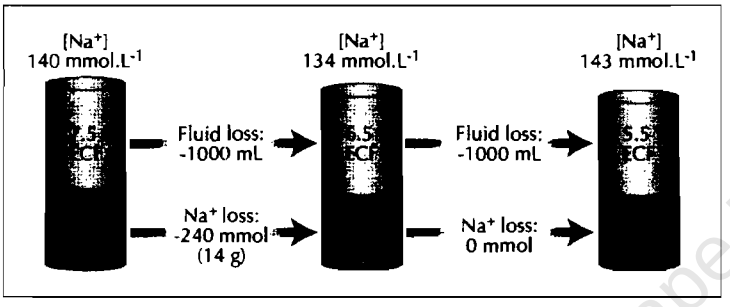

Figure 2. If 240 mmol of sodium is lost from the extracellular fluid (ECF), the serum sodium concentration will fall to 134 $mmol.L^{-1}$ if the ECF decreases by only 1 L, but will rise to 143 $mmol.L^{-1}$, if the ECF decreases by 2 L.

marked alterations in cerebral function, usually convulsions and coma, associated with serum sodium concentrations that were substantially below the values of 135 $mmol.L^{-1}$ used to diagnose clinical hyponatremia in ill patients, usually studied at rest in the hospital setting. Indeed serum sodium concentrations in affected athletes were usually well below 125 $mmol.L^{-1}$. Subsequently, it became apparent that the serum sodium concentrations of some athletes, perhaps as many as 10% of all participants completing ultradistance events [2,16,17], could drop below the clinically diagnostic value of 135 $mmol.L^{-1}$ without causing symptoms. These athletes with asymptomatic hyponatremia were usually identified only by random blood testing while participating in other research projects [16,17]. These asymptomatic athletes therefore fulfilled the biochemical criteria for a diagnosis of hyponatremia, yet they were asymptomatic and were clearly not in the same dire physical condition as are athletes with symptomatic hyponatremia [2,18•]. Incorrect conclusions about the relative importance of abnormalities in sodium and fluid balance in the etiology of these two separate conditions may have been drawn from studies of athletes with asymptomatic hyponatremia, on the assumption that the same physiologic abnormalities also cause the symptomatic form of this condition. Because of the conclusion that athletes with asymptomatic hyponatremia are dehydrated, this hypothesis may have been more easily accepted [19,20] than the alternate theory [1,2,14,17], which proposed the exact opposite etiology (excessive fluid intake) for the symptomatic form of this condition.

The asymptomatic form of hyponatremia is usually present in athletes who ingest hypotonic replacement fluids during prolonged exercise at lower rates than their weight loss from urine, sweat losses, and fuel oxidation. As a result, they develop varying degrees of weight loss, which has incorrectly been assumed to indicate dehydration [21]. However, the less the weight loss or the more normally hydrated are these athletes at the end of ultra distance races, the greater the reduction in their postrace serum sodium concentrations [17,21,22]. Whereas mild dehydration is almost always present in athletes with asymptomatic hyponatremia, it cannot be the direct cause of symptomatic hyponatremia, because those who have lost the least weight are the most hyponatremic and vice versa.

The hyponatremia must indicate a physiologic failure to contract the extracellular fluid (ECF) volume appropriately in response to a progressive sodium deficit generated in athletes who fail to replace their sweat and urine sodium losses from the hypotonic solutions they ingest in moderate amounts during exercise. The additional evidence that supports this conclusion is the historic finding that the postrace serum sodium concentrations of ultradistance athletes competing before 1975 when fluid ingestion was discouraged [23], were uniformly elevated [24–26] indicating that more marked levels of dehydration cause hyper- not hyponatremia, provided that little fluid is ingested during exercise (Figs. 1 and 2). The reason fluid ingestion appears to lower the absolute serum sodium concentrations for any given level of dehydration has yet to be

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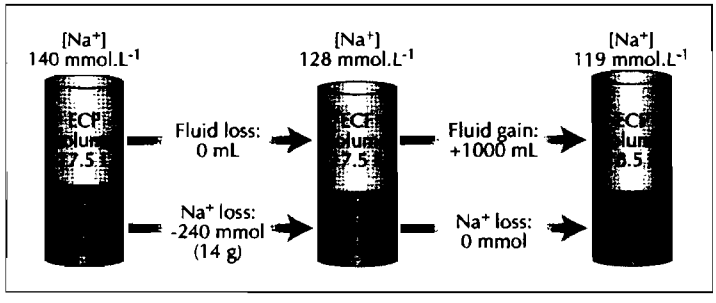

Figure 3. The serum sodium concentration of an athlete who lost 240 mmol of sodium during exercise but who drank enough to keep the extracellular fluid (ECF) volume unchanged, would fall to 128 mmol.L^{-1}. If that athlete were to drink so much during exercise that the TBW rose by 3 L and the ECF volume rose by 1 L to 18.5, the serum sodium concentration would fall to 119 mmol.L^{-1} and the athlete would be desperately ill.

explained. It is likely related to abnormalities in regulation of the ECF volume, with an anomalous expansion of the ECF volume relative to its sodium content, consequent to frequent fluid ingestion during very prolonged exercise (Fig. 3).

Shortly after the publication of the first papers describing the condition [1,13,27,28], two conflicting theories of its etiology immediately became entrenched. On the basis of the history we obtained from the first group of athletes identified with the condition, we concluded that all the athletes had ingested more fluid than was the more common practice at that time [23]. High rates of urine production were also reported during recovery in some athletes, and one ultradistance triathlete reported that she gained 4.5 kg during the race. Hence, we proposed that the athletes were suffering from water intoxication as a result of simply drinking too much during exercise and concluded that athletes should be warned that "the intake of hypotonic solutions in excess of that required to balance sweat and urine losses may be hazardous in some individuals" [1].

Indeed, the first subsequently published case reports also attested to the very high rates of fluid ingestion in US ultra-marathon runners hospitalized for the treatment of the condition [13]. In one athlete, the urine volume during recovery from an 80-km race exceeded fluid intake by 2 L indicating that he had accumulated a minimum fluid excess of 2 L during the race.

A subsequent study of eight athletes who were hospitalized for the treatment of severely symptomatic hyponatremia following the 90-km Comrades Marathon foot race [14] confirmed that all had developed a fluid excess of between 2 and 6 L during the race (Fig. 4), whereas their mean calculated sodium deficit was relatively small (153 mmol), and was no greater than that calculated in control athletes who finished other ultra-marathon races with normal serum sodium concentrations.

We have consistently proposed that symptomatic hyponatremia cannot occur in the absence of fluid overload, and the expected sodium deficit incurred during exercise probably plays an insignificant role [1,2,12,14,23,29].

Surprisingly, these apparently valid scientific findings already published between 1985 and 1992 have had little influence on the practical advice given to athletes on how they might avoid hyponatremia during exercise [19,20]. Indeed, the clear evidence is that they have been either dismissed or ignored [30•,31••,32].

The opposing theory for the etiology of this condition has now passed through three successive modifications in 15 years. Originally it was argued that the hyponatremia of exercise occurs in athletes who develop dehydration and large sodium deficits [21,27,28,33–35], both as a result of the high sweat rates sustained for very many hours during very prolonged exercise. Thus, it was stated, for example, that "despite Dr Noakes' assertions, all of the race participants we've seen who were hyponatremic were also dehydrated, and we believe that the mechanism responsible for their hyponatremia was large sweat and sodium losses, coupled with ingestion of large volumes of sodium-free fluids. In retrospective studies of more than 1000 athletes, we have had only one overhydrated athlete who gained 2 kg during the Hawaiian Ironman" [34] and that "the majority of the hyponatremic athletes at the Ironman are markedly clinically dehydrated, and the mechanism for their hyponatremia would appear to be related to high sodium losses in association with inadequate sodium and fluid intake" [35].

Because it was concluded that large unreplaced fluid and sodium deficits caused the problem, the obvious solution was to advise athletes to drink larger volumes of electrolyte-containing sports drinks at higher rates during prolonged exercise. This advice was disseminated to competitors in a recent Hawaiian Ironman Triathlon, for example, and is frequently repeated in the publications of one influential US sports drink manufacturer.

The second modification to the original theory seems to have occurred in response to the belated acceptance either 1) that this condition only occurred after athletes and US military personnel were encouraged to increase substantially the amount of fluid they ingested during exercise [3,4,5•,6], or 2) that, if appropriately questioned, most athletes with symptomatic hyponatremia admit to high rates of fluid intake during the events in which they developed the condition. Hence, this modification proposes that the hyponatremia of exercise occurs in athletes who develop large sodium deficits during exercise but who fail to replace that deficit, even though they ingest large volumes of hypotonic fluids, especially water, at high rates during military activities or

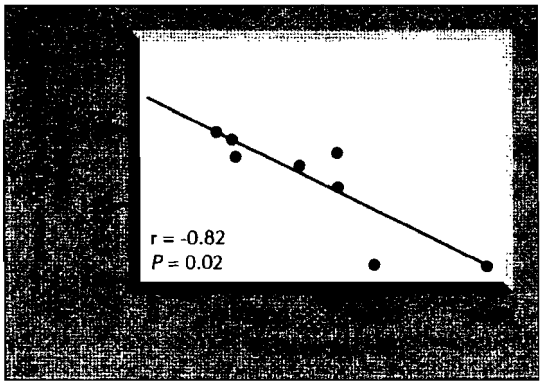

Figure 4. The fluid balance study of eight ultra marathon runners with symptomatic hyponatremia reported by Irving *et al.* [14] established that there was an inverse relationship between the serum sodium concentration in these athletes and the fluid excess they excreted during recovery.

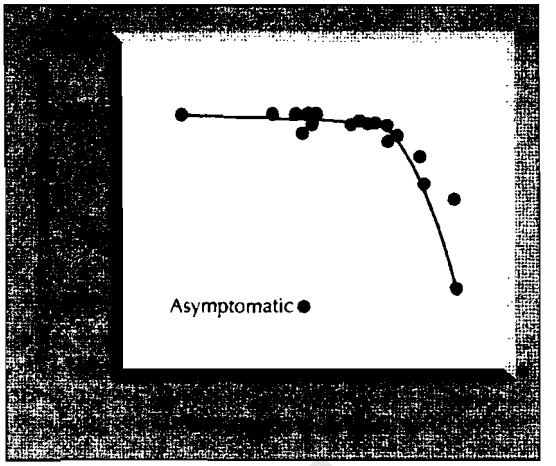

Figure 5. Speedy *et al.* [16] found an inverse relationship between the weight lost during the race and the post race serum sodium concentrations. There was a wide scatter in the relationship so that athletes with the same serum sodium concentrations could show quite large differences in their individual degrees of weight change. But, with one exception, all athletes with serum sodium concentrations below 128 $mmol.L^{-1}$ either did not lose weight or they actually gained weight during the race. Thus, it is the increase in the extracellular fluid volume due to marked fluid overload that causes the symptomatic hyponatremia of exercise.

ultradistance athletic events. Thus, the prevention of the condition requires that athletes continue to ingest fluid at high rates during prolonged exercise. But to insure that they do not incur those large sodium deficits that really cause the condition, they are also advised to ingest only electrolyte-containing sports drinks during exercise and to supplement their sodium intakes from other sources both before and during exercise [19,20].

All these documents [19,20] are ambivalent on the possibility that it is the overhydration (water intoxication) caused by over-drinking that might cause symptomatic hyponatremia. Rather, the focus is on the failure to replace the sodium deficit even in those who ingest fluid at high rates.

The advice contained in the American College of Sports Medicine (ACSM) guidelines is that, whereas high rates of fluid ingestion may indeed be associated with hyponatremia, "one major rationale for the inclusion of sodium in rehydration drinks is to avoid hyponatremia" [20]. This advice is correct only if it is the sodium deficit and not the fluid overload that causes hyponatremia. If water intoxication causes hyponatremia, then the advice to drink fluid at high rates during exercise promotes the development of hyponatremia (Fig. 3).

The third and most recent modification to these theories finally acknowledges that overhydration may play at least some role in the etiology of this condition. Yet its role is still of a lesser importance than is that of the large sodium deficit that develops during prolonged exercise in persons who fail to ingest sufficient sodium (because they ingest either water or other hypotonic drinks that lack the sodium contents of the sports drinks). Montain *et al.* [6] propose that "both large salt losses via sweat and excessive water intake, singly or in combination, contribute to lowering serum sodium during prolonged exercise." They base this conclusion on a set of theoretic calculations, but these calculations conflict with the actual findings in real patients treated for symptomatic hyponatremia.

With the benefit of this background information, it is now possible to review the most relevant, recently published studies that have helped to establish which of these different hypotheses is likely to be the more correct.

The studies of Dr. Dale Speedy and colleagues

Dale Speedy is a sports physician from Auckland, New Zealand whose interest in the hyponatremia of exercise arose from an early study in the 1996 New Zealand Ironman Triathlon [22] of which he was then the Chief Medical Officer. The weights and serum sodium concentrations of 95 competitors in that race were measured before and after the race. The study found an inverse relationship between the postrace serum sodium concentrations and the extent of the weight lost during the race. Only one athlete developed significant hyponatremia (serum sodium concentration of 130 $mmol.L^{-1}$) associated with a weight gain during the race of 2.5 kg. The authors concluded that these findings are consistent with the hypothesis of fluid overload as the cause of hyponatremia. This same study design was used the following year to study 605 of 660 entrants in the 1997 New Zealand Ironman Triathlon [17]. Again, the athletes who lost either the least weight or who indeed gained weight during the race had the lowest serum sodium concentrations. Furthermore, when only those athletes with the lowest serum sodium concentrations of

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below 130 mmol.L^{-1} are included (Fig. 5), it is apparent that whereas serum sodium concentrations above 128 mmol.L^{-1} can be associated with a large variation in weight changes during the race with one exception, all athletes with serum sodium concentrations below 128 mmol.L^{-1} gained substantial absolute weight during the race. Once the weight gain exceeded 2.5%, there was a steep and apparently linear fall in the serum sodium concentration, as also shown by Irving *et al.* [14] (Fig. 4).

Fluid balance was studied in 18 competitors during the 1997 New Zealand Ironman race [38]. The mean hourly fluid intake during the race was 716 mL/h and there was again an inverse relationship between the amount of weight lost during the race and the postrace serum sodium concentrations. The two athletes who gained weight (1% and 2.5%) during the race were the only athletes with serum sodium concentrations below 129 mmol.L^{-1}. Perhaps the most interesting novel finding of the study was that despite a mean weight loss of 2.5 kg during the race, athletes lost an additional 1 kg during the first 12 hours after the race. Because mean serum sodium concentrations did not change during the race, and the plasma volume rose, the authors concluded that despite the 2.5-kg weight loss during the race, the average athlete probably finished the race optimally hydrated. They estimated that this 2.5-kg weight loss might include 260 g of fat and 535 g carbohydrate oxidized during the race, as well as 1400 g of water originally stored with muscle glycogen, which was released as the glycogen was metabolized. The point of these calculations is to suggest that the total fluid excess of athletes who complete races with a positive weight gain will be even greater than is measured solely by the weight changes during the race.

Fluid and sodium balance was also studied in seven athletes who were hospitalized for the treatment of symptomatic hyponatremia after the 1997 New Zealand Ironman [39]. Whereas control subjects lost 3.0 kg during the race, and a further 0.5 kg during the first 12 hours of recovery, the mean weight loss during the race in the hyponatremic triathletes was 0.3 kg, with a further weight loss of 2.7 kg during overnight recovery. As a result, median weight loss over the course of the race and recovery was the same in both groups. The sodium deficits that developed during exercise were again relatively small in most athletes. Furthermore, mean antidiuretic hormone concentrations were significantly lower in subjects than in controls, in keeping with the more dehydrated state of triathletes in the control group. Hence, all these data are entirely consistent with the findings of Irving *et al.* [14] in a group of more severely symptomatic athletes.

For the 1998 New Zealand Ironman race, entrants were provided with regular pre-race newsletters in which they were advised to drink at safe rates of between 500 and 1000 mL/h during the race [40••]. This information was again emphasized in the pre-race briefing. In addition, the frequency of the aid stations on the cycle course was decreased from every 12 km to every 20 km and on the run course from every 1.8 km to every 2.5 km. Athletes were also weighed before the race so that this information could be used to guide treatment in the medical tent at its completion.

With the introduction of these radical changes for the 1998 race, the number of triathletes treated for hyponatremia in the medical tent fell from 25 to four, and the number of hospital admissions for the treatment of this condition fell from 14 to one [40••]. Despite the introduction of these more conservative drinking guidelines, the overall percentage of entrants seeking medical care after the race did not change significantly (~ 20%).

This study showed that the incidence of symptomatic hyponatremia can be substantially reduced by limiting fluid intake, not increasing it, as is the usual advice [19,20,28,33–35], by reducing the opportunities for athletes to ingest fluid during exercise and by advising them to keep their rates of fluid intake within certain limits so that they do not drink as much as possible. This mirrors the original experience in which three of the original four athletes described with the condition were able to return to competitive ultradistance endurance events without the recurrence of symptomatic hyponatremia, simply by drinking less [1].

Recent clinical studies from US standard 42-km marathon races

The first case of hyponatremia in a marathon runner was reported in the United States during the 1986 Pittsburgh marathon [41]. One of the first deaths in a marathon runner as a result of suspected hyponatremia occurred in the 1998 Chicago marathon [11], although an earlier case may have occurred in the 1993 Big Sur marathon in California (Dr. Tamara Hew; Personal Communication). This was a surprising development, given that most cases of the hyponatremia of exercise elsewhere in the world have occurred in ultradistance running events of at least 80 km, or in Ironman Triathlon events.

In 2001, Davis *et al.* [8] reported the first large-scale study of 26 patients who were treated intensively for the hyponatremia of exercise after the 1998 and 1999 San Diego 42-km standard marathons. Their paper includes three significant findings. First, that the affected athletes were more likely to be female, to have used nonsteroidal anti-inflammatory agents, and to have finished the race amongst the back markers. That females and those who run slowly are at greater risk for this condition had already been noted from the original studies [2], as subsequently confirmed with the expanded clinical experience [18•]. Second, that all these athletes reported that they had drunk as much as possible during the race, despite information published after the 1998 race warning of the dangers of drinking too much during marathon races. Third, they evaluated the value of sodium infusion on the rate of recovery in those athletes with the more severe hyponatremia.

On the basis of these findings, the authors concluded that "the development of exercise-associated hyponatremia is associated with excessive fluid consumption during and after extreme athletic events," so that "there is a need to develop more rational fluid replacement strategies and educate runners to optimize rather than to maximize fluid intake during extreme exercise" [8].

The review of Dr. Scott Montain and colleagues

Scott Montain *et al.* [6] from the US Army Research Institute of Environmental Medicine in Natick, MA, were among the first to address the issue of a rising incidence of hyponatremia in the US military, such that an average of 19 US military personnel were hospitalized with this condition annually between 1989 and 1999. This rise followed the introduction of new, more liberal drinking guidelines to the US military sometime between 1982 [4] and 1988 [3].

The recent epidemic of hyponatremia in distance runners and in military personnel shows a close temporal relationship to changes that either encouraged higher levels of fluid ingestion during exercise or made it substantially easier to drink larger volumes during exercise. In addition in the military there is also "the presence of a strict authority that emphasizes forced hydration, such as the chain of command for military trainers" [4]. In running, this strict authority exists in the form of apparently scientifically-based, well-intentioned and widely distributed advice to the effect that one should drink as much as is tolerable during exercise [19,20].

Recently, Montain *et al.* [6] have provided more conservative guidelines for fluid replacement during military activities. Interestingly, these guidelines cover only the ingestion of water during exercise and are silent on the role of sodium replacement during exercise. This is especially surprising if it is believed that a sodium deficit alone can cause exercise-related hyponatremia, and that sports drinks containing sodium are the preferred solutions for ingestion during exercise, at least in civilian populations [19,20]. The effects of these new guidelines have yet to be reported.

Theoretically, to distinguish between the two opposing theories for the etiology of exercise-associated hyponatremia, Montain *et al.* [6] have calculated the magnitude of the sweat sodium losses that would be necessary to produce hyponatremia in athletes who drank sufficiently during a 90-km ultra-marathon race so that their total sweat losses were completely replaced with only water.

Using the principle that total body water (TBW) is 62.9% of the body mass (or 44 L in a 70-kg athlete), and the ECF volume is 39.8% of the TBW (or 17.5 L in a 70-kg athlete), they calculated that athletes who completely replaced their 8.6 L of total sweat loss with pure water during the 90-km race would develop sodium deficits of 215, 430, and 650 mmol if their sweat sodium concentrations were respectively 25, 50, and 75 $mmol.L^{-1}$. As a result, their postrace serum sodium concentrations would be respectively 135, 130, and 125 $mmol.L^{-1}$, only the latter of which might possibly cause symptomatic hyponatremia. The authors concede that "these are exceptionally high sweat sodium concentrations for physically-fit and heat-acclimatized athletes." They also concede that even if such losses were indeed physiologically possible, they would still not be sufficient to lower the serum $[Na^+]$ to the average value of 121 $mmol.L^{-1}$ measured in the total group of athletes with symptomatic hyponatremia [18•], and most certainly not to the very lowest values of 112 to 116 $mmol.L^{-1}$ reported in the most seriously affected athletes [1,14,29,36]. They also conclude that a fluid excess of 5.1, 3.3, or 1.6 L must also be present to cause the serum $[Na^+]$ to fall to 121 $mmol.L^{-1}$ in athletes with the respective low, moderate, or pathologically high sweat sodium concentrations. These concessions are in line with the predictions in Figure 2, and the measurements made in real patients with this condition.

The calculations disprove the theory that a sodium deficit alone can cause the symptomatic hyponatremia of exercise. With one possible exception, symptomatic hyponatremia has only ever been reported in athletes who either gained weight during exercise or who showed a positive fluid balance during recovery. The finding that, on occasion, very low serum sodium concentrations have been measured in asymptomatic athletes who lost weight during exercise was recognized in an early study [2]. The cause of this anomaly remains uncertain, as is the absence of symptoms in those cases. But the important practical point is that those subjects did not have symptoms, and were identified only because they were participating in other research projects.

Laboratory-based studies

Two separate studies show that a progressive hyponatremia can be produced even under resting conditions, simply by having subjects ingest fluid at high rates for 2 to 3 hours [42,43••].

Noakes *et al.* [42] showed that subjects who ingested water at rates of 1.5 L/h for 3 hours developed a progressive hyponatremia because their peak rates of urine production (780 mL/h) were unable to prevent a progressive fluid retention. Calculations indicated that all the fluid excess could be accounted for by increases in TBW so that there was no unabsorbed fluid unaccounted for because it was still present in the gastrointestinal (GI) tract. Hence, there was no evidence that this form of hyponatremia results from a "third space" effect in which there is reverse sodium movement into unabsorbed fluid in the intestine, a mechanism that we had originally postulated could contribute to the hyponatremia of exercise [2], but which now appears to be definitely incorrect [18•].

The authors concluded that whereas the maximum rate of GI absorption was more than 1.5 L/h at rest, the peak rates of urine production are less. As a result, when fluid is ingested at rates faster than about 800 mL/h, TBW must

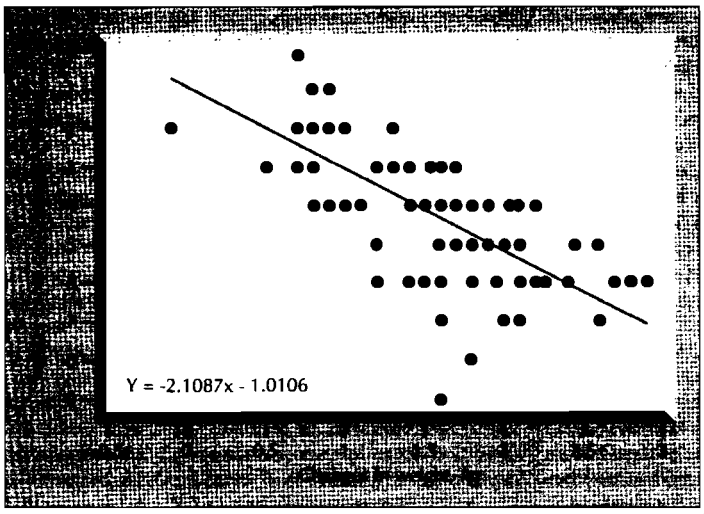

Figure 6. In response to progressive fluid overload developing at rest, both normal athletes and those who had previously developed hyponatremia during the New Zealand Ironman Triathlon, showed a linear reduction in their serum sodium concentrations with increases in body weight. Significant sodium losses could not have contributed to this hyponatremia since the subjects were at rest and their sole source of sodium loss was via increased urine production. (*Adapted from* Speedy *et al.* [43••].)

increase and serum sodium concentrations fall proportionally due to a progressive expansion of ECF volume. Thus, the probability of developing hyponatremia in response to high rates of fluid ingestion at rest is determined simply by whether or not that rate of fluid ingestion exceeds any individual's fixed maximum capacity to produce urine. In this model there is no need to invoke additional physiologic mechanisms as causative factors for this condition.

Speedy *et al.* [43] extended these observations by showing that New Zealand Ironman triathletes with a previous history of exercise-associated hyponatremia did not respond any differently to sustained oral fluid overload (1750 mL/h) than did other Ironman triathletes who completed that race without developing hyponatremia. As in the South African study, all the ingested fluid could be accounted for by an increase in calculated TBW, so that the same conclusions could be drawn. Furthermore, there was a linear relationship between the change in body weight (and TBW and ECF volume) and the reduction in the serum sodium concentrations (Fig. 6), similar to the relationship between the estimated fluid excess and the serum sodium concentrations in athletes with symptomatic hyponatremia (Figs. 4 and 5).

In summary, these studies confirm that there is a limited renal capacity to produce urine in response to high rates of fluid ingestion. When that rate is exceeded, the excess fluid must accumulate in the body, causing a progressive expansion of the ECF and a corresponding reduction in the serum sodium concentration. The extent of this reduction is linearly related to the extent of the fluid overload, as also found in athletes with the symptomatic hyponatremia of exercise (Figs. 4 and 5).

Thus, there is a simple physiologic explanation for the production of hyponatremia in response to oral fluid overload, and which does not require the action of other mechanisms. It is the renal response to fluid ingestion and not the sodium content of the ingested fluid that protects against hyponatremia during exercise when fluid is ingested at rates that equal the rates of weight loss [49].

Optimum Treatment

There is one absolute in the management for the symptomatic form of this condition. Because these athletes have an expanded TBW (Figs. 3–5), there is an absolute contraindication to giving additional fluids, except as a vehicle to deliver sodium to the abnormally expanded ECF and therefore to increase the ECF sodium content and concentration until it again retracts to its appropriate volume.

My clinical experience has been that patients with this condition follow one of two paths. Either they begin a diuresis within the first hour or two of stopping exercise and will pass urine at rates of 600 mL/h or more for many hours thereafter with a corresponding reduction in the severity of their symptoms, or else they show scanty urine production for many hours after exercise without clinical improvement and may only start the therapeutic diuresis in response to a diuretic challenge with furosemide.

Most patients with the mild form of this condition should recover spontaneously if given nothing other than supportive care and perhaps furosemide if the onset of their diuresis is delayed. Thus, when fatalities occur in athletes who initially present with mild symptoms, the question must be asked whether the patient was treated inappropriately in particular with intravenous fluids at high rates for the management of a supposed dehydration [12]. This error is particularly likely to occur if the attending clinicians believe the dehydration myth [12], and if they interpret the absence of urine production as a confirmatory sign of dehydration.

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A belief that this condition should not have a fatal outcome is strengthened by the evidence that there has been only one reported death [7••] in those very ill patients who were treated appropriately with fluid restriction, concentrated (3%) intravenous sodium given at slow rates (100 mL/h), and furosemide [1,8••,13,14,29,36,41,45–47]. Death is usually a consequence of cardiorespiratory arrest secondary to profound cerebral edema causing brainstem herniation through the foramen magnum [7••].

Although there are as yet no controlled clinical trials, the comparative data of Davis *et al.* [8••] shows that the use of intravenous 3% sodium solution given at rates of 100 mL/h can produce a rapid correction of hyponatremia (3.4 mmol.L^{-1}/h). Recalculation of those data indicate that some of the variance in the rate of recovery from hyponatremia in response to intravenous sodium is likely to be explained simply by differences in body weight so that heavier (~ 70 kg) athletes would likely benefit from higher rates of intravenous sodium delivery, because they have a larger ECF volume (Fig. 1). This latter point may be clinically important, given that there is no evidence that a slow rate of recovery from acute hyponatremia is either beneficial or desirable [7••,8••,13].

In summary, the current evidence is that patients who are conscious with only mild hyponatremia, without other complications including pulmonary edema, can probably be treated expectantly by avoiding further fluid ingestion, and with furosemide administration if the onset of diuresis is delayed. However even in this group, the use of intravenous sodium is likely to reverse the condition more rapidly. In contrast, in the presence of more severe hyponatremia with coma or seizures, the danger of brainstem herniation requires the most urgent treatment with intravenous sodium and furosemide plus other specialist neurologic interventions to reduce cerebral edema.

Prevalence in the United States

The sport of ultradistance running has been popular at least since the mid to late 19th [48]. Yet during the first century of the sport there were no reports of the symptomatic hyponatremia of exercise, and all studies showed that runners developed hypernatremia during those races [24–26], because they drank little and became quite markedly dehydrated as a result [24]. The mechanism for their hypernatremia is that shown in Figure 1, namely a loss of more fluid than sodium from the ECF, causing the remaining sodium to be more concentrated. This occurs because the sweat of trained, heat-acclimatized athletes is an hypotonic solution with a low sodium content [6,48].

The finding that the incidence of this condition has increased substantially especially in the US military and in US marathon runners in the past decade poses the question, Are those modern runners and military personnel who have developed the condition uniquely different from those of previous decades who appear to have been immune to this condition, or is there some novel but unidentified environmental factor at work?

David E. Martin, co-author of two definitive texts on marathon running [49,50], has shown that the bulk of modern US marathon runners require as much as 60 minutes more to complete standard 42-km marathon races than did the very slowest marathon runners even as recently as the mid 1970s (Personal communication).

Therefore, modern US marathon runners are indeed different from those of the previous generation. In particular, there has been a large increase in that group of runners who are most likely to develop this condition because they take more than 5 hours to complete the standard marathon [8]. But are these runners really a specific human subpopulation, uniquely prone to the development of hyponatremia during prolonged exercise of quite low intensity? Or has this condition arisen in response to a specific alteration in the environment, in which modern endurance races are held, first in ultradistance running and triathlon events around the world, and more recently in the 42-km standard marathon specifically in the United States?

The point has been made repeatedly [2] that the single most obvious change in the conduct of marathon and other ultradistance events since 1976 has been a paradigm shift in the approach to fluid ingestion during prolonged exercise. Whereas before the 1970s, athletes were actively discouraged from drinking at all during exercise, regardless of its duration or intensity [23,48], thereafter the message was popularized that athletes who failed to drink as much as possible during exercise risked both their performances and, more especially, their lives.

It was only at the 1976 Olympic marathon in Montreal that fluid was first provided more freely during marathon races [2]. The evolution of the Big City marathons, first in New York in 1976 and then in London in 1981, extended this development so that the 30,000 or more participants in these very popular marathon races now have the opportunity to drink as much as they choose at between 25 and 40 aid or seconding stations that provide liquid and other refreshments along the marathon route. That the number of such aid stations appears to play a role in this condition is shown by the observations that 1) reducing the number of aid stations in an Ironman triathlon substantially reduced the number of triathletes requiring hospitalization for symptomatic hyponatremia [40], and 2) that there is a high incidence of this condition in the Houston marathon, which has aid stations located approximately every 1.6 km on the course. In contrast, few if any cases of hyponatremia have ever been recognized in the Honolulu marathon (Dr. Tamara Hew; Personal communication) in which, despite the more severe environmental conditions in which that race is run, aid stations are located only every 4 km.

Providing easier access to fluid during endurance events will not cause athletes to over-drink. Rather, they must also be indoctrinated to believe in the value of that

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practice. Factors that contributed to this might include the growth of the sports drink industry in both North America and Europe in the 1980s [32], aided by the publication of the American College of Sports Medicine guidelines for fluid replacement during exercise [19,20], because these guidelines have helped to entrench this new paradigm of aggressive hydration [8••] during exercise.

Thus, not only are athletes now encouraged to drink as much as possible both before but especially during exercise, they have also been informed that "the perception of thirst (is) an imperfect index of the magnitude of the fluid deficit (and) cannot be used to provide complete restoration of water lost by sweating" [20]. To my knowledge, there is no conclusive evidence that the perception of thirst is inadequate during exercise, because it is not known whether or not all the fluid lost by sweating during exercise needs to be replaced for there to be optimum performance [31••].

Interestingly, one study found that athletes who began exercise in a dehydrated state, drank more avidly immediately when they began to exercise and continued so until they reached the same levels of weight loss as they did when, on another occasion, they began exercise fully hydrated [51]. This seems to prove that the thirst mechanism was appropriate in both conditions, because prior dehydration caused an appropriately accelerated drinking response that was not inhibited by the act of exercise. Only when the athletes had appropriately rehydrated during exercise was this more avid drinking response curtailed [51]. This study proves that athletes could drink more during exercise but that this response is only activated if they begin exercise in a more dehydrated state.

If the thirst mechanism is indeed appropriate during exercise, then exhortation that athletes should ignore their thirst and drink as much as possible during prolonged exercise must cause the hyponatremia of exercise in those who ingest fluid at faster rates than they are able to lose any fluid excess as urine [42,43••], sweat or vomitus.

Conclusions

Hyponatremia of exercise was unheard of prior to 1981, during which time athletes were encouraged to not drink during exercise [23]. As a result, all completed marathon and ultra-marathon races with varying degrees of dehydration and, without exception, were hypernatremic at the race finish [24–26]. These historic data prove that dehydration and unreplaced sodium losses during prolonged exercise cause hypernatremia, not hyponatremia (Figs 1 and 2).

The very low incidence of hyponatremia even in modern athletes who ingest fluid but who do not replace their sodium losses during prolonged exercise continues to prove that sodium losses alone cannot cause the hyponatremia of exercise [29], as confirmed by the most recent calculations [6] and all the clinical evidence.

The first cases of hyponatremia were reported in the first decade after there had been a paradigm shift in the approach to fluid replacement during exercise. The intellectual basis for this shift were the twin beliefs that 1) dehydration has an adverse effect on athletic performance and safety, and 2) perceptions of thirst are an inaccurate guide to the real fluid requirements during exercise. Later the idea was added that adequate sodium replacement is also important if hyponatremia is to be avoided during prolonged exercise.

By showing that fluid overload was present in at least some of the first cases of hyponatremia, the earliest clinical case reports [1,13,41] suggested that this advice was totally inappropriate. Irving *et al.* [14] proved that fluid overload was indeed the cause of symptomatic hyponatremia. They established a linear relationship between the degree of fluid excess and the postrace serum sodium concentrations such that the most severely affected athlete with a serum sodium concentrations of 113 $mmol.L^{-1}$, had a calculated fluid excess of 6 L [2,14] (Fig. 4). Calculated sodium deficits in these athletes were no greater than in other ultra-marathon runners who maintained normal serum sodium concentrations during prolonged exercise.

The idea that hyponatremia can be due principally to abnormalities in sodium metabolism conflicts with an established teaching in clinical medicine, which holds that acute symptomatic hyponatremia is a condition caused by abnormalities in the regulation of fluid and not sodium balance [52]. It has never been possible to develop hyponatremia as a result of an acute sodium deficiency alone. The classic studies of McCance [52,53] showed that it required at least 3 days of total exclusion of all sodium from the diet before a sodium deficiency hyponatremia could develop. Because these conditions cannot be reproduced but in laboratory experiments in consenting subjects, there is no possibility that the same mechanisms could ever be found in free-living humans with free access to salt-containing foods and fluids.

Next came a series of studies that consistently showed an inverse relationship between the weight changes during exercise and the postrace serum sodium concentrations, so that those who either lost the least weight or who gained weight during exercise had the lowest serum sodium concentrations [17,21,22,38–40,54].

On the basis of recent publications, there is no longer any possibility to conceal the conclusion that fluid overload as a result of voluntary over drinking, is the only important etiologic factor causing the hyponatremia of exercise. The symptoms are caused by edema of the vital organs, brain, and lungs in particular. Thus, the possibility remains that even if athletes were to ingest very large amounts of sodium during exercise, they might still develop cerebral edema if they over-drank, because it is the cerebral edema and not the serum sodium concentration that causes the symptoms in this condition. There is evidence that high rates of sodium ingestion during exercise

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reduce the rate of urine production [55], thereby perhaps increasing the possibility that fluid overload will develop when voluntary over-drinking is combined with high rates of sodium ingestion.

By limiting fluid intake during prolonged exercise, symptomatic hyponatremia is as preventable today as it was before 1981 when the condition simply did not exist.

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Editor's Note

This manuscript was recruited for publication following suggestions from Noakes concerning the importance of Mitchell's presentation of his work at the ACSM annual meeting of 1990 in Salt Lake City. In this issue Mitchell's complete data are published along with Houmard's data in articles juxtaposed to Noakes et al.'s review article, in which he reviews the physiological factors involved in gastric emptying during exercise. This experimental format has been established as a means to focus the reader's attention on a pertinent question of exercise science and sports medicine.

BASIC SCIENCES/REGULATORY PHYSIOLOGY

ORIGINAL INVESTIGATIONS

The importance of volume in regulating gastric emptying

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ABSTRACT

NOAKES, T. D., N. J. REHRER, and R. J. MAUGHAN. The importance of volume in regulating gastric emptying. *Med. Sci. Sports Exerc.*, Vol. 23, No. 3, pp. 307–313, 1991. There is now substantive evidence that the provision of exogenous carbohydrate at high rates (1–2 g·min^{-1}) can enhance performance during prolonged exercise. This finding has revived research into the factors determining the rate of exogenous carbohydrate delivery during exercise. While the rate of muscle oxidation of exogenous carbohydrate could be determined by the rate of gastric emptying or of intestinal carbohydrate absorption or of muscle glucose uptake and oxidation, most physiologists seem to have assumed that gastric emptying is the factor that limits the rate of exogenous carbohydrate delivery during exercise. Furthermore, studies of gastric emptying have suggested that the carbohydrate content of the ingested solution is an important factor determining its rate of gastric emptying. However, the findings of recent studies employing a repeated drinking design suggest that the gastric volume and therefore the pattern of drinking during exercise will have a significant, possibly major, influence on the rate of both carbohydrate and water delivery from any solution. This review considers this evidence and its practical implications for athletes who wish to ingest carbohydrate during exercise and for exercise physiologists designing studies to optimize carbohydrate delivery to muscle during exercise. It is proposed that, if gastric volume is an important determinant of the rate of gastric emptying, a more standardized method for reporting the rates of gastric emptying of different solutions should be adopted.

GASTRIC EMPTYING, EXOGENOUS CARBOHYDRATE, GASTRIC VOLUME, CARBOHYDRATE SOLUTIONS

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There is now firm evidence that carbohydrate ingested during prolonged exercise can delay the onset of fatigue and enhance performance (3–5,10). The effect is due to the provision of exogenous carbohydrate at rates sufficiently fast to prevent or reverse hypoglycemia and to sustain high rates of carbohydrate oxidation by the active muscles (3–5,10).

These findings have stimulated investigation of those factors, particularly the carbohydrate and electrolyte content of the ingested solution, that will optimize the rate of exogenous carbohydrate delivery to blood and muscle (6,9,11–15,24–29,31–36).

Two important assumptions have been made by the

authors of many of these studies. First, it is assumed that the rate of gastric emptying is the factor limiting the rate of carbohydrate delivery to the site at which its utilization exerts beneficial effects (7). This assumption ignores the obvious anatomical consideration that the ingested carbohydrate can influence performance only once it has been absorbed as glucose from the intestine into the bloodstream and, possibly, only when the absorbed glucose is oxidized by the active muscles. This assumption is not addressed in this review. It should, however, be noted that the rate of exogenous carbohydrate oxidation by the active muscles increases with increasing carbohydrate content of the ingested fluid (31), an addition which would be expected to reduce the rate of gastric emptying of fluid (see below), but not necessarily of carbohydrate. Thus, it is important to distinguish between the effects of an ingested solution on the rate of gastric emptying of fluid and of carbohydrate.

The second assumption is that the rate of gastric emptying is inversely proportional to the energy density of the ingested solution. This is a quite natural conclusion given the historical emphasis on the effect of the osmolality and energy content of the ingested solutions on their rates of gastric emptying (6,19,21). However, if this assumption is indeed correct, it means that the concentration of the solution ingested during exercise is of no consequence for substrate delivery; the rate of substrate (but not fluid) delivery to the intestine would always be constant and independent of the solution concentration.

In this review we consider the evidence that this is not the case and that, whereas the carbohydrate content of the ingested solution is indeed an important regulator of the rate of gastric emptying, it may not be the most important determinant of the rate of fluid delivery to the intestine.

FACTORS INFLUENCING THE RATE OF GASTRIC EMPTYING OF CARBOHYDRATE-CONTAINING SOLUTIONS DURING EXERCISE

A number of factors are known to influence the rate of gastric emptying (Table 1) (6). Of fundamental relevance to the exercise physiologist is to decide which of these factors are the most important and should therefore be manipulated in the experimental setting. We present here our analysis of the factors that we consider to be the most important regulators of the rates both of gastric emptying and of fluid delivery to the intestine.

TABLE 1. Factors known to influence the rate of gastric emptying.

Constituents of the ingested solution
Volume
Caloric density
Electrolyte content
Osmolality
Temperature
pH
Exercise variables
Intensity of exercise
Mode of exercise
Subject variables
Level of hydration
Individual variability

Gastric volume. In the original studies to determine the rates of gastric emptying for different carbohydrate-containing solutions, gastric volume was inadvertently introduced as a controlled variable as the rate of gastric emptying was always studied following ingestion of a single fluid bolus of constant volume. Thus, the starting gastric volume was held constant for all the different solutions that were tested.

This technique clearly established that the rate of gastric emptying was a function of the carbohydrate content of the solution. Thus, solutions containing as little as 2.5% carbohydrate were shown to reduce the rate of gastric emptying (7,9,14). Therefore, the practical advice offered at that time was that only solutions with low carbohydrate content should be ingested during prolonged exercise as only these solutions emptied sufficiently rapidly to prevent the development of dehydration during exercise (1).

However, a number of more recent studies (8,25, 26,30,32–34,36) have shown that, when ingested repeatedly during prolonged exercise, the rates of gastric emptying for solutions with quite different carbohydrate contents may be more similar than predicted on the basis of the original studies, which used the single ingestion model. This has stimulated interest in those factors differing between the two experimental methods which might explain this discrepancy (6).

A second relevant feature of the early studies using the single ingestion model was that the rate of gastric emptying was calculated on the basis of a single gastric aspiration usually measured 15–30 min after ingestion of the initial fluid bolus. Figure 1 shows how erroneous conclusions can be drawn from this experimental method.

The top panel of Figure 1 depicts the time course of gastric emptying for different (0.4–20%) carbohydrate solutions (24); the lower panel, which demonstrates the amounts of glucose emptied in the same time periods, shows that the amount of glucose emptied is not constant for all solutions, thereby disproving the theory that a constant rate of energy delivery determines the rate of gastric emptying, at least for carbohydrate.

Initial emptying rates for the 0.4% solution were faster than for all other solutions. However, differences in total fluid emptied diminished with time, so that after 40 min there were only small differences in the volumes of fluid emptied from the 0.4% and 5% solutions. A more rapid fall with time of the emptying rate for the 0.4% solution than for the other solutions would explain this effect. With hindsight, this result could be explained if this time-dependent fall in the rate of

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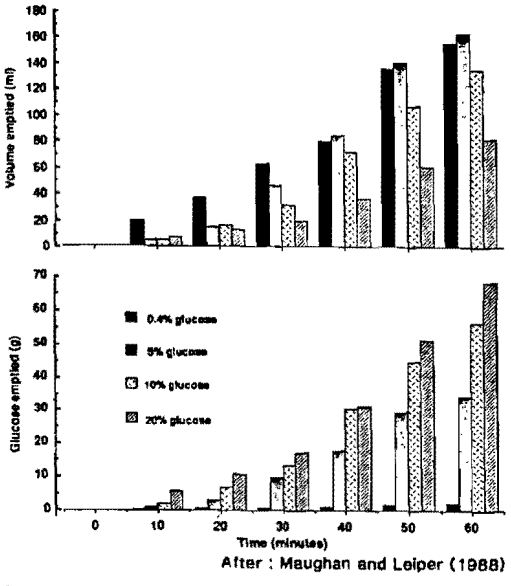

Figure 1—The *top panel* shows the cumulative volumes of fluid emptied from the stomach every 10 min following the ingestion of four different carbohydrate containing solutions at time 0. The *lower panel* shows the cumulative amount of glucose emptied from the stomach every 10 min in the same experiments. From Maughan and Leiper (24). Reprinted with permission of Excerpta Medica.

gastric emptying was due to a progressive reduction in the volume of fluid retained in the stomach.

More direct evidence for this postulate that gastric volume influences the rate of gastric emptying can be found in the initial study of Costill and Saltin (7). They showed that average rates of gastric emptying of up to 40 ml·min^{-1} could be achieved when very large volumes of fluid were ingested. Such high rates of gastric emptying over prolonged periods had not been reported again until recently (11). Further direct evidence for the importance of gastric volume in determining the rate of gastric emptying is provided by the recent studies of Rehrer et al. (32,33).

Rehrer et al. (32) showed that the rate of gastric emptying falls exponentially with time, as previously noted by others (6,18,20,23). However, their more critical and novel finding was that, following a single ingestion, the rate of gastric emptying for any solution falls as a logarithmic function of the volume of fluid contained in the stomach. Stated differently, this means that, during any equivalent time period, a constant percentage of the drink that was present in the stomach at the start of that period would have been emptied. They found that approximately 65% of a water solution, 50% of an isotonic 7% carbohydrate solution, and 25% of a 15% or 18% carbohydrate solution emptied during each successive 10 min period during exercise at approximately 70% $\dot{V}O_{2max}$.

The data from that study (32) have been used to construct Figure 2, which predicts the volume of fluid remaining in the stomach at successive 10 min intervals after ingestion of 600 ml of either water or a 7% or 18% carbohydrate solution at time 0. The critical observation is that the volume of fluid in the stomach can be manipulated to compensate to some extent for the inhibitory effect of its carbohydrate content and so to increase the volume of fluid emptied.

For example, the rate of gastric emptying of the 18% carbohydrate solution between 0 and 10 min is 150 ml·10 min^{-1} (15 ml·min^{-1}), which exceeds the rate of emptying of water at all times after 10 min (<7.4 ml·min^{-1}) and of the 7% carbohydrate solution at all times after 20 min (<7.5 ml·min^{-1}).

Figure 3 uses this information to show the hypothetical effects on the rates of water and carbohydrate delivery from these same three solutions when drunk according to two different drinking schedules. An important but not critical assumption is that the rate of gastric emptying remains the same during repetitive drinking as it does following ingestion of a single bolus. As discussed subsequently, it is clear that this does not necessarily apply for more concentrated carbohydrate solutions when ingested repeatedly in small to moderate volumes during prolonged exercise (33).

The top panels of Figure 3 show changes in gastric volume for a subject who, with repetitive drinking, is able to maintain a maximum gastric volume of 800 ml; the lower panels are for a subject who can tolerate a maximum gastric volume of only 400 ml.

In this hypothetical experiment, both subjects fill their stomachs to capacity immediately prior to exercise. Every 10 min thereafter, each again drinks sufficiently to replace the volume of the solution that has emptied during that 10 min period, thereby refilling the stomach to the individual maximum tolerable gastric volume.

The volumes of fluid that each can ingest every

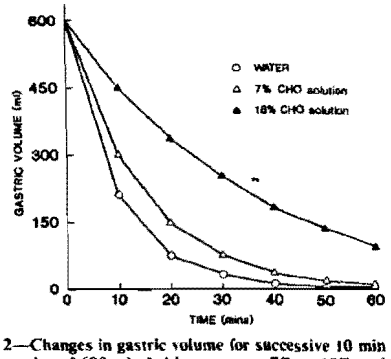

Figure 2—Changes in gastric volume for successive 10 min intervals after ingestion of 600 ml of either water or 7% or 18% carbohydrate (CHO) solution at time 0. Redrawn from the data of Rehrer et al. (32).

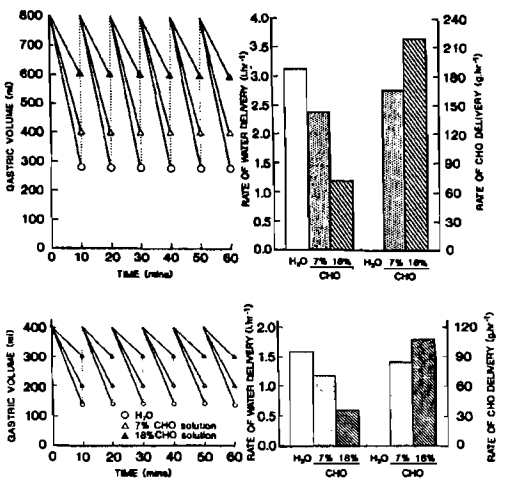

Figure 3—The *top left panel* shows changes in gastric volume after ingestion of 800 ml of either water or 7% or 18% carbohydrate (CHO) solution at time 0. Every 10 min thereafter, a volume of each solution equal to the volume emptied during the preceding 10 min is ingested so that the initial starting gastric volume of 800 ml is again achieved. The *top right panel* shows the predicted hourly rates of water and carbohydrate delivery from the different solutions drunk in this manner. The *lower panels* show the same variables for an initial starting gastric volume of 400 ml. The data are predicted from the findings depicted in Figure 2.

subsequent 10 min will depend on the carbohydrate content of the ingested solution and would be 65% of the initial volume of water ingested (520 or 260 ml), 50% of the 7% carbohydrate solution (400 or 200 ml), or 25% of the 18% carbohydrate solution (200 or 100 ml). At the completion of exercise, average rates of gastric emptying for the three solutions would have been 52, 40, and 20 ml·min^{-1}, respectively, for the athlete able to maintain a gastric volume of 800 ml (Fig. 3, top panels) and half those rates (26, 20, and 10 ml·min^{-1}) for the athlete able to maintain a gastric volume of only 400 ml during exercise (Fig. 3, lower panels). The respective rates of carbohydrate delivery for these drinking patterns would be 0, 168, and 216 g·h^{-1} (Fig. 3, top panels) and 0, 84, and 108 g·h^{-1} (Fig. 3, lower panel). The predictions from this hypothetical model are sufficiently accurate to explain the results of three recent studies.

Ryan et al. (34) reported an average rate of gastric emptying in excess of 17 ml·min^{-1} (1.0 l·h^{-1}) in subjects who drank 5% glucose, glucose polymer, or glucose polymer/fructose solutions at rates of 350 ml every 20 min, similar to the drinking pattern proposed in the lower panels of Figure 3. In contrast, a rate of gastric emptying of only 7.7 ml·min^{-1} (0.5 l·h^{-1}) for a similar (6%) carbohydrate solution was reported by Mitchell et al. (26) in subjects who ingested only 150 ml every 15 min.

Clearly the low rates of gastric emptying in the study of Mitchell et al. (26) can be adequately explained by the low rates of fluid ingestion in that study. When Mitchell and Voss (27) studied higher rates of fluid intake, they showed much higher rates of gastric emptying even from a 7.5% carbohydrate solution (see below).

Similarly, Sole and Noakes (36) reported average rates of gastric emptying in excess of 11 ml·min^{-1} (0.66 l·h^{-1}) for a 10% carbohydrate solution ingested at a rate of 800 ml·h^{-1} during prolonged exercise at 75% $\dot{V}O_{2max}$.

At present, we are aware of three other studies that approximate the conditions of our theoretical model. The results of these studies provide further evidence to support the postulate that gastric volume is a more important regulator of the rate of fluid delivery to the intestine than is the carbohydrate content of the ingested solution.

Rehrer et al. (33) reported a study of repeated drinking of small volumes (150 ml·20 min^{-1}) after an initial large bolus. They showed that the percentage of gastric volume emptied during each subsequent 20 min period increased from 79 to 86% for a 7% isotonic carbohydrate solution when gastric volumes were maintained at between 600 (starting volume) and 250 ml. Under these circumstances, the average rate of gastric emptying during 1 h of exercise at 70% $\dot{V}O_{2max}$ was 14.2 ml·min^{-1}, and the corresponding rate of carbohydrate delivery was 59.5 g·h^{-1}. However, the percentage of fluid delivered from the 18% carbohydrate solution each successive 20 min period did fall from 66% during the first period to 44% between 40 and 60 min, indicating that, at high carbohydrate concentrations, the inhibitory effect of a high carbohydrate concentration begins to override the stimulatory effects of a large gastric volume. This indicates that modification must be made to the hypothetical model if it is to explain the gastric emptying characteristics of 18% carbohydrate solutions ingested repeatedly during prolonged exercise.

Despite this partial inhibitory effect of high carbohydrate concentration, the average rate of gastric emptying for the 18% carbohydrate solution was 10.8 ml·min^{-1}, and that for 7% carbohydrate was 117 g·h^{-1}; the latter is among the highest yet reported in the literature. These figures are similar to those predicted for repeated drinking of an 18% carbohydrate solution when a peak gastric volume of 400 ml is maintained (Fig. 3, lower panels).

Similarly, Mitchell and Voss (27) have reported high rates of fluid (19.0 ml·min^{-1}) and carbohydrate (85 g·h^{-1}) delivery from a 7.5% carbohydrate solution ingested at a rate of approximately 400 ml every 15 min.

These workers also showed that the rate of gastric emptying increased with increasing ingested volume

but that the ingestion of large volumes at frequent intervals caused an increased frequency of complaints of gastric fullness.

This indicates that not only high carbohydrate concentrations in the ingested solution (33), but also large ingested volumes, cause a progressive alteration in gastric emptying characteristics during repetitive feeding (27). This too is not included in the hypothetical model (Fig. 3, upper and lower panels).

Finally, Duchman et al. (11) have reported rates of gastric emptying of 41.5 $ml \cdot min^{-1}$ for water and 25.7 $ml \cdot min^{-1}$ (1.54 $l \cdot h^{-1}$) for a 10% carbohydrate solution when ingested at a rate of 180 ml every 10 min for 40 min following an initial bolus ingestion of 750 ml. The rate of carbohydrate delivery from the 10% carbohydrate solution was 154 $g \cdot h^{-1}$, the highest rate yet recorded. These values approximate those predicted for the 7% carbohydrate solution with an average gastric volume of 800 ml (Fig. 3, upper panels).

In summary, the critical significance of the studies of Rehrer et al. (32,33), Mitchell and Voss (27), and Duchman et al. (11) is to show that the maximum rate at which carbohydrate and water can be delivered from an ingested solution is very strongly influenced by the average volume of fluid in the stomach, which is, in turn, determined by the volume ingested and the drinking pattern. Thus, the greater the degree of gastric distention a subject is able to tolerate during exercise, the more carbohydrate and water that will be delivered to the intestine from any ingested solution.

Although this is not a novel finding (6,7,18,23), its importance has not been widely appreciated (13).

Carbohydrate concentration of the ingested solution. That the carbohydrate concentration of the ingested solution influences gastric emptying has been repeatedly shown (6,7,9,13,14,19,25,26,28,36) and is confirmed by the studies of Rehrer et al. (32) (Fig. 2) and Maughan and Leiper (24) (Fig. 1).

However, for reasons presented in the previous section, it is clear that the volume of fluid in the stomach is the more important regulator of the volume of fluid emptied, at least after ingestion of a single fluid bolus. With repeated drinking of small to moderate volumes, especially of solutions with high carbohydrate content, it is apparent that the carbohydrate content of the solution will retard the stimulatory effect of the gastric volume.

But, in essence, the study of Rehrer et al. (32) can be interpreted to show that the *rate* of gastric emptying (expressed as percentage emptied per unit time) is regulated by the carbohydrate content of the solution but that the *volume* of the solution that is emptied is determined by the gastric volume, which is a function of the drinking pattern.

Osmolality. When the gastric emptying characteristics of simple carbohydrates are studied, there is a close relationship between the rate of gastric emptying and both the carbohydrate concentration and osmolality of the ingested solution (13). This has been interpreted as evidence that it is the osmolality of the ingested carbohydrate solution that regulates its rate of gastric emptying.

However, this does not explain why the rates of gastric emptying for glucose polymer or starch solutions either are not different from glucose solutions of equivalent concentration but much higher osmolality (26,32) or are found only at specific concentrations (14,32,36).

This finding could, however, be explained if rapid, near-total hydrolysis of the glucose polymer and starch solutions occurred by the time these solutions reached the postulated osmoreceptor controlling gastric emptying. Were this to occur, the osmolality of the ingested solutions would be significantly altered; if hydrolysis to glucose had been completed, these solutions would be expected to show the same gastric emptying characteristics as glucose solutions of equivalent concentration. The data of Sole and Noakes (36) can be interpreted to indicate that the glucose polymer (average chain length of 6 glucose units) used in their study acted as if it had been digested to maltose (glucose chain length of 2) by the time it reached the postulated osmoreceptors.

Thus, the conclusion must be that it is not the osmolality of the ingested carbohydrate solution that determines its rate of gastric emptying but rather the osmolality of that solution when it is in contact with the appropriate receptors that regulate gastric emptying (17). The finding that starch solutions do not empty more rapidly from the stomach than do glucose (17) or glucose polymer solutions (15) indicates that hydrolysis of these solutions must occur rapidly in the small intestine, prior to their arrival at the postulated osmoreceptors.

Effect of exercise. It is well established that the rate of gastric emptying is influenced by the exercise intensity so that, at the higher exercise intensities, some inhibition of gastric emptying does occur (2,7,12,14, 16,32). However, it is clear that the effect is small up to an exercise intensity of 70% $\dot{V}O_{2max}$ (7,12,13,32) and may even be stimulatory (28). Furthermore, the effect may be greater on water than on carbohydrate-containing solutions so that, at higher exercise intensities, the magnitude of the difference in gastric emptying rates for water and carbohydrate solutions may be considerably reduced (13,36) and may even disappear at exercise intensities of 90% $\dot{V}O_{2max}$ or higher (13).

Of relevance to this review is the magnitude of the effect of exercise in comparison with the effects of the other variables already reviewed. The data of Foster (13) show that the average rate of gastric emptying for carbohydrate-containing solutions fell from 750 $ml \cdot h^{-1}$

at an exercise intensity of 70% $\dot{V}O_{2max}$ to 660 ml·h^{-1} at 80% $\dot{V}O_{2max}$ and to 450 ml·h^{-1} at 90% $\dot{V}O_{2max}$. These changes, at least up to an exercise intensity of 80% $\dot{V}O_{2max}$, are therefore relatively small in comparison with the large effects produced by changes in carbohydrate concentration (Fig. 2) or gastric volume (Fig. 3).

PRACTICAL RELEVANCE OF THESE STUDIES

The demonstration that gastric volume is a significant determinant of the volume of fluid delivered to the small intestine during exercise has three important practical implications.

First, it explains why it is theoretically possible to ingest very large volumes of fluid during exercise if one drinks frequently and maintains a large gastric volume. This would explain why it is possible for some predisposed athletes to ingest such large fluid volumes during prolonged exercise that they develop hyponatremia as a result of fluid overload (22).

Second, it predicts that different drinking patterns can produce the same rates of carbohydrate delivery during exercise from solutions with quite different carbohydrate concentrations. (Compare total carbohydrate delivery from the 18% carbohydrate solution in the top panels of Fig. 3 with the 7% carbohydrate solution in the lower panels of the same figure.) However, the rates of fluid delivery from such solutions will differ, as will their effects on intestinal fluid transport; solutions with high carbohydrate content will initially cause net fluid movement into the small bowel and may therefore contribute to the development of dehydration.

Third, it provides the exercise physiologist with a reasonable model for the design of studies to optimize carbohydrate and fluid delivery from different carbohydrate-containing solutions during exercise.

Fourth, the finding that gastric volume has an important influence on the rate of gastric emptying raises the question of how gastric emptying rates should be expressed. Clearly, comparisons of rates of gastric emptying (expressed in ml·min^{-1}) from different studies are only valid if the volumes ingested in the studies are identical and the drinking patterns are comparable. For studies in which these variables are not controlled, it might be preferable to express the gastric emptying rate as a percentage of the initial volume emptied in a specified time. For example, an index such as GE_{10} expressed as a percentage might indicate the percentage of the initial volume ingested that was emptied during a subsequent 10 min period. Alternatively, comparing the slopes of the log-transformed data may be useful in studies in which the multiple sampling technique is used (32,33).

Finally, it must also be appreciated that there are large individual differences in rates of gastric emptying for the same solutions (13). It is probable that this reflects, in part, different individual responses to changes in gastric volume. This is a topic which requires further study.

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PEAK RATES OF DIURESIS IN HEALTHY HUMANS DURING ORAL FLUID OVERLOAD

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Objective. To determine whether rates of intestinal fluid absorption and renal diuresis can match high rates of fluid ingestion in healthy humans exposed to oral fluid overload, thereby preventing the development of hyponatraemia either by reverse sodium movement across the intestine (the Priestley-Haldane effect) or by expansion of the extracellular fluid volume.

Methods. Changes in renal function and in plasma chemical measurements in response to an oral fluid overload (0.9 - 1.8 l/h x 3 h) were investigated in 6 healthy control subjects at rest, and in a subject with a history of exercise-induced symptomatic hyponatraemia, during both prolonged (160-minute) exercise and at rest.

Findings. All control subjects gained weight (2.7 ± 0.2 kg, mean ± standard error of mean (SEM)) because the rate of oral fluid intake exceeded the peak rate of urine production (778 ± 39 ml/h). Blood volume rose by 7.1 (± 0.5)% and plasma sodium concentrations fell progressively from 144 ± 2.6 to 136 ± 1.1 mmol/l ($P < 0.05$) in the control subjects. Plasma potassium and angiotensin II concentrations were unchanged and creatinine clearance was normal (~125 ml/min). Free water clearance reached a maximum of 11.2 ± 0.9 ml/min after 2 hours. The increase in body mass could be accounted for by calculated or measured changes in extra- and intracellular fluid volumes. Similar changes were measured in the subject with a previous history of symptomatic hyponatraemia.

Conclusion. The rate of intestinal fluid absorption appeared to match the rate of oral fluid ingestion and there was no evidence of fluid accumulation in the intestine with reverse sodium movement from the extracellular space into intestinal fluid. The results of this study are therefore at variance with the Priestley-Haldane hypothesis and suggest that reverse sodium movement did not contribute to the hyponatraemia induced by oral fluid overload in these subjects. Rather it appears that humans may have a limited capacity to excrete fluid at rates in excess of ~900 ml/h in response to higher rates of oral fluid intake. When the rate of intestinal fluid absorption matches the rate of fluid ingestion and exceeds the kidneys' maximum capacity for fluid excretion, the excess fluid accumulates in the extra- and intracellular fluid compartments, inducing the dilutional hyponatraemia of water intoxication. These findings may have relevance to other clinical conditions in which hyponatraemia develops in response to high rates of oral or intravenous fluid provision.

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Since it was first reported in 1981,[1] symptomatic hyponatraemia of exercise induced by oral fluid overload[2,3] has been increasingly recognised in athletes competing in ultra-endurance events including 90 km[3,4] and 160 km/24 footraces,[5-7] and the 226 km Ironman Triathlon.[8] More recently the condition has been described in 42.2 km marathon runners,[9] in military personnel[10] and even in recreational hikers.[11,12]

There are two potential mechanisms by which oral fluid overload can induce hyponatraemia. If the rate of fluid absorption from the intestine exceeds the maximum rate of renal diuresis, then the total body water will increase causing dilution of the serum sodium concentration.

Alternatively, as proposed by Priestley[13] in 1916, '*Pari passu* with absorption of water from the intestine, salts at first pass out of the blood into the water in the intestine. As a consequence of this loss of salts the conductivity of the blood plasma is diminished, and its proportion of salts to water is similarly diminished.' If it is of a sufficient magnitude, this reverse sodium movement into the unabsorbed intestinal fluid could induce hyponatraemia by a third space effect. It is now well established that, when hypotonic solutions with low (< 50 mmol/l) sodium content are ingested, sodium is rapidly transferred from the extracellular space into the ingested fluid as it enters the duodenum.[14-16]

Accordingly, the principal aim of this study was to determine whether normal humans have a limited capacity for diuresis when they ingest fluid at high rates and whether this causes hyponatraemia either due to rapid fluid absorption with dilution of the serum sodium concentration, or as the result of a probable third space effect if the rate of intestinal fluid absorption is less than the rate of oral fluid ingestion.

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To evaluate this, we compared the changes in renal function and in plasma chemical measurements in response to oral fluid overload in 6 healthy control subjects under resting conditions and in 1 experimental subject who had developed severe symptomatic hyponatraemia during the 1992 90 km Comrades Marathon, the ultramarathon race where hyponatraemia of exercise was first recognised.[14]

MATERIAL AND METHODS

The experiments on 6 healthy, athletic male controls with ages ranging from 28 to 44 years (34 ± 2.6 years, mean ± standard error of the mean (SEM) with masses of 64.9 - 90.3 kg (78.8 ± 3.77 kg) and 1 male ultramarathon runner aged 32 years, with a body mass of 69.5 kg and a history of hyponatraemia during exercise, were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association and approved by the Research and Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. All subjects signed an informed consent before participating in the study and were free to withdraw at any time.

The 6 control subjects were studied while each drank 1 500 ml of fluid per hour. Fluid was ingested for 3 hours at a rate of 250 ml every 10 minutes in order to maximise the rate of gastric emptying.[15] Subjects then recovered for a further 2 hours. Subjects remained at rest during the study.

Body mass (Seca Balance, Germany) and urine volume were measured at regular 15-minute intervals during the trial. Blood samples were collected for subsequent determination of haemoglobin concentrations. After centrifugation for 10 minutes at 2 500 *g* the plasma was removed and stored frozen for subsequent analyses. Total plasma protein content was determined using the Biuret method. Plasma creatinine, sodium and potassium, and urinary creatinine, sodium and potassium concentrations were determined on a Beckman Astra Synchron AS8 multichannel analyser (Beckman Instruments, California). Plasma angiotensin II concentrations were determined by radio-immunoassay, as previously described.[16,17] Haemoglobin was determined by the standard spectrophotometric cyanomethaemoglobin technique. Changes in blood volume were calculated from the measured dilution of the haemoglobin concentration.

Plasma and urine osmolalities were measured in an Osmerte A Automatic osmometer (Precision Systems Inc., Newton, Mass., USA).

The experimental subject was studied because he had been admitted to hospital with severe symptomatic hyponatraemia following his participation in the 90 km Comrades Marathon footrace. He estimated that he had ingested approximately 1 500 ml/h during the 10 hours 28 minutes that he ran the race (average speed 8.6 km/h). Following the race, he became confused and was referred to hospital where, on admission, he was found to be semi-comatose with a serum sodium concentration of 123 mmol/l, a haemoglobin concentration of 14 g/dl and a haematocrit of 42%. Plasma vasopressin concentration was 7.6 pg/ml (normal range 2 - 10 pg/ml), plasma renin activity was 9.8 ng/ml/h (normal range 1.0 - 2.4 ng/ml/h (erect), 0.5 - 2.6 ng/ml/h (supine)) and plasma aldosterone concentration 632 ng/100 ml (normal range 50 - 350 ng/100 ml). Urinary sodium concentration ranged from 10 to 21 mmol/l. He was treated with the diuretic, furosemide, and a slow intravenous infusion of normal saline (1 000 ml/12 h).

During the next 36 hours he passed 6.1 litres of urine, indicating a fluid excess on admission of greater than 3 litres. After 36 hours, serum sodium concentration stabilised at 141 mmol/l, haemoglobin concentration was 12.6 g/dl and haematocrit 37%, plasma vasopressin concentration was 9.4 pg/ml, plasma renin activity was 1.6 ng/ml/h and plasma aldosterone concentration was 169 ng/100 ml. Plasma volume increased 17% during recovery, as estimated from the equations of Dill and Costill.[20] Further recovery was uneventful. The athlete returned to running within a week of hospital discharge.

Five months after this episode of hyponatraemia, the subject consented to being studied in the laboratory in order that his response to high rates of fluid ingestion both at rest and during exercise might be compared with those measured in the control subjects.

In the first study, he ingested 900 ml/h (150 ml every 10 minutes) of tap water for 3 hours while resting in the supine position. This was followed by a 3-hour recovery period during which he did not ingest any additional fluid.

On the following day he ran on a treadmill for 4 hours at the average pace he had sustained during the Comrades Marathon (8.6 km/h). He began by ingesting tap water, as before, at a rate of 900 ml/h for the first 80 minutes of the trial. Thereafter the rate of fluid ingestion was doubled to 1 800 ml/h (300 ml every 10 minutes) while he continued to run for a further 160 minutes. He then recovered for a further 2 hours while lying supine on a bed. He did not drink any additional fluid during recovery.

Attempts to contact and study additional South African subjects who have developed hyponatraemia of exercise, have yet to be successful. However, a collaborative study of subjects who developed hyponatraemia during the Auckland Ironman Triathlon has been initiated (D Speedy *et al.* — completed manuscript in press).

Calculations and statistical methods

Creatinine and free water clearance were calculated according to conventional equations.[21,22]

Extracellular fluid (ECF) volumes were calculated from

changes in blood volume (dBV) according to the following equation:

$$ECF_2 = ECF_1 + (ECF_1 \times \frac{dBV\%}{100}).$$

Similarly, intracellular fluid (ICF) volumes were calculated from changes in plasma osmolality (dOSM) according to the following equation:

$$ICF = ICF_1 + (ICF_1 \times \frac{dOSM\%}{100}).$$

The initial ECF volume (l) was calculated as 0.375 (0.57 × body mass in kg) and the ICF volume (l) as 1.66667 × ECF volume.[23]

Statistical methods

Results from the control group are the means (± SEMs) of 6 subjects. The statistical significances of changes over time were assessed with a one-way analysis of variance (ANOVA) for repeated measures and located using a Scheffé *post hoc* test. A value of $P < 0.05$ was regarded as significant.

Results

Responses to high rates of fluid intake in the control subjects are shown in Fig. 1. Cumulative urine production was less than the rate of fluid ingestion, hence body mass rose progressively with fluid ingestion; the peak increase was in excess of 2.5 kg after 3 hours of fluid ingestion. Body mass was still elevated by more than 1 kg at the end of the experiment, 2 hours after the cessation of fluid ingestion.

Plasma sodium concentrations and osmolality fell progressively for the first 2 hours of the experiment and were significantly below the starting value from 100 - 180 minutes. Plasma sodium concentrations then rose during the final 80 minutes of the experiment.

Blood volume rose progressively by up to 7.1 (± 0.5)% for the first 240 minutes of the experiment and was still elevated at 300 minutes. Neither plasma potassium nor angiotensin II concentrations changed during the water ingestion experiment, whereas plasma protein and creatinine concentrations fell, albeit insignificantly.

Measures of renal function in the control subjects are shown in Fig. 2. Urinary sodium, potassium and creatinine concentrations and urine osmolality fell steeply in the first 90 minutes of the experiment and remained low thereafter. Total urinary sodium and potassium losses during the first 3 hours of the study were 120 ± 24 and 26 ± 8 mmol respectively.

Creatinine clearance calculated from successive urine samples was in the normal range and did not change between 60 and 300 minutes. The unphysiologically high initial values

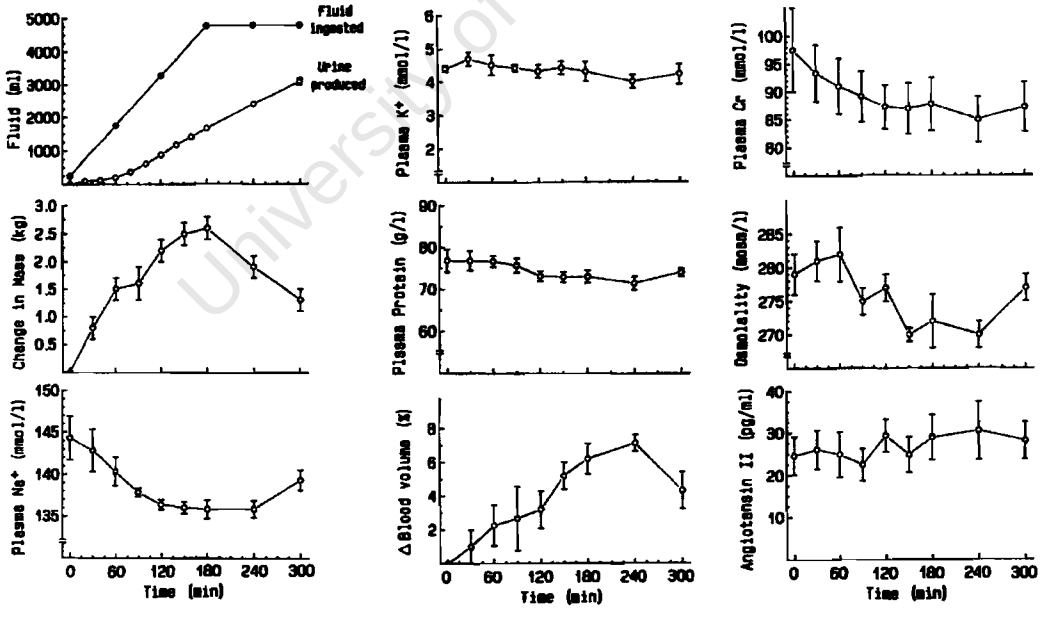

Fig. 1. Serial changes in cumulative fluid ingested and urine produced, mass, plasma sodium (Na^+), potassium (K^+) and protein concentrations, blood volume, plasma creatinine (Cr) concentrations, osmolality and angiotensin II concentrations in 6 control subjects studied at rest for 5 hours.

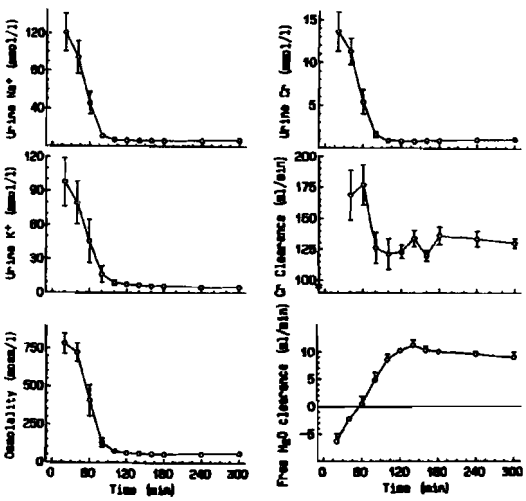

Fig. 2. Serial changes in urine sodium (Na^+) and potassium (K^+) concentrations, osmolality, urine creatinine (Cr) concentrations, and free water (H_2O) clearance in response to oral fluid overload in 6 control subjects studied at rest for 5 hours.

presumably result from the delay in the initial diuresis (Fig. 1) causing unrepresentative urinary samples.

Free water clearance increased for the first 150 minutes of the study, reaching a plateau thereafter. The peak rate of free water clearance was 11.2 (± 0.9) ml/min.

Fig. 3 shows cumulative volumes of fluid ingested and urine produced, and the hourly changes in body mass, plasma sodium, protein and angiotensin II concentrations in the symptomatic subject at rest and during exercise.

Under both experimental conditions, rest and exercise body mass increased steadily while fluid was ingested. In both trials, the change in mass was similar and exceeded 2 kg at the end of fluid ingestion. Plasma protein concentrations rose during exercise but fell progressively under resting conditions. Plasma sodium concentrations fell while fluid was ingested in both trials but began to rise when fluid ingestion ceased. The extent of the fall was similar in both trials. Plasma angiotensin II concentrations also fell progressively and equally in both trials. The rate of urine production lagged behind the rate of fluid ingestion but was similar in both trials. The greater evaporative sweat losses during exercise probably explains why the change in mass was the same in both trials even though considerably more fluid was ingested during the exercise trial.

During both trials, the symptomatic subject first passed urine at 3 hours by which time there was already a large fluid excess (Fig. 3). Palpation of the bladder confirmed that retention of urine in the bladder did not explain this failure of urine production. Rates of urine production continued to rise and were highest (660 ml/h) during the last hour of the experiment, that is 4 hours after the initiation of drinking and 1 - 2 hours after the cessation of drinking.

When compared with the control subjects, the extent of the fall in the plasma sodium concentration was similar in the symptomatic subject. Indeed, responses to oral fluid loading in the symptomatic subject and the controls were essentially the same except that the control subjects began to pass urine at higher maximum rates in excess of 799 ml/h within 120 minutes of initiation of fluid ingestion. In contrast the peak rate of urine production tended to be lower (660 ml/h) but not significantly so in the symptomatic subject and was reached only 4 hours after commencement of fluid ingestion.

In addition, the onset of urine production was significantly delayed in the symptomatic subject (180 v. 20 minutes). Plasma angiotensin II concentrations declined over time in the symptomatic subject during both exercise and control experiments but were maintained in the controls (compare Figs 3 and 1).

Fig. 4 shows cumulative changes in calculated intra- and extracellular fluid volumes and measured changes in urine

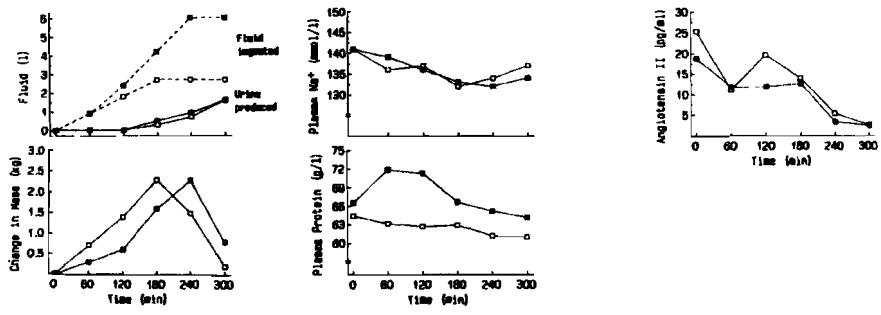

Fig. 3. Serial changes in cumulative fluid ingested and urine produced, mass, plasma sodium (N^+), protein and angiotensin II concentrations in the symptomatic subject studied at rest for 5 hours (□), and during 4 hours of low-intensity exercise followed by 1 hour of rest (■).

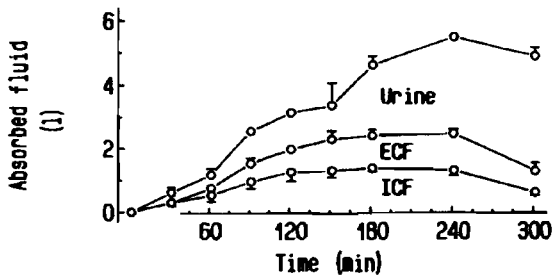

Fig. 4. Serial changes in absorbed fluid in 6 control subjects studied at rest for 5 hours. Cumulative urine production and fluid accumulation in the intracellular (ICF) and extracellular (ECF) spaces matched the rate of oral fluid ingestion suggesting that intestinal fluid absorption matched the rate of oral fluid ingestion.

production. Summing these volumes at each time point indicates that these changes account for the measured changes in body mass. Thus the calculated rate of intestinal fluid absorption matched the rate of fluid ingestion in these subjects.

Discussion

The most striking finding of this study was that none of the control subjects nor the ultramarathon runner with a history of symptomatic hyponatraemia was able to increase his rate of urine output to equal the high rates of fluid intake. As a result each subject gained weight during the trial. The maximum rates of urine production varied from 735 to 970 ml/h (Fig. 1) in the control subjects. In the symptomatic subject, the rate of urine production was somewhat lower (660 ml/h) and the onset of diuresis was delayed until 3 hours after the start of fluid ingestion (Fig. 3).

Coincident with the increase in body mass, plasma sodium concentrations declined progressively in all subjects, recovering only after fluid ingestion had terminated. The extent of the fall was similar in both the symptomatic subject who drank 900 ml/h at rest and in the control subjects who drank 1 500 ml/h at rest, despite large differences in ingested volumes (Figs 1 and 3).

There are two possible explanations for the lower rates of urine production than of fluid ingestion leading to fluid retention and the development of hyponatraemia in all these subjects. The first possibility is a limiting maximal rate of urine production of about 1 000 ml/h.[24] As a result subjects retained fluid and gained weight when they ingested fluid at faster rates. This hypothesis predicts that the maximum intestinal absorptive capacity exceeds the maximum capacity of the kidneys to excrete a fluid load, leading to fluid retention. This retained fluid would distribute to all body compartments leading to dilutional hyponatraemia. Figs 1 and 4 provide evidence to support this explanation in these subjects under these experimental conditions.

Fig. 1 shows that the calculated blood volume rose progressively for the first 240 minutes of the experiment as plasma sodium concentrations fell significantly. The peak rise in the blood volume (7%) approximates the magnitude of the peak reduction in plasma sodium, protein and creatinine concentrations (Fig. 1).

Fig. 4 shows the calculated distribution of the ingested fluid at the different time points during the experiment. It shows that, at each time point, all the ingested fluid can be accounted for either as urine produced or as an increase in intra- or extracellular fluid volume.

Fig. 4 also shows that the time course of fluid distribution into the different compartments matched closely the rate at which the fluid was ingested. This suggests that the rate of intestinal fluid absorption closely matched the rate of fluid ingestion of 1.5 l/h. Hence this study suggests that the maximum rate of intestinal water absorption in these subjects exceeded 1.5 l/h, at least at rest. If this is correct, the corollary must be that the maximum rate of renal free water clearance is somewhat less than that value.

Other studies[25,26] have indeed calculated maximum rates of intestinal fluid absorption at rest and found rates of 0.82 and 1.7 l/h respectively. Intestinal function may indeed be designed to provide 'enough but not too much',[27] but the results of this study suggest that sufficient capacity for intestinal fluid absorption exists to exceed the maximum capacity of the kidneys to excrete the ingested fluid load.

Hence this study would seem to confirm the belief that the maximum rate of urine production is less than 1 000 ml/h.[24] Indeed, in keeping with the findings of Haldane and Priestley,[28] we found that the maximum rate of diuresis in the control subjects was around 900 ml/h (Fig. 1). Fig. 5, redrawn from the data of Haldane and Priestley,[28] shows the response of Priestley to high rates of fluid intake. The maximum rate of urine production was similar in both experiments despite different rates of fluid ingestion.

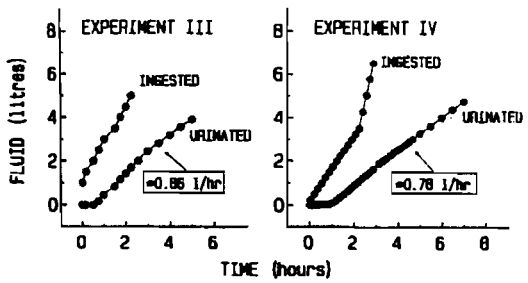

Fig. 5. Priestley's cumulative fluid intake and urine output during two separate experiments in which he ingested fluid orally at high rates. Redrawn from Haldane and Priestley.[28]

The contrasting explanation for the development of hyponatraemia in response to high rates of fluid ingestion, first suggested by Priestley[13] and Haldane and Priestley,[28] is that the low rates of urine production result from rates of intestinal water absorption that are lower than the rates of fluid ingestion, leading to fluid accumulation in the small bowel. Movement of sodium from the extracellular fluid space into the unabsorbed fluid, which has been demonstrated experimentally,[14-16] therefore provides a possible mechanism for hyponatraemia according to the original postulate of Priestley.[13]

For the reasons already described, this study finds no evidence in support of this theory. All the fluid ingested can be accounted for (Fig. 4), without postulation of delayed intestinal fluid absorption with reverse sodium movement from the extracellular fluid into the unabsorbed fluid in the small bowel.

In summary, this study shows that hyponatraemia can be induced in normal subjects at rest, simply by increasing the rates of fluid intake to greater than the maximum rates of urine production of about 900 ml/h in normal humans,[24] and sustaining these rates for some hours. At such high rates, the rate of intestinal water absorption matched the rate of fluid ingestion with distribution of the retained water into the extra- and intracellular fluid volumes. Movements of fluid into the intracellular compartment occurred in proportion to changes in osmolality and acted to buffer larger changes in ECF osmolality. Hence the conclusion is that the human has a limited capacity to maintain fluid and electrolyte homeostasis when challenged by a sustained high rate of fluid intake in excess of 1 l/h.[29-32]

The practical significance of this study is to show that hyponatraemia can occur in healthy subjects with normal renal function when the rates of hypotonic fluid ingestion exceed their maximum rates of urine production of about 1 000 ml/h either at rest (this study) or during exercise.[2,31] Hence, at least at rest, persons should not ingest fluid at rates > 1 000 ml/h. During exercise, it would be possible to ingest fluid at higher rates as another source of fluid loss, sweating induced by exercise, would assist in preventing an abnormal expansion of the ECF volume, leading to hyponatraemia. However, if exercise reduces the rate of urine production, then hyponatraemia might still occur at these rates of oral fluid ingestion if sweat rates are relatively low, as seems likely in the typical athlete who develops hyponatraemia of exercise.[3]

Persons with a reduced capacity for diuresis, for whatever reason, would be at greatest risk for the development of hyponatraemia; hence rates of water ingestion should probably be less in those subjects. Both the symptomatic subject reported in this study and that of Armstrong *et al.*[32] had maximal rates[32] of urine production somewhat lower than the maximal values measured in the healthy control subjects in this study (Fig. 1) or in Priestley (Fig. 5).

Finally, these findings may be relevant to other clinical conditions in which hyponatraemia develops in response to high rates of fluid provision either orally[29-32] or intravenously.[33,34]

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BMJ

Overconsumption of fluids by athletes

Advice to overdrink may cause fatal hyponatraemic encephalopathy

A recent report that a female participant in the 2002 Boston marathon died from hyponatraemic encephalopathy because she ingested excessive volumes of a sports drink before and during the race,[1] exposes an emotive debate that has raged for more than a decade.[2] At issue is how much should athletes drink during exercise.[3]

From antiquity to the late 1960s, athletes were advised not to drink during exercise since it was believed that fluid ingestion impaired athletic performance.[4] The publication in 1969 of an incorrectly titled article, "The danger of an inadequate water intake during marathon running,"[4] provided the impetus for change, even though the study neither examined a 42 km marathon race nor did it identify any dangers.[2] Rather, the most dehydrated athletes won those 32 km races, as is usually the case.[2] This article's incorrect title provided the intellectual incentive for numerous studies, many funded by a fledgling sports drinks industry, culminating in specific guidelines for ingestion of fluids during exercise.[3 5]

These guidelines make four assumptions. Firstly, that all the weight lost during exercise must be replaced if health is to be protected and performance is to be optimised, since, as the guidelines state, the greatest threat to health and wellbeing during prolonged exercise, especially when performed in the heat, is dehydration.[6] Secondly, that the sensations of thirst underestimate the real fluid requirements during exercise. Thus athletes must be told how much to drink during exercise. Thirdly, that the fluid requirements of all athletes are always similar so that a universal guideline is possible. Fourthly, high rates of fluid intake can do no harm. Thus athletes are now advised to replace all the water lost through sweating (that is, loss of body weight), or consume the maximal amount that can be tolerated or drink 600-1200 ml per hour.[5]

But none of these ideas is evidence based.[2 3] In particular, there is no evidence that athletes must drink "the maximal amount that is tolerable" to optimise performance and prevent medical consequences. Thus the hyperbolic statement, "If strenuous exercise is undertaken by hypohydrated subjects, the medical consequences can be devastating," has no factual basis.[7] Nor is it proved that all the weight lost during exercise must be replaced immediately, since the resting human may carry a fluid reserve of about 2 litres.[2 3] Nor were prospective trials undertaken to ensure that these guidelines are always safe. Thus it was not then appreciated that unrestrained drinking, either at rest[8] or during exercise[9] can have fatal consequences.[1 2 8–12]

The first reports of hyponatraemic encephalopathy in athletes, army personnel, and hikers appeared shortly after the change to this new "drink the maximal amount that can be tolerated" dictum.[2 3 9 10] To date at least seven fatalities and more than 250 cases of this condition have been described in the medical literature.[9–12] Presumably reported cases represent a small proportion of all such cases.

Aside from military personnel, the athlete most likely to develop hyponatraemic encephalopathy is a female marathon runner, who runs those 42 km races at speeds slower than 8-9 km/h (about 5 mph). She gains weight during exercise because she drinks excessively both before and during exercise, sometimes in excess of 100 cups of fluid during the race (about 15 litres of fluid during 5-6 hours of exercise.)[12] She does not develop a marked sodium deficit, nor does she have evidence of inappropriate secretion of antidiuretic hormone, although antidiuretic agents are clearly active.[10] Since the cause of the condition is now known, prevention is possible. Thus Gardner has concluded that further deaths from hyponatraemic encephalopathy in the United States army will reflect the failure of the system to protect adequately its personnel through policy, procedures, and implementation.[9]

To protect all exercisers from this preventable condition, rational and evidence based advice must be provided.[3] In particular, exercisers must be warned that the overconsumption of fluid (either water or sports drinks) before, during, or after exercise is unnecessary and can have a potentially fatal outcome. Perhaps the best advice is that drinking according to the personal dictates of thirst seems to be safe and effective.[2 3] Such fluid intake typically ranges between 400 ml and 800 ml per hour in most forms of recreational and competitive exercise; less for slower, smaller athletes exercising in mild environmental conditions, more for superior athletes competing at higher intensities in warmer environments.[3]

The recent adoption of these guidelines by USA Track and Field (www.usatf.org) provides the hope that this sad scientific aberration has finally run its tragic course.[3]

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Van die Redaksie/Editorial

Why marathon runners collapse

For 12 000 of the more dedicated South African runners, the year reaches its climax on 31 May when they accept the challenge of trying to cover the 90 km between Durban and Pietermaritzburg on foot in less than 11 hours — and thus earn one of sport's most coveted possessions, a Comrades' Marathon finisher's medal.

For the 1988 race there would appear to be at least two certainties — that Bruce Fordyce will win for the 8th successive year in a time of about 5 hours and 34 minutes, and that 500 or more runners will be sufficiently exhausted at the finish to require urgent, and often sophisticated, medical attention. Why should so many apparently robust athletes become so severely incapacitated after participating in what is generally believed to be a healthy activity?

The earliest and still the most popular explanation is that runners who collapse after marathon or ultramarathon races are suffering from dehydration-induced hyperthermia. The origin of this theory can be traced to a classic study by the late Professors Wyndham and Strydom,[1] then of the Chamber of Mines in Johannesburg, who studied groups of runners competing in races of 32 km and showed that those who were dehydrated by more than 3% had elevated body temperatures. They concluded that one of the most important determinants of the rectal temperature in marathon runners during competition was their level of dehydration. Interestingly, this conclusion failed to take account of their own[2] and other findings,[3] which showed that metabolic rate is a significant determinant of body temperature during exercise. On the basis of their findings,[1,4] they suggested that runners needed to drink at least 900 ml of fluid per hour during competition to prevent collapsing from heatstroke. It took only a small leap of faith to conclude that all runners who collapsed after marathon and ultramarathon running must be both dehydrated and hyperthermic. Remarkably, nearly two decades later, this belief continues to dominate clinical practice despite a wealth of evidence to the contrary.

As reviewed in detail elsewhere,[5,6] the overwhelming majority of marathon and ultramarathon runners are only mildly hyperthermic at the finish of these races. The range of average post-exercise rectal temperature in all reported studies is between 38°C and 40°C — that in the majority of runners being below 38,9°.[5,6]

In marathon and ultramarathon runners who have collapsed and in whom rectal temperatures have been measured, the same has been found;[7] their mildly elevated temperatures indicate that hyperthermia could not be even a minor factor contributing to their collapse. Paradoxically, hypothermia has been found in some runners who have collapsed after competing in marathon or longer races run in cold, wet and windy conditions.[7,9] The possibility that some runners who collapse may be suffering not from heatstroke but from hypothermia emphasises that even in field-side sports medicine, clinical diagnoses must be confirmed whenever possible by appropriate clinical or laboratory tests. Undoubtedly, in the past some hypothermic runners have been treated for 'heatstroke'.

Why should the rectal temperatures of marathon and ultramarathon runners be quite low and why do they risk developing hypothermia when competing in cold conditions? The answer would seem to be that the main determinant of the rectal temperature and also the sweat rate during marathon and ultramarathon running is almost certainly not the level of dehydration (T. D. Noakes *et al.* — unpublished observations)[6] but the metabolic rate (T. D. Noakes *et al.* — unpublished observations)[8,9] which is determined principally by the athlete's mass and running speed. As the running speed falls with running distance,[10] it follows that the rectal temperature, the sweat rate and the risk of developing heatstroke will in fact be lowest in runners competing at the longest distances. Unfit athletes who are forced to walk in marathon or ultramarathon races under cold conditions risk collapsing from hypothermia;[7–9] only those running very fast for short distances in severe environmental conditions are at high risk of developing environmentally and exercise-induced heatstroke.[6,11]

Clinically serious levels of dehydration have never been recorded in large numbers of subjects competing in any modern ultradistance event including some run in severe environmental conditions.[6,12–15] A diagnosis of 'dehydration' can only be accurately confirmed if the subject's mass loss during exercise is measured or if there is evidence of a marked change in plasma volume. The evidence is that the average mass loss during marathon and ultramarathon races is seldom more than 3 kg,[5,6] of which at least 2 kg represents the obligatory losses of oxidised metabolic fuel (200-400 g) and the water stored with glycogen (1,8 kg) that is released as the glycogen is mobilised during exercise.[6] Thus a mass loss of even 3 kg in a marathon runner would comprise a real fluid loss of less than 1 kg or about 2% of total body water.

It is therefore not surprising that many studies have shown that plasma volume changes little during marathon[5,16] and ultramarathon running (R. A. Irving *et al.* — unpublished observations) in those who lose up to 3 kg body weight during these races. In the only such study yet reported,[17] the plasma volumes of 21 of 25 women marathon runners either increased or stayed the same during the race. This suggests that the majority of these women runners may have ingested too much fluid during the race.

Renal function is well maintained during marathon and ultramarathon races in runners who lose up to 3 kg of body mass (R. A. Irving *et al.* — unpublished observations),[18] confirming that clinically significant dehydration is not present even in those who undergo quite large mass losses during prolonged exercise.

If the majority of marathon and ultramarathon runners are neither hyperthermic nor dehydrated, why do so many collapse?

Clearly, some runners do collapse because they fail to drink enough fluids and to ingest sufficient carbohydrate either before ('carbohydrate loading') or during marathon and ultramarathon races and so become hypoglycaemic.[7] Some may even develop heatstroke,[19,20] but it is probable that this type of runner has an hereditary predisposition and may, in fact, be suffering from stress-induced malignant hyperthermia.[21,22] This is particularly likely in those who collapse when running in relatively mild environmental conditions.[19] Others may suffer acute myocardial infarction or ventricular fibrillation.[23]

Of great concern at preent is the small number of runners (less than 0,3% of all runners in the 1985 and 1986 Comrades' Marathons (T. D. Noakes *et al.* — unpublished observations)) who develop profound life-threatening hyponatraemia[24-26] almost certainly because of an excessive fluid intake — usually during events lasting more than 8 hours. It would appear that women are at greater risk than men, probably because their lower body mass and generally slower running speed makes it more likely that fluid intake will exceed requirements. The danger of this condition is that not only does it have a high mortality but that it may result in permanent brain damage.[27] At least some of the responsibility for the prevalence of this condition lies with those who continue blindly to overemphasise the dangers of 'dehydration' in marathon and ultramarathon runners.

While it is obviously important to recognise that these specific medical conditions may be present in runners who collapse, it is also clear that the vast majority of them do not fit any of these diagnostic categories. Thus another explanation must be offered.

Initially, it would seem that the principal physical sign common to all runners who collapse is postural hypotension, which is shown by their inability to stand without support. If these runners do not have reduced plasma volume,[5,16] then intravascular volume depletion cannot explain the hypotension. Consequently, intravenous fluid therapy is not a rational form of treatment. It is most likely that hypotension results from a persistence, after exercise, of the large fall in total peripheral resistance that develops during exercise.[12] Provided the athlete maintains cardiac output by exercising, blood pressure will not fall excessively. However, on cessation of exercise, the fall in cardiac output will cause profound hypotension if it is not matched by an equivalent rise in total peripheral resistance. This mechanism would explain why the majority of athletes collapse shortly after they stop running in marathon and ultramarathon races. If this theory is correct, it suggests that rational treatment of these patients is not administration of intravenous fluids but induction of vasoconstriction in the persistently dilated peripheral vessels in the previously active skeletal muscles.

Are there circulating factors activated by exercise which might explain the persistence of postural hypotension in runners who collapse? The novel study by Brock-Utne *et al.*,[28] showing that 81% of Comrades' Marathon runners who collapsed had elevated plasma lipopolysaccharide (LPS) and reduced anti-LPS antibodies, raises intriguing questions: (*i*) whether endotoxaemia explains the hypotension; and (*ii*) how the endotoxin breached the gut wall given that the highest endotoxin levels were measured in the slowest runners who were under the least physiological stress during the race and who would also have finished with the lowest body temperatures. Clearly, these are fundamentally important questions, answers to which may well contribute significantly to our understanding of this perplexing problem.

But probably the most important practical message from all these studies is that each runner who collapses deserves a firm clinical diagnosis made on the basis of a carefully taken medical history and clinical examination. The history should determine whether the athlete has specific symptoms; whether he or she drank too much or too little fluid during the race; whether sufficient carbohydrate was ingested before and during exercise; and whether progressive clouding of consciousness is present suggesting hyponatraemia, hypoglycaemia or even hypo- or hyperthermia. The presence of muscle twitching, muscle fasiculation or an epileptic fit suggests hyponatraemia. The clinical diagnosis should be confirmed by the use of at least some basic tests, including the measurement of the rectal temperature and the blood glucose level. When both are normal and the runner reports an adequate fluid intake of 500 ml or more of fluid per hour of exercise,[6] the temptation to give intravenous fluids should be resisted, at least until the serum sodium level has been measured and shown to be elevated. Simply to conclude that all runners who collapse are 'dehydrated' and require intravenous fluids is no longer acceptable, particularly when such treatment may exacerbate life-threatening hyponatraemia (T. D. Noakes *et al.* — unpublished observations).[24]

In the final analysis, masterful inactivity may prove to be a highly effective form of treatment for the majority of hypotensive marathon and ultramarathon runners who collapse and who are shown on simple tests to be neither hypoglycaemic, hypo- nor hyperthermic nor hyponatraemic, and who have taken adequate fluids at regular intervals during the race.

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clinical investigations

Clinical and biochemical characteristics of collapsed ultramarathon runners

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ABSTRACT

HOLTZHAUSEN, L.-M., T. D. NOAKES, B. KRONING, M. DE KLERK, M. ROBERTS, and R. EMSLEY. Clinical and biochemical characteristics of collapsed ultramarathon runners. *Med. Sci. Sports Exerc.*, Vol. 26, No. 9, pp. 1095–1101, 1994. To evaluate the characteristics of runners with exercise-associated collapse (EAC), we studied the time of onset of collapse, rectal temperatures, cardiovascular status, and incidence of readily identifiable medical conditions in 46 male athletes who collapsed during or after a 56-km ultramarathon footrace run on a cool day. Data were compared with 65 control runners who did not collapse in the same race. Weight changes during recovery were studied in a subsample of both groups. The majority (85%) of runners with EAC collapsed after they had completed the race; rectal temperatures (38.5 ± 1.3°C, mean ± SD; range 35.5–42.0°C) and supine heart rates (87.5 ± 17.2 min^{-1}; range 60–138) were only modestly elevated. Postrace serum sodium concentrations, changes in plasma volume, and mass during recovery were not significantly different from values in control runners. We conclude that: (i) most cases of EAC (85%) occur after the finish line; (ii) runners collapsing during the race are more likely to have a readily identifiable medical condition than runners collapsing after the finish line; (iii) runners collapse most frequently near cutoff times for medals and race closure times; and (iv) 16% of EAC casualties and 19% of control runners have identifiable biochemical abnormalities.

EXERCISE-ASSOCIATED COLLAPSE, DEHYDRATION, FLUID STATUS, POSTURAL HYPOTENSION, HYPOTHERMIA

Mass participation in endurance events lasting more than 2 h had led to an alarming increase in the number of athletes presenting with exercise-associated collapse (EAC) (1,12,26,31). Although EAC is one of the commonest disorders presenting at the medical facilities supporting such events (1,12,31), it is the least understood. EAC is not in itself a diagnosis as it gives no indication of the cause of the condition. Rather it describes the main complaint, which is an inability to stand or walk unaided as a result of light-headedness, faintness, dizziness, or syncope (26,27,31). More severe symptoms usually resolve in the recumbent position. In some cases a medical condition such as exercise-induced hypoglycemia or exertional heatstroke (27) may be readily identified. But in the majority of cases no clear-cut diagnosis is apparent (27).

Uncertainty regarding the true nature of this condition has led to the charge that the majority of such cases may be receiving inappropriate management (21). Since it has traditionally been believed that most collapsed runners suffer from exercise-induced dehydration with or without hyperthermia (1,12,13,37), intravenous rehydration has traditionally been considered the first line of therapy for patients with EAC (10).

We have recently reported that some ultramarathon runners with EAC treated with intravenous fluids developed iatrogenic hyponatremia (16,24), suggesting that they may have been euhydrated or even overhydrated rather than dehydrated (16,22) at the finish of their race. Clearly, the underlying cause of EAC, even though probably multifactorial, must be established so that the safest and most appropriate treatment protocols can be developed.

This study was designed to identify the clinical and biochemical characteristics of EAC and determine the role that factors such as dehydration, postural hypotension, and hypoglycemia might play in its pathogenesis.

MATERIALS AND METHODS

The study was undertaken in the medical tent situated at the finish of the 1990 56-km Two Oceans Marathon that is run annually in Cape Town, South Africa. Written informed consent was obtained from all subjects on ad-

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mission to the trial, which had been approved by the Research and Ethics Committee of the Faculty of Medicine of the University of Cape Town.

Thirty-eight male runners (0.006% of the 6334 race finishers) who collapsed after the finish line were admitted to the medical tent. Another eight runners (0.001% of the race finishers) who collapsed during the race and not at the finish were also admitted to the medical tent and included in the study.

Runners with EAC had their vital signs assessed within 5 min of their admission to the medical tent. Measurement included rectal temperature, supine and erect blood pressures, and pulse rates measured with a Dinamap 8100T monitor (Johnson and Johnson, Johannesburg, South Africa). Blood pressure was first measured in the supine position. The runner was then asked to assume the standing, erect position and the supine blood pressure was taken within 1 min of assuming the erect posture.

Blood samples were then taken from an antecubital vein. These were processed immediately by centrifugation at 2000 revolutions·min^{-1} for 10 min and the serum stored frozen at −20°C until analysis. The unclotted samples were analyzed within 24 h.

Collapsed athletes were then treated with oral fluids and elevation of the pelvis and lower limbs. Ice packs were placed over the abdomen and extremities in runners (N = 6) with rectal temperatures greater than 39.5°C. Intravenous (IV) fluid therapy was given if there was no clinical response to this treatment within 20 min. As a result, 12 (26%) collapsed runners were given IV therapy. All recovered fully and none required hospitalization.

On discharge the runners were weighed on a Seca electronic scale (Vogel and Halke, Hamburg, Germany). They were given a plastic 2-l container in which to urinate over the next 24 h and a fluid balance chart to record their fluid intake over the same period. They were asked to return the next day to be reweighed and to have repeat blood samples and blood pressure measurements taken.

A control group of 65 male runners, who completed the race without collapsing, volunteered to participate in the study and gave their written informed consent. These runners were recruited by randomly asking for volunteers as they crossed the finish line. They were weighed and blood samples were taken as above within 10 min of finishing the race. For logistical reasons, rectal temperatures and blood pressure measurements were not taken in this group. They too were asked to return the following day with a 24-h urine sample and fluid balance chart.

Forty-eight control runners and 15 runners with EAC returned the following day. The low compliance among runners with EAC was probably because most (74%) came from distant cities and returned home soon after the race finish. This very low return of study group participants is a major drawback of this study and may have introduced some bias into the study, at least for data collected 24 h after the race.

The blood samples were analyzed for plasma and urinary electrolytes by flame photometry (Model 543 Beckman Instruments Inc., Galway, Ireland); creatinine by the Jaffe reaction measured on a spectrophotometer (Model 919 Beckman Instruments Inc.); chloride by CMT10 chloride titrator (Beckman Instruments Inc.); serum albumin and total protein by Technicon SMAC autoanalyzer (Beckman Instruments Inc.); and osmolality using an automatic osmometer (Osmotte A, Precision Instruments Inc., Newton, MA). Plasma renin activity was determined by the radioimmunoassay of generated angiotensin I using a ^{125}iodine gammacoat plasma renin activity immunoassay kit (CA-553). Aldosterone activity was obtained by a coated-tube nonextraction method (Diagnostic Products Corporation, Los Angeles, CA). Vasopressin activity was determined by a radioimmunoassay method developed locally. Blood drawn for hemoglobin concentration, hematocrit, and white cell count were analyzed with a Coulter S+2 automatic cell counter (Miami, FL).

Plasma volume changes were calculated according to the equations of Dill and Costill (7).

During the race the wet bulb globe temperature (WBGT) index was measured with a locally designed instrument.

Statistical Methods

The results were calculated as the mean and standard deviation. Statistical significance (P) was determined as follows: (i) for single, within group postrace and 24 h later differences with a paired Student's t-test using two-tailed P values corrected for unequal variance, and (ii) for multiple, between-group differences with a one-way analysis of variance and an unpaired Student's t-test using P values corrected for the total possible number of comparisons.

RESULTS

Both the start and finish of the race are situated geographically at the same point—a latitude of 33° 59′S and a longitude of 18° 24′. The race start was at 0600 h with cutoff times at the standard marathon distance (42.2 km) of 4.5 h and at the finish of 6 h. Runners not achieving these cutoff times are asked to stop running and could not continue the race.

Environmental conditions during the race were mild; the WBGT index measured 13.2°C at the start of the race. This rose to 15.6°C 3 h later and to 18.9°C at the cutoff finish time of 6 h.

Eight runners collapsed before finishing the race. All had identifiable medical conditions (Table 1) and were excluded from further analysis. The etiology of the gas-

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TABLE 1. Clinical diagnoses in eight runners who collapsed before finishing a 56-km ultramarathon.

Hypoglycemia (<3.8 mmol·l^{-1})	3
Gastroenteritis	3
Angina	1
Asthma	1

troenteritis, manifest by severe nausea, vomiting, and diarrhea in three runners, was not established.

There were no differences between runners with EAC and controls (C) in age (EAC: 33 ± 8 vs control C: 32 ± 8 (mean ± SD) yr), weight (EAC: 69.8 ± 10.4 vs C: 70.8 ± 8.9 kg), or race finishing time (EAC: 272 ± 53 vs C: 276 ± 42 min). When compared with the group of total finishers, the finishing times of runners with EAC were abnormally distributed with increased representation in the groups finishing between 225 and 240 min (4-h silver medal cutoff time) and between 345 and 360 min (race finish cutoff time). Runners with EAC were underrepresented in the groups finishing between 270 and 345 min (Fig. 1).

Table 2 lists the clinical findings in the runners with EAC at the time of collapse and 24 h later. No such data were collected in the control group. The mean pulse rate at the time of collapse was only moderately elevated but was significantly lower 24 h later. Mean supine blood pressure was essentially normal but fell by an average of 10 mm Hg on assuming the erect position. This posture-related drop in systolic blood pressure was not present 24 h later at which time systolic blood pressure in the supine and erect positions, and diastolic blood pressure in the erect position had all increased significantly (Table 2).

Postrace rectal temperatures ranged from 35.5–42.0°C (Fig. 2); 25% of values fell below 37°C and only 2.5% were above 40.5°C. Rectal temperatures, which were significantly lower 24 h after the race (Table 2), did not correlate with finishing time (r = 0.004); the highest rectal temperature was measured in one of the slowest

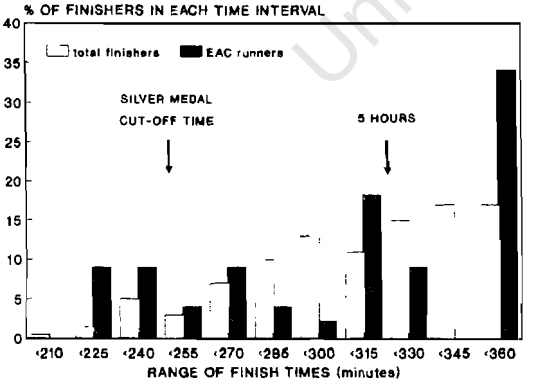

Figure 1—Comparison of distribution of finishing times of runners with EAC with that of all finishers in the 56-km ultramarathon. Note that runners with EAC were overrepresented in the groups finishing the race between 225 and 240 min and between 345 and 360 min.

TABLE 2. Cardiovascular measurements and rectal temperatures in runners with EAC immediately after the race and 24 h later.

	5 min after Race		24 h after Race	
	N	Mean ± SD	*N*	Mean ± SD
Heart rate (beats·min^{-1})				
Supine	35	88 ± 17	12	61 ± 8*
Erect	35	106 ± 14	12	72 ± 5*
Systolic blood pressure (mm Hg)				
Supine	34	121 ± 17	12	132 ± 9*
Erect	34	111 ± 16	12	134 ± 12*
Diastolic blood pressure (mm Hg)				
Supine	34	68 ± 17	12	67 ± 11
Erect	34	66 ± 16	12	78 ± 11*
Rectal temperature (°C)	33	38.5 ± 1.3	12	37 ± 0.8*

* $P < 0.03$ 5 min after vs 24 h after the race.

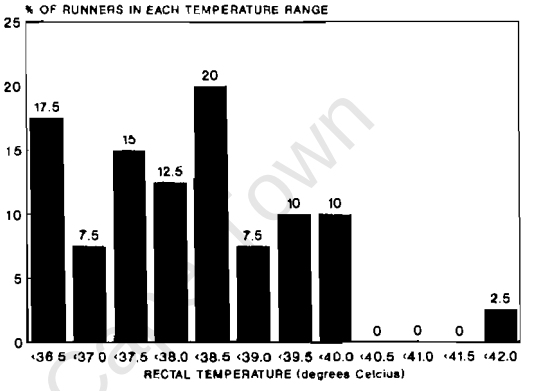

Figure 2—Distribution of postrace rectal temperatures in runners with EAC. Note that the rectal temperature of only one runner (2.5%) was greater than 40.5°C, whereas temperatures were subnormal (>37.0°C) in 17.5% of collapsed runners.

runners. Conversely, the lowest temperature (35.5°C) was measured in an athlete who completed the race in 259 min.

Table 3 shows that serum sodium, potassium, chloride, and glucose concentrations were not different between controls and runners with EAC, nor were they significantly altered 24 h later in either group. Hemoglobin, hematocrit, white cell counts, and total protein concentrations were also not different between groups. White cell counts and total protein concentrations fell in both groups during recovery. Serum renin activity and vasopressin concentrations showed a wide variance in both groups but were not significantly different between groups.

Serum urea and creatinine concentrations and serum aldosterone concentrations were significantly higher in runners with EAC. Although the urea concentrations normalized 24 h later and were not significantly different between the two groups, the creatinine concentrations remained significantly higher in runners with EAC. Urine volume (EAC: 1.1 ± 0.5 vs C: 1.5 ± 0.6 l), fluid intake (EAC: 2.3 ± 1.1 vs C: 2.5 ± 1.4 l), percent change in plasma volume (EAC: 14 ± 8 vs C: 7 ± 10%), mass

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TABLE 3. Blood biochemical and hematological measures in runners with EAC and in controls, 5 min and 24 h after a 56-km ultramarathon.

	5 min after Race				24 h after Race			
	Runners with EAC		Control Runners		Runners with EAC		Control Runners	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Glucose (mmol·l^{-1})	38	5.8 ± 1.5	59	6.1 ± 1.2	12	4.9 ± 0.4	44	4.8 ± 0.8
Sodium (mmol·l^{-1})	37	141 ± 3	60	142 ± 4	12	137 ± 5	44	138 ± 4
Potassium (mmol·l^{-1})	37	4.8 ± 0.7	60	4.6 ± 0.4	12	4.3 ± 0.4	44	4.1 ± 0.3
Chloride (mmol·l^{-1})	37	102 ± 3	56	103 ± 4	10	102 ± 4	43	103 ± 3
Total protein (g·l^{-1})	37	73 ± 6	56	73 ± 4	10	60 ± 6*	43	65 ± 6
Urea (mmol·l^{-1})	37	7.4 ± 1.9*	60	6.8 ± 1.4	12	5.8 ± 2	44	6.5 ± 1.4
Creatinine (pmol·l^{-1})	36	141 ± 26**	60	123 ± 23	12	104 ± 13*	44	95 ± 13
Serum osmolality (mOsm·kg^{-1})	37	284 ± 5.6	56	285 ± 7.1	10	275 ± 11	43	278 ± 8
Plasma renin activity (mg·l^{-1}·h^{-1})	20	18.1 ± 9.5	55	18 ± 10				
Vasopressin (pg·ml^{-1})	25	1434 ± 690	60	1278 ± 626				
Aldosterone (pmol·l^{-1})	25	5.8 ± 5.3*	64	3.8 ± 3.6				
Hemoglobin (g·dl^{-1})	37	15.8 ± 1	65	15.3 ± 1.2	9	15 ± 0.7	48	15 ± 1
White cell count (×109·l^{-1})	37	17.6 ± 3.7	65	16.8 ± 3.6	9	7.7 ± 3.1	48	6.5 ± 1.8
Hematocrit (%)	37	45 ± 0.1	65	44 ± 0.1	9	43 ± 0.1	48	43 ± 0.1

* $P < 0.05$; ** $P < 0.01$ between controls and EAC runners.

changes (EAC: 1.3 ± 1.7 vs C: 1.4 ± 1.4 kg) during the 24 h after the race were the same in the subgroups that were studied.

Table 4 shows the prevalence of identifiable medical conditions in the control runners and those with EAC. Hypothermia (11%), hyponatremia (8%), and hyperthermia (7%) were the common diagnoses in runners with EAC, but hyponatremia (10%) was more common in the controls.

DISCUSSION

There were four principal findings in this study, all of which add to an understanding of the etiology of EAC.

First, 85% of all the studied runners collapsed after finishing the race. Hence, any theory must explain why the cessation of exercise is an essential etiological factor for EAC.

Second, the prevalence of identifiable medical conditions was significantly more in those who collapsed before finishing the race (100%—Table 1) than in those who collapsed at the race finish (34%—Table 4).

Third, runners collapse more frequently near cutoff times for medals and race closure, suggesting that extreme physical effort, perhaps beyond the capabilities and training status of the participants, may play a role in the etiology of this condition.

Fourth, there was a high but equal incidence of abnormal biochemical and clinical findings in the collapsed (16%) and control (19%) runners. Hence, the real significance particularly of these biochemical changes including asymptomatic hyponatremia, which was present in 10% of control runners, is unclear. It must, however, be stressed that hyponatremia associated with symptoms, in particular alterations in the level of consciousness, is a potentially lethal condition (22) and should be suspected in collapsed subjects who do not respond to usual treatment.

TABLE 4. Incidence of identifiable medical conditions in runners with EAC and in controls.

	Runners with EAC % of Total Sample	Control Runners % of Total Sample
Hypothermia (<36.4°C)	11	0
Hyponatremia (<135 mmol·l^{-1})	8	10
Hypoglycemia (<3.8 mmol·l^{-1}	8	3
Hyperthermia (>40°C)	7	0
Hypernatremia (>150 mmol·l^{-1})	0	3
Hyperosmolality (>300 mosm·kg^{-1})	0	3

We also found that the cardiovascular status of the runners with EAC was essentially normal in the supine position; the mean systolic blood pressure of 121 mm Hg and a mean heart rate of 88 beats·min^{-1} are within the normal range for the postexercise recovery period. In contrast, patients with exercise-induced heatstroke or shock due to blood loss are markedly hypotensive and have heart rates in excess of 100 beats·min^{-1} (11).

Although a definitive conclusion cannot be drawn as rectal temperatures were not measured in the control group, this study provides no evidence that abnormalities in body temperature, especially hyperthermia, were a critical factor in the genesis of EAC.

The distribution of rectal temperature in the runners with EAC (Fig. 2) was not different from that reported in marathon and ultramarathon runners who do not collapse after these events (17,23,25) and in runners with EAC (1,26,27,31). Only one runner had a rectal temperature in excess of 40°C (Fig. 2), but there were no other clinical features of heatstroke in that subject. Rectal temperatures in excess of 40°C are found commonly in asymptomatic subjects performing exercise of moderate to high intensity (14).

The finding that hypothermia (25%) was a more common diagnosis than hyperthermia can probably be explained by the relatively mild weather conditions prevailing during this particular race. There was no relationship between race time and the probability that hypothermia would develop; race finishing times of hypothermic runners varied from 215–360 min.

On the basis of these findings we suggest that the term

"heat exhaustion" should not be considered synonymous with EAC, nor vice versa, as the rectal temperature is seldom markedly elevated in EAC (1,26,31) or in "heat exhaustion". For the same reason, neither EAC nor "heat exhaustion" should be considered a mild form of exertional heatstroke (4,12,30) as there is no evidence for impaired thermoregulation and elevated rectal temperatures in persons with so-called "heat exhaustion."

Perhaps the strongest indicator for the etiology of EAC in our subjects were the findings that (i) the great majority (85%) of such collapses occurred after the cessation of exercise and (ii) that all exhibited a postural change in blood pressure after the race (Table 2); this change was not present 24 h later. A potential link for these observations might be that the cessation of exercise causes inactivation of the muscle pump, which results in pooling of a sufficiently large volume of blood in the lower extremities and pelvis to cause circulatory decompensation leading to syncope. Any reduction in venous return resulting from blood pooling would be exacerbated by a number of additional variables.

First, a work-induced vasodilation in the muscles of the lower limb may further increase peripheral blood pooling. Also, the temperature-induced dilation of skin blood vessels resulting from the hot environment will further increase venous capacitance peripherally and therefore reduce the central blood volume (28).

This additional factor may explain why the incidence of EAC increases with the duration of exercise and is greatest after the longest races (20,21,26,31). Training, too, may attenuate the vasoconstrictor response to any hypotensive stress such as the sudden cessation of exercise particularly involving the lower limbs (32). Finally, fluid loss due to a combination of excessive sweating, diarrhea, or vomiting may further reduce central blood volume or venous return, or both.

Interesting, the early work of Adolph (2), Adolph and Fulton (3), Eichna and co-workers (8,9), Talbott et al. (33), and Weiner (34) drew attention to the possible role of postural hypotension in the etiology of "heat exhaustion" during or following exercise.

Adolph (2) noted that patients with "heat exhaustion" were "still producing sweat and keeping cool" but that they showed evidence of postural hypotension. Adolph and Fulton (3) concluded: "The peripheral blood vessels are greatly dilated during exposure to high temperatures, and this dilation continues indefinitely. The lack of a high resistance in the peripheral blood vessels prevents blood from returning to the heart. The heart rate increases steadily and rapidly, and is even able to increase the systolic blood pressure. In spite of this compensating activity on the part of the heart, the blood flow back to the heart finally becomes inadequate. At this point circulatory collapse or shock is complete, with faintness." Adolph (2) also noted that patients with this condition usually needed "merely to lie down to feel better. The shock-like circulatory failure appears to be the crucial element in this condition."

Talbott et al. (33) also concluded that "heat prostration is associated with vasomotor collapse. It is known that peripheral dilation of blood vessels and tachycardia accompany exposure to high temperature. During muscular activity in high environmental temperatures, the peripheral dilatation with vasomotor collapse may approach pathological proportions."

Similarly, Eichna et al. (8) showed that 58% of subjects developed syncope on their first exposure to "exhausting" exercise in the heat. Despite the finding that the rectal temperatures were not greatly elevated (<38°C) and were similar to those measured in our subjects with EAC, those authors labeled the condition "heat exhaustion." Others had also noted that the rectal temperature was either "submaximal or slightly elevated" in heat exhaustion 6). In common with the other early workers, Eichna et al. (9) proposed that postural hypotension explained the syncope present in their subjects with "heat exhaustion." They concluded that this postural drop in blood pressure resulted from pooling of blood in the lower extremities on cessation of exercise due to a work-induced vasodilatation in the lower limb muscles and inactivation of the muscle pump that aids venous return during exercise.

In an experimental study of heat collapse in South African gold miners, Weiner (34) concluded that the "collapse and the associated circulatory findings are explained as being due to extensive vasodilation of the peripheral vascular bed with consequent 'pooling' of the blood by the action of heat." Oral temperatures measured during exercise showed that "a high degree of pyrexia is definitely not associated with heat collapse. The mouth temperature taken during work of subjects who subsequently collapsed is of the same order as those of non-collapsing individuals."

Thus, the conclusion from these early studies must be that, historically, the terms "heat exhaustion," "heat prostration," or "heat syncope" were used only to describe a condition of collapse due to postural hypotension that develops in persons exercising in the heat. The terminology should not be misinterpreted to indicate that the collapse is caused by an elevated body temperature and is therefore a mild form of heatstroke. It would seem that the possibility that postural hypotension could explain EAC has been overlooked since these early studies (20,21).

We also found that runners most likely to collapse were those attempting to finish the race within certain cutoff times (Fig. 1). This suggests that extreme personal effort beyond the athlete's capability and training level, brought on by the competitive nature of the event, may place undue stress on the athlete's circulatory system that predisposes to syncope when the athlete stops suddenly

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at the finish line. Interestingly, athletes with EAC had significantly higher serum creatinine and urea concentrations both immediately postrace and 24 h after the event (Table 3) than did controls. This could indicate that the EAC runners had exerted themselves to a greater extent and thus induced greater muscle damage than did controls.

The extent to which dehydration contributed to collapse in the runners with EAC could not be determined directly by this study. Published data provide little firm evidence that clinically severe dehydration, equal to a fall in body weight of 5–10%, develops routinely in athletes participating in prolonged exercise. Indeed most authors report no more than a 2–4% loss of body weight during prolonged exercise such as marathon running (12,15,17–20,23,35,36). Furthermore, levels of dehydration are usually less in those who have participated in events of even longer duration (29), possibly because these events are performed at a lower exercise intensity resulting in lower than expected sweat rates (23,25).

Our results suggest that high levels of dehydration alone are not the sole cause of EAC. First, it is difficult to understand why dehydration not sufficiently severe to cause collapse *during* exercise when the stress on the cardiovascular system is the greatest, should be a critical factor in the postexercise period as cardiovascular stress is reducing. Second, we found that 35% of the control runners gained more than 2.5 kg during the 24 h after the race. As the controls were asymptomatic, similar mass losses cannot by themselves have caused EAC in collapsed runners. Mass losses in that small subgroup of runners with EAC who returned for study was not different from that measured in controls. Third, postrace plasma renin activity and plasma vasopressin concentrations were the same in runners with EAC and controls and were 3 times normal resting values. Serum sodium concentrations were also similar in these groups. Even though plasma aldosterone concentrations were significantly higher in runners with EAC, the difference was small and of dubious physiological significance.

In summary, possibly the most significant finding of this study was identification of the likely etiology of collapse on the basis of whether subjects collapsed before or after finishing the race. The vast majority collapsed after completing the race; although those runners had higher serum urea and creatinine concentrations than controls, there were no distinguishing biochemical characteristics indicating the likely nature of the condition. In contrast, all runners who collapsed before the race finish had identifiable medical conditions that were treatable by conventional medical protocols.

On the basis of these findings, we hypothesize that the most likely mechanism for EAC is a syncopal episode resulting from postural hypotension (5) caused by a sudden cessation of exercise and loss of the skeletal muscle pump in the lower limbs with pooling of blood in the pelvis and lower extremities. It is possible that a number of other factors, including mild dehydration, excessive racing effort, and a training-induced reduction in the vasoconstrictor response to any hypotensive stress, may contribute to EAC. Hyperthermia would likely be a more important factor in shorter races run at higher exercise intensities (25) under more severe environmental conditions.

The modern management of EAC should take account of these several possibilities, rather than assuming that one single factor, in particular dehydration, is the sole etiological factor for EAC.

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clinical investigations

The prevalence and significance of post-exercise (postural) hypotension in ultramarathon runners

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ABSTRACT

HOLTZHAUSEN, L-M. and T. D. NOAKES. The prevalence and significance of post-exercise (postural) hypotension in ultramarathon runners. *Med. Sci. Sports Exerc.*, Vol. 27, No. 12, pp. 1595–1601, 1995. A consistent finding in exercise-associated collapse is a marked postural fall in the systolic blood pressure associated with a tachycardia. The prevalence and significance of these post-exercise (postural) changes in blood pressure among noncollapsed ultradistance athletes has not been well documented. The aim of this study was to compare pre- and post-race changes in systolic and diastolic blood pressures with changes in body weight and plasma volume and with symptoms of post-exercise hypotension, including the effects of posture, among a group of 31 runners competing in an 80-km footrace. During the race, runners developed a mean (±SD) weight loss of 3.5 (±1.2) kg and plasma volume change of 12.8% (±9.1). Asymptomatic postural hypotension defined as a fall in systolic blood pressure of greater than 20 mm Hg from the supine to the erect position without syncopal symptoms was present in two runners (7%) before the race and in 21 runners (68%) afterward. The degree of postural variation in systolic blood pressure was unrelated to changes in body weight or a fall in plasma volume. We conclude that (i) all runners were dehydrated by the race activity with a range of 1% to 7% and an average of 4.6%; (ii) asymptomatic post-exercise (postural) hypotension developed in the majority (68%) of ultramarathon runners in this study; (iii) the post-exercise hypotension is likely of multifactorial origin and is not entirely related to whole body dehydration or a reduction in plasma volume; and (iv) despite marked levels of dehydration among our sample of runners, their cardiovascular status in the supine position was not greatly compromised.

POST-EXERTIONAL POSTURAL HYPOTENSION, DEHYDRATION

Exercise, especially if it is prolonged, has a blood-pressure lowering effect (6). When the effect is marked, post-exercise postural hypotension, defined as a decline in systolic blood pressure of at least 20 mm Hg below supine values on assuming the upright (erect) posture (27) associated with syncopal symptoms, may develop.

There is a consensus that the term orthostatic or postural hypotension should be used only if this degree of fall in systolic blood pressure is accompanied by appropriate symptoms (27). Appropriate symptoms of postural or orthostatic hypotension range from lightheadedness, blurring of vision, a sense of profound weakness, faintness, and unsteadiness, to syncope. These usually last no longer than a few seconds; the resumption of the supine position quickly normalizes the blood pressure and reverses these symptoms.

This condition was first described in 1907 by Gordon (7) and additional studies were reported by Jokl (10), Mateef and Petroff (13), and Eichna et al. (5). In the latter study (5), postural hypotension of this degree developed in 50% of normal, healthy, fit young army recruits after vigorous exercise; furthermore, 25% of all subjects developed syncopal symptoms. Eichna et al. (5) postulated that "a pooling of blood in the dependent lower extremities, presumably due to failure of the muscular venopressure mechanism in the legs, plus a work induced dilatation of their vascular beds" caused the hypotension and syncope. The authors did not consider that alterations in fluid balance, specifically dehydration, might have influenced the postural hypotension.

This blood-pressure lowering effect of exercise may also be quantified as the difference in the systolic blood pressures measured in the supine position before and after exercise. Fleg and Lakatta (6) suggest that post-exercise hypotension, as distinct from post-exercise postural hypotension, can be defined as a decline in systolic BP measured in the seated or supine positions of at least 20 mm Hg below the pre-exercise value to values of 90 mm Hg or less.

While the post-exercise fall in blood pressure is generally considered to be beneficial for health, if large, an acute reduction in blood pressure may produce symptom-

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atic hypotension. Recently, we reported that a marked postural fall in both the systolic and diastolic blood pressures associated with a tachycardia (9) is a consistent finding in ultramarathon runners with exercise-associated collapse (EAC). But neither the range of posture-related decreases in systolic blood pressure in runners after ultramarathon races nor the possible contribution of this phenomenon to EAC is currently known.

Accordingly, the aim of this study was to determine the prevalence and magnitude of posture-related changes in blood pressure among a group of ultramarathon runners and to determine its relationship to the fluid status of the runners and to any reported symptoms they might experience after the ultramarathon race.

MATERIALS AND METHODS

The study, which was sanctioned by the Research and Ethics Committee of the Faculty of Medicine of the University of Cape Town, was conducted at the 1990 80-km Karoo Marathon held annually in the vicinity of Laingsburg, South Africa. Each of the 240 race entrants received a letter explaining the aim of the study. Thirty runners volunteered to participate in the study and signed an informed consent form. Weather conditions during the day varied from a minimum of 14°C to a maximum of 25°C; humidity fell from 44% at the race start to 24% at 12:00.

After admission to the trial, before the race each athlete was weighed in running shorts and vest but without running shoes on a Seca electronic scale (Vogel and Halke, Hamburg, Germany). Body weight was remeasured at the 40-km mark and after the race in the same manner.

Supine and erect blood pressures and heart rates were measured the day before the race and shortly after the race finish with a Dinamap 81 OOT monitor (Johnson and Johnson, Johannesburg, South Africa). The blood pressure in the supine position was measured only after 10 min of rest in that position. Measurements in the erect position were made after the normal time-delay of 30–60 s required for the automated machine to measure blood pressure. All blood pressures were measured once while subjects remained motionless.

Blood samples were drawn with minimal stasis from an antecubital vein while the athlete was in a seated position, the night before the race and immediately after the blood pressure determinations, that is, within 15 min of completing the race. Subjects did not ingest fluid during this time. To exclude any acute effects on body weight and biochemical measures, runners had rested for at least 72 h before the initial measurements were made. Blood samples were centrifuged immediately and the sera were stored frozen at −20°C for subsequent analysis of osmolality, sodium, potassium, chloride, total protein, creatinine, urea, and glucose concentrations. Plasma electrolytes were determined using a flame photometer (Model I.L 543, Beckman Instruments Inc., Galway, Ireland); osmolality by depression of freezing point, using an automatic osmometer (Gonotec Osmomat 030 Precision Instruments Inc., Newton, MA); creatinine by the Jaffee reaction measured on a Model I.L. 919 spectrophotometer (Beckman Instruments Inc.); and chloride using a CMT10 Chloride Titrator (Beckman Instruments Inc.). Serum albumin and total protein concentrations were measured using a Technicon SMAC Auto Analyzer (Beckman Instruments Inc.). Blood drawn for hemoglobin concentration, hematocrit, white cell count, and red cell volume was stored at room temperature and analyzed within 24 h with an automated Coulter S-II counter (Miami, FL).

Calculations and Statistical Analysis

Body weight changes during the race were calculated as the difference from the pre-race weight. Plasma volume changes were calculated from the changes in hemoglobin concentration and hematocrit according to the equations of Dill and Costill (4).

All the results were calculated as the mean and standard deviation (SD). Statistical significance ($P < 0.05$) was determined for pre- and post-race data with a paired Student's t-test. Significance ($P < 0.05$) of between-group data (Table 3) was determined with a Student's t-test assuming equal variance. Pearson's correlation coefficients were determined to seek associations between weight loss and the other variables of fluid status.

RESULTS

The mean age (±SD) of the 31 runners studied was 38.9 (±7.8) yr; their mean weight was 73.9 (±9.9) kg, and their race time was 498 (±65) min, representing a mean speed of 9.8 (±1.4) $km \cdot h^{-1}$, equivalent to a standard marathon time of about 4.5 h.

Total weight loss during the race was 3.5 (±1.2) kg. The mean weight loss for the first and second 40 km of the race was essentially identical [1.9 (±0.9) and 1.7 (±0.8) kg, respectively]. This weight loss represented a mean percentage dehydration of 4.6% (±1.3%) with a range of 1.3%–6.7%.

Table 1 lists the blood biochemical and hematological measures before and after the race. Serum sodium and chloride concentrations were the only variables that did not change significantly during the race. Blood glucose, potassium, total protein, creatinine, and urea concentrations rose significantly, as did serum osmolality, hemoglobin concentrations, hematocrit, and the white cell count.

Table 2 lists the changes in supine and erect systolic, diastolic and mean arterial blood pressures, and heart rates before and after the race. With the exception of the

TABLE 1. Blood biochemical and hematological measures before and after an 80-km ultramarathon.

	24 h Before Race (Mean ± SD)	Within 5 min of Race Finish (Mean ± SD)
Glucose (mmol · l^{-1})	4.3 ± 1.5	5.9 ± 1.2**
Sodium (mmol · l^{-1})	141 ± 2	142 ± 6
Potassium (mmol · l^{-1})	3.9 ± 0.2	4.5 ± 0.5**
Chloride (mmol · l^{-1})	104 ± 2	103 ± 5
Total protein (g · l^{-1})	68.7 ± 3.8	77.5 ± 4.8**
Creatinine (pmol · l^{-1})	93.4 ± 13	151.7 ± 33.4**
Urea (mmol · l^{-1})	5.7 ± 1	8.2 ± 1.7**
Serum osmolality (mOsm · kg^{-1})	302 ± 7	307 ± 11**
Hemoglobin (g · dl^{-1})	14.9 ± 0.9	16.3 ± 1.3**
Hematocrit (%)	0.44 ± 0.03	0.47 ± 0.04**
White cell count (×10^9 · l^{-1})	8.8 ± 10	19.6 ± 5.2*
Blood volume (% change)		−8.7 ± 4.9
Cell volume (% change)		−3.5 ± 5.2
Plasma volume (% change)		−12.8 ± 9.1

Data are for 31 runners; * $P < 0.05$, ** $P < 0.01$ after versus before the race.

TABLE 2. Blood pressure and heart rate changes with posture before and after an 80-km ultramarathon.

	24 h Before Race (Mean ± SD)	Within 5 min of Race Finish (Mean ± SD)
Systolic blood pressure (mm Hg)		
Supine	137 ± 15	128 ± 14*
Erect	134 ± 12	102 ± 12**
Supine-erect	3 ± 11	27 ± 11**
Diastolic blood pressure (mm Hg)		
Supine	82 ± 14	78 ± 8
Erect	85 ± 12	69 ± 12**
Supine-erect	−3 ± 7	9 ± 10**
Mean aterial blood pressure (mm Hg)		
Supine	100 ± 13	95 ± 9*
Erect	101 ± 11	80 ± 11**
Supine-erect	−1 ± 6	15 ± 8**
Heart rate (beats · min^{-1})		
Supine	64 ± 10	99 ± 15**
Erect	71 ± 13	116 ± 14**
Supine-erect	7 ± 9	17 ± 8**

Data are for 31 runners; * $P < 0.05$, ** $P < 0.01$ after versus before the race.

diastolic blood pressure measured in the supine position, all blood pressures were significantly lower after the race.

Figure 1 (bottom panel) shows that heart rates were elevated after the race, especially in the erect position compared with pre-race values (top panel). But in the majority (58%) of runners, supine heart rates after the race were 100 beats · min^{-1} or less and were not sufficiently elevated in the supine position to suggest cardiovascular compromise (Fig. 1, bottom panel). But in the erect position, heart rates exceeded 120 beats · min^{-1} in 65% of subjects (Fig. 1, bottom panel).

Figure 2 shows the distribution of systolic blood pressures in the erect position measured before and after the race. The leftward shift of the distribution curve to lower blood pressures after the race is clearly apparent. Thirty-one percent of the runners had systolic and diastolic blood pressures greater than 140 and 90 mm Hg, respectively, before the race. This incidence fell to 6.5% after the race. Sixty-five percent of subjects had systolic blood pressures lower than 105 mm Hg after the race.

Figure 3 shows the distribution of supine minus erect

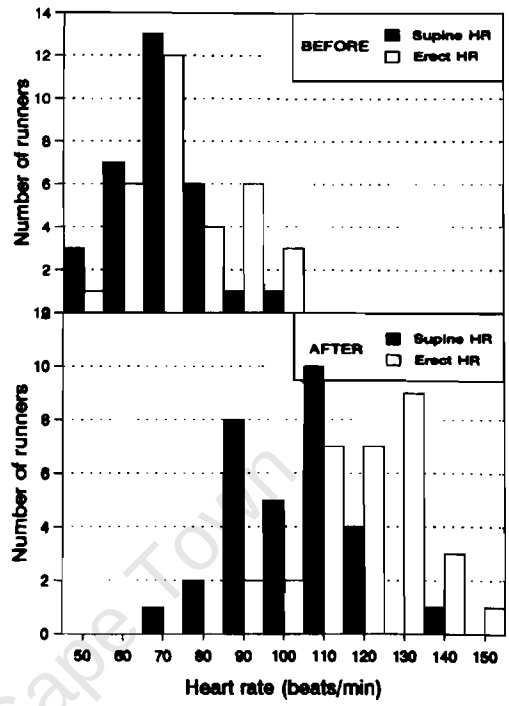

Figure 1—Comparison of the distribution of supine and erect heart rates before (top panel) and after (bottom panel) the 80-km ultramarathon.

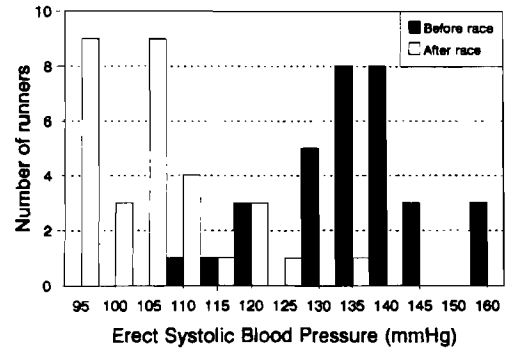

Figure 2—Comparison of distribution of erect systolic blood pressures before and after the 80-km ultramarathon. Note the leftward shift of the distribution curve to lower erect systolic blood pressures after the race.

systolic blood pressures before and after the race. There was a marked rightward shift to greater supine-erect differences after the race, indicating a large postural component in the reduction of post-race blood pressures. The result was that a posture-induced change in systolic blood pressure greater than 20 mm Hg was present in two athletes (7%) before the race and in 21 athletes (68%)

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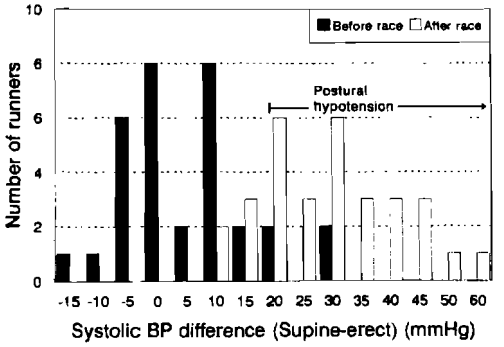

Figure 3—Comparison of systolic blood pressure difference (supine minus erect blood pressure) before and after the 80-km ultramarathon. Note the postural hypotension, defined as a supine minus erect systolic blood pressure difference greater than 20 mm Hg, developed in the majority of runners after the race.

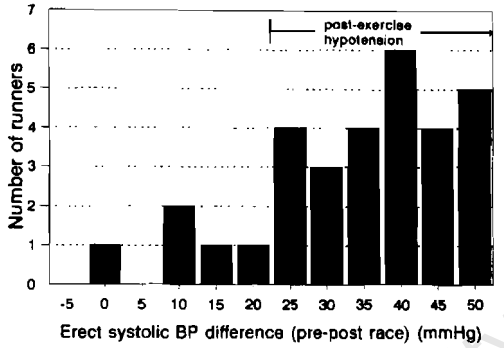

Figure 4—The distribution of the pre- to post-race difference in erect systolic blood pressures. Note that the majority of runners developed post-exercise hypotension defined as a fall of more than 20 mm Hg in the pre- to post-race systolic blood pressure.

after the race. In 16% of runners the posture-related fall in systolic blood pressure was severe and exceeded 40 mm Hg. The mean supine minus erect systolic blood pressure difference was 26.5 (±10.6) mm Hg after, compared with 3 (±11) mm Hg before, the race.

Figure 4 shows the distribution of changes in the systolic blood pressure measured in the erect position before and after the race. Eighty-one percent of runners showed a posture-related difference in systolic blood pressure in excess of 20 mm Hg and would therefore satisfy the criteria for a diagnosis of post-exercise hypotension.

Table 3 lists the characteristic of three groups of runners, divided on the basis of the change in the systolic blood pressure as a result of the race. In Group 1, the pre- to post-race fall in systolic blood pressure after the race was less than 20 mm Hg, in groups 2 and 3 the fall was greater than 20 mm Hg but only in group 3 was the post-race systolic blood pressure less than 90 mm Hg in the erect position. The seven (23%) runners in group 3 with erect systolic blood pressures after the race of less than 90 mm Hg all complained of dizziness and nausea on standing upright, but none experienced syncope.

Surprisingly, there were no significant differences in age, total weight loss, change in plasma volume, or pulse rate before or after the race between the three groups. By design, systolic blood pressures after the race were significantly lower in groups 2 and 3 than in group 1. Systolic blood pressure before the race was significantly higher in group 2 than in group 3.

No significant correlation was found between weight loss during the race and either the systolic blood pressure difference before and after the race measured in the erect position, or the change in plasma volume (Fig. 5).

Figure 6 shows that the difference in systolic blood pressures measured in the supine and erect positions after the race was unrelated to the change in plasma volume during the race.

DISCUSSION

The first important finding of this study was that both systolic and diastolic blood pressures were reduced after prolonged exercise, but that the effect was much greater for blood pressures measured in the erect than in the supine position (Figs. 2 and 3). As a result, asymptomatic postural hypotension, defined as a systolic blood pressure drop of 20 mm Hg or greater between the supine and erect positions, was found in 68% of subjects after the race compared to only 7% before the race.

Since 1907, when Gordon (7) described a 25-mm Hg decrease in systolic blood pressure in two healthy players after a rugby match, several investigators have documented asymptomatic post-exercise hypotension in healthy young men after assumption of the upright posture (1,3,5,8–10). The prevalence of 68% found in our study is higher than that of 50% reported by Eichna et al. (5). The pre-race prevalence of 7% is similar to that of 10% found by Patel et al. (20) among a group of healthy volunteers with a similar mean age of 33 yr.

A more rigorous definition of post-exercise hypotension has been suggested by Fleg and Lakatta (6), who investigated the post-exercise systolic blood pressure response after maximal treadmill exercise in 781 healthy asymptomatic volunteers with a mean (±SEM) age of 51 ± 16 yr (range, 21–96 yr). Subjects exercised to exhaustion following the modified Balke protocol for an exercise duration of 12 (±2) min. Fifteen percent of subjects showed a pre- to post-exercise decline in erect systolic blood pressure of at least 20 mm Hg; in only 2% of subjects did the systolic blood pressure also fall below 90 mm Hg, thereby fulfilling both of their diagnostic criteria for post-exercise hypotension.

By comparison, 68% of the runners in this study showed a pre- to post-race drop in erect systolic blood

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TABLE 3. Cardiovascular measures in three groups of runners divided according to the degree of post-exercise hypotension.

	Group 1 (N = 5)	Group 2 (N = 18)	Group 3 (N = 7)
Age (yr)	43 ± 9	37 ± 8	37 ± 6
Total weight loss (kg)	4.0 ± 1.0	3.2 ± 1.2	3.85 ± 1.2
Change in plasma volume (%)	11 ± 4	12 ± 11	15 ± 5
Erect systolic BP difference (pre- − post-race)	10 ± 8	35 ± 9	40 ± 9*
Systolic BP before race (mm Hg)	122 ± 12	140 ± 11**	127 ± 7
Systolic BP after race (mm Hg)	112 ± 9	105 ± 9**	87 ± 5*
Pulse rate before race (beats · min $^{-1}$)	64 ± 14	69 ± 13	78 ± 11
Pulse rate after race (beats · min^{-1})	108 ± 24	117 ± 13	117 ± 9

Group 1 has systolic BP difference between pre- and post-race of <20 mm Hg but erect post-race systolic BP >90 mm Hg.
Group 2 has systolic BP difference between pre- and post-race of >20 mm Hg and post-race erect systolic BP >90 mm Hg.
Group 3 has systolic BP difference between pre- and post-race of >20 mm Hg but erect post-race systolic BP <90 mm Hg.
* $P < 0.05$ between group 1 and 3; ** $P < 0.05$ between group 2 and 3.

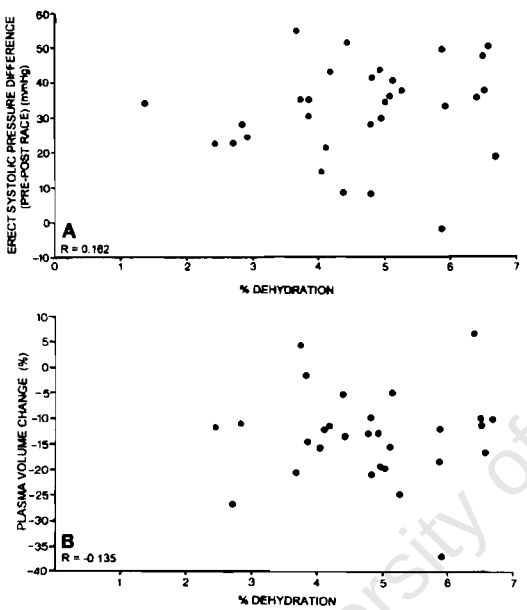

Figure 5—Regression of % dehydration during the 80-km ultramarathon on (A) post-race systolic blood pressure difference in the supine and erect positions and (B) percent change in plasma volume. Note that there was no significant correlation between any of these measures (r = 0.16 and r = −0.14, respectively).

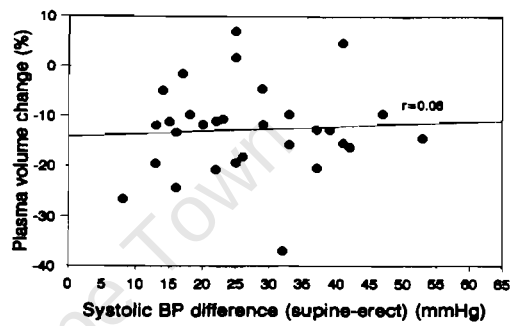

Figure 6—No relationship was found between the post-race systolic blood pressure difference in the supine and erect positions, and the change in plasma volume during the race (r = 0.06; $P > 0.1$).

pressure exceeding 20 mm Hg; in 23% of runners the post-race systolic blood pressure in the erect position was also below 90 mm Hg. No runners experienced syncope, but dizziness and nausea was present in all runners whose erect systolic blood pressures after exercise were 90 mm Hg or less. By comparison, Eichna et al. (5) found that 50% of their subjects whose erect systolic blood pressures fell below 100 mm Hg after prolonged exercise, developed syncope.

In our protocol, subjects were encouraged to sit or lie down within 1 min of the race finish, which may have afforded some protection from syncopal symptoms. The constraints introduced by this experimental protocol contrast to the practical situation at another ultramarathon race studied by us (9) in which 75% of the field, approximately 5000 runners, finished in the last hour of the race, resulting in considerable crowding at the finish, forcing the athletes to stand in a slowly moving queue for some minutes before their finishing times and positions could be recorded. It was during that time-interval between stopping running and officially finishing the race that the majority of runners in that study developed EAC (9).

It is conceivable that the seven runners who experienced dizziness may have collapsed after the race had they been forced to stand for any length of time, for example, in the extended finishing queue that commonly develops at most marathon and ultramarathon races in this country.

The postulated mechanism for post-exercise (postural) hypotension and EAC (17) is based on the work of Rowell (21), showing that thermal stress, either environmental or endogenous, increases cutaneous blood flow and cutaneous vascular volume, and blood flow to the working muscle with increased blood volume in the muscle vascular beds. As a result, blood volume is redistributed from the thoracic and abdominal organs to the periphery, causing a fall in atrial filling pressure and stroke volume. The peripherally distributed blood volume can only be returned to the central circulation by continual activation of the skeletal muscle pump, as oc-

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curs with running or walking. The sudden cessation of exercise would immediately promote peripheral blood pooling as originally postulated by Eichna et al. (5). If the runner does not have the opportunity to sit or lie down immediately on cessation of exercise, syncope may develop.

It has also been suggested that endurance-trained athletes have a reduced capacity to compensate for any acute hypotensive stress. There are two possible mechanisms for this effect. First, Luft et al. (11,12) have reported that the incidence of syncope during lower body negative pressure is greater in trained humans than in untrained controls, possibly as a result of a greater displacement of blood into the veins of the lower limbs in trained athletes (26).

Second, a training induced alteration in the function of the autonomic nervous system (19,22–26) seen as an increased resting parasympathetic (vagal) activity and an attenuated sympathetic activity associated with a blunted vasoconstrictor response, may increase the susceptibility of the athlete to any hypotensive stress.

It is thus possible to propose that training-induced adaptations in lower limb venous compliance and in the sympathetic response to the hypotensive stress associated with the cessation of exercise, especially in the heat, could explain why postural hypotension occurs so commonly after ultramarathon running.

The second important finding of this study was that the level of dehydration developed during the race was unrelated to the degree of postural hypotension (see Figs. 5 and 6). It would appear that dehydration does not play a major role in the development of postural hypotension, although it may contribute to the symptoms experienced. Despite signs of marked extracellular dehydration as indicated by a mean plasma volume change of 13%, the cardiovascular status of our subjects, measured as heart rate (Fig. 1) and blood pressure (Fig. 2) especially in the supine position were not grossly abnormal, indicating that the circulating blood volume was adequate to maintain cardiovascular status when lying. This is especially important because the mean level of dehydration (4.7%) achieved by these athletes are among the highest reported in the literature (18). This confirms that more severe levels of dehydration must be necessary for the development of dehydration-induced circulatory collapse in otherwise healthy individuals (2,15), at least in runners who lie down immediately after exercise.

These findings could also have implications for the way in which EAC is treated. If posture-related reductions in systolic blood pressure are so common in ultramarathon runners, then it would seem appropriate that any possible contribution that postural hypotension might play in patients with EAC should be corrected, even if at this stage such treatment will be largely empirical. Thus, a trial of pelvic and lower limb elevation with oral rehydration could be initiated in the collapsed athlete and recovery of a stable cardiovascular status should be monitored before more aggressive intravenous therapy is begun (9). This method aimed at restoring the central blood volume by redistributing peripherally displaced blood stored in dilated cutaneous veins (17) has proved successful in our hands. The possibility of inducing overhydration and severe hyponatremia with injudicious fluid therapy in subjects with EAC who are already overhydrated, unlike the subjects in this study, all of whom were dehydrated, has been documented (16).

In summary, this study has demonstrated that the athletes of this study developed marked levels of dehydration (mean = 4.6%; range 1%–7%) and that asymptomatic post-exercise (postural) hypotension developed in the majority (68%) but was likely of multifactorial origin as it was not entirely related to whole body dehydration or a reduction in plasma volume. Rather, we speculate that the postural hypotension was also influenced by blood volume shifts to the periphery, exacerbated by thermal stresses and a training-induced impairment in the capacity to activate an adequate sympathetic nervous system response to any acute hypotensive challenge.

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PostScript

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RESEARCH LETTERS

The forgotten Barcroft/Edholm reflex: potential role in exercise associated collapse

Approximately 80% of the athletes who collapse in marathon and other long distance sporting events do so only after they have crossed the finish line.[1] Although it is usually taught that "dehydration" explains this phenomenon, logic suggests this to be unlikely because any dehydration induced hypovolaemia should cause cardiovascular failure when cardiac stress is highest—that is, during rather than after exercise when cardiovascular function is returning to the resting state. Instead it is clearly the act of stopping exercise that is the consequent, albeit paradoxical, cause of post-exercise collapse.

We have previously proposed that this form of exercise associated collapse is caused by the persistence into recovery of a state of low peripheral vascular resistance, compounded by removal of the skeletal muscle pump that maintains the right atrial filling pressure during exercise.[1] According to this theory, the combination of a low peripheral vascular resistance and a sudden reduction in venous return would reduce stroke volume and cardiac output acutely, causing hypotension. Indeed this mechanism was used to explain the development of postural hypotension due to "dehydration exhaustion" in military personnel exposed to eight or more hours of exercise in desert heat without fluid replacement, in the classic studies of Adolph.[2]

Thus Adolph[2] wrote that "the ultimate failure of the circulation (in dehydration exhaustion) is of a peripheral type . . . Dilated blood vessels of the skin require additional blood to fill them; correspondingly, the available compensation for vertical posture are diminished, for the blood vessels of the legs compromise between dilating to carry heated blood and constricting to preserve a greater flow to the head" (p 235). He also reported that: "Lying down promptly relieves the circulation and the symptoms" (p 236). Similarly, Lee[3] defined the physiological abnormality causing heat exhaustion as: "A low arterial blood pressure is the critical event, resulting partly from inadequate output by the heart and partly from the widespread vasodilation". He also noted that: "Treatment is simple – recumbency, fluid and salt administration, gentle cooling, and rectification of any predisposing cause" (p 571).

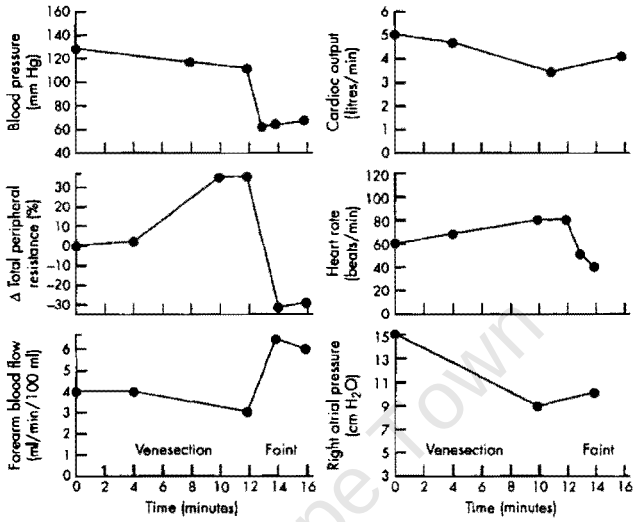

Figure 1 Changes in blood pressure, total peripheral resistance, forearm blood flow, cardiac output, heart rate, and right atrial pressure in subjects who underwent rapid venesection of about 1 litre of blood in 12 minutes. Note that fainting is caused by a sudden reduction in peripheral vascular resistance resulting from an increase in forearm blood flow as right atrial pressure falls, the Barcroft/Edholm reflex. Redrawn from data in Barcroft *et al*.[5]

However, these explanations fail to explain why a compensatory tachycardia is not a usual feature of this form of hypotension,[2] or why the onset of symptoms occurs so rapidly and why they are reversed so rapidly when subjects lie supine in the head down position.[3]

An historic study identifying a potentially forgotten reflex and published in *The Lancet* in 1944 suggests an alternative explanation. Barcroft *et al*[4] studied the effects of rapid venesection of about 1 litre on cardiovascular function measured with right heart cannulation and forearm plethysmography. Studies continued until subjects fainted from the sudden onset of hypotension. Figure 1, redrawn from those historic data, shows the salient findings. Initially, cardiovascular function adapted to progressive blood loss by increasing peripheral vascular resistance and heart rate, each by about 30%. Despite this, average cardiac output, right atrial pressure, and systolic blood pressure all fell by about 40%.

However, the crucial finding was that fainting occurred only when there was a sudden fall in the peripheral vascular resistance associated with an unexpected increase in forearm blood flow (fig 1).

A second study evaluated the authors' hypothesis that it was the fall in right atrial pressure induced by blood loss that activated the reflex reduction in peripheral vascular resistance. A tourniquet was applied to the lower limb and inflated before the beginning of the venesection. Hypotension again developed but after a smaller blood loss of only about 550 ml. Release of the tourniquet immediately corrected the hypotension by reducing forearm blood flow (fig 2). The authors concluded that removal of the tourniquet produced a sudden infusion of blood from the lower limb thereby increasing the right atrial pressure, abolishing the reflex and normalising cardiovascular function.

Hence they proposed the existence of a potent skeletal muscle vasodilator reflex that is activated when the right atrial pressure either falls below some critical value or begins to fall at a particular rate. This reflex appears atavistic because it compounds rather than corrects the hypotension associated with blood loss. The similarity in the rapidity with which hypotension occurs with either progressive venesection or after the cessation of exercise, and without an associated tachycardia, suggests that this right atrial reflex may also cause exercise associated collapse.[1]

To my knowledge, some contemporary texts of cardiovascular control during exercise do not specifically mention this reflex. For example, Rowell[6] refers to a later 1945 paper in the *Journal of Physiology* by Barcroft and Edholm,[7] in which the physiological basis for this skeletal muscle vasodilation was studied. However, the relevance of this specific reflex to the development of syncope is not directly discussed. Rather, Rowell presents the findings of

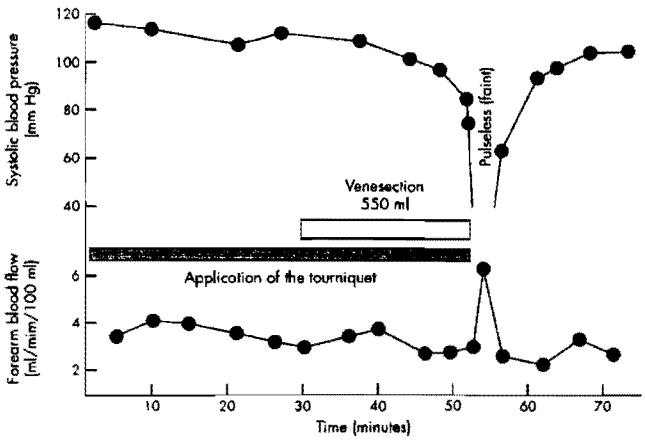

Figure 2 The sudden reduction in systolic blood pressure and the associated increase in forearm blood flow with progressive venesection is immediately reversed by release of a lower limb tourniquet. Redrawn from data in Barcroft *et al*.[3]

Barcroft and Edholm as a possible example of neurogenic sympathetic cholinergic vasodilation in skeletal muscle.

It is of interest that we had empirically discovered some years ago[1] that the optimum management of post-exercise collapse is achieved by elevating the feet and pelvis of collapsed athletes above the level of the right atrium. The results of this manoeuvre are usually dramatic, with rapid reversal of hypotension and the symptoms of dizziness. According to the Barcroft/Edholm reflex, the adoption of this head down position would produce this dramatic response by immediately reversing the low atrial pressure that develops on the cessation of exercise in some susceptible athletes. Hence the effect would not result simply by increasing venous return and hence cardiac output, the more usual explanation,[4] but also by reversing the skeletal muscle vasodilation induced by the Barcroft/Edholm reflex.

Finally, I would like to make the obvious point that the Barcroft/Edholm reflex explains why nursing in the head down (Trendellenberg) position would be the more logical treatment for post-exercise collapse than the provision of intravenous fluids.[1] The reason is that nursing in the Trendellenberg position rapidly increases the right atrial pressure whereas any effect of intravenous fluids on right atrial pressure is likely to be smaller and much delayed.

Furthermore the contribution of the Barcroft/Edholm reflex to exercise associated collapse can be very rapidly evaluated by studying the response of the athlete's blood pressure to changes in posture. Failure of the blood pressure to rise when placed in the head down position must indicate that the Barcroft/Edholm reflex is not active and some other cause for the hypotension, such as myocardial dysfunction or a persistent reduction in peripheral vascular resistance for reasons other than this postulated reflex, must be considered.

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THE COLLAPSED ENDURANCE ATHLETE – TIME TO RETHINK OUR MANAGEMENT?

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The belief that dehydration-induced hyperthermia explains the exercise-associated collapse found in marathon runners and other endurance athletes is widely held; yet there is little published scientific support for this conclusion. This article reviews the evidence which shows that neither hyperthermia nor dehydration are common findings in endurance athletes regardless of whether or not they collapse. Rather, the exercise-associated collapse conforms almost exactly to the description of a post-exercise postural hypotension reported in unacclimatized soldiers on first exposure to exercise in jungle heat during the Second World War. The condition resolved spontaneously with supine rest in a cold environment and was prevented by repeated exposure to exercise in the heat.

One of the unfortunate consequences of this overemphasis on dehydration as the sole cause of exercise-associated collapse has been a rising incidence of hyponatraemia in runners and triathletes who ingest excessive volumes of fluid during ultradistance races. The injudicious use of intravenous fluid therapy is also responsible for the iatrogenic production of hyponatraemia in some collapsed athletes. If exercise-associated collapse is indeed due to postural hypotension, then treatment should primarily aim to reverse the conditions responsible for its development. These include elevating the legs and lowering the skin temperature to induce venoconstriction in the lower limbs. A protocol for determining the appropriate treatment for collapsed runners is proposed.

Keywords: **Collapse; postural hypotension; hyponatraemia; dehydration; hyperthermia; marathon running.**

INTRODUCTION

Ultradistance running has a long and distinguished history in my country. This is largely because of the influence of one event, the 90 km Comrades Marathon, run annually between the two major cities, Pietermaritzburg and Durban in the Province of Natal. The

race which was run for the first time in 1921 currently attracts in excess of 14,000 runners. In order to join the Comrades Association, runners must, in the great tradition of the race, "suffer for one day in memory of those who did not return from the (First) Great War" (Noakes, 1985).

Unfortunately, in recent years, the suffering of the runners has extended to include the medical support teams who, with each successive year, have had to cope with increasingly more runners who are sufficiently collapsed after the race to require medical attention.

For obvious reasons, this phenomenon of exercise-associated collapse, its aetiology and how best it might be prevented has begun to occupy our minds in the past few years (Noakes, 1988a; Noakes 1988b; Noakes 1988c; Sandell et al. 1988). This article will present an overview of what is known of this condition and will propose a testable hypothesis of why it develops.

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The aetiology of exercise-associated collapse

(i) Epidemiological observations

Untested clinical observations suggest that the following are features of the type of exercise-associated collapse commonly seen in this country.

First, the vast majority of persons who collapse, do so within 1-2 minutes of *stopping* exercise.

Second it appears that collapse occurs much more frequently after running than after cycling events. In our experience, the incidence of collapse after ultra-marathon cycling events is almost negligible.

Third, both fast and slow runners collapse.

Fourth, the incidence of collapse increases in direct proportion to the environmental temperature and humidity (Adner et al. 1988; Richards and Richards, 1984). Many have interpreted this finding as proof that post-exercise collapse must be due to a disorder of body thermal balance.

Fifth, collapsed runners appear to recover relatively spontaneously within 1-4 hours, regardless of the treatment given. In particular, no scientific study has yet been undertaken to establish whether treating the condition with intravenous fluids alters the time course for recovery or is in any way more beneficial than doing nothing (Noakes, 1988a; Noakes 1988c). In fact, the indications seem to be that fewer collapsed runners are now receiving intravenous fluids than was the case in the recent past (Adner et al. 1988; Roberts, 1989).

Clearly any hypothesis of the aetiology of this condition must explain all these observations.

(ii) The role of dehydration and hyperthermia

The majority of clinicians probably believe that hyperthermia of varying degrees including heatstroke, is the most important component of post-exercise collapse and that severe dehydration causes this hyperthermia and therefore predisposes to the development of exercise-associated collapse. If this is correct, the rational way to prevent and treat this condition is to ensure that all athletes ingest sufficient fluid and therefore do not become dehydrated during competition, and to treat all collapsed athletes with copious amounts of intravenous fluids. There are a number of reasons why these beliefs are so prevalent.

First, is the legend of Pheidippides who reputedly died suddenly after he had completed the mythical first marathon from Marathon to Athens (Martin et al. 1977). Despite the absence of confirmatory evidence from an adequate autopsy, at least one enthusiastic neophyte has concluded that heatstroke caused this tragedy (Noakes, 1973).

Second, were the real but no less dramatic cases of heatstroke amongst famous marathon runners - the Italian Dorando Pietri and the English Jim Peters, both of whom achieved legendary status by collapsing with heatstroke at the finish lines of the Olympic and Empire Games marathons respectively (Noakes, 1985).

What many seem to overlook is that millions of athletes worldwide have subsequently completed marathon and ultramarathon races and triathlons safely without ever developing heatstroke. Thus the only realistic conclusion that can be drawn from these isolated, albeit dramatic events, is that heatstroke occurs with extreme rarity amongst endurance athletes.

Third, were the studies of Wyndham and Strydom (1969) and Wyndham (1977) which were interpreted as conclusive evidence that severe dehydration occurred commonly in marathon runners and that such dehydration predisposes to the development of heatstroke.

Wyndham and Strydom (1969) based their historic conclusions on the results of 2 studies of runners competing in different 32 km foot races. These studies were designed principally to determine the effects of sugar ingestion on marathon running performance (McKechnie et al. 1970). The relevant finding of this study was that athletes who became dehydrated by more than 3% had elevated post-race rectal temperatures. There was also a linear relationship between the athletes' levels of dehydration and their post-race rectal temperatures (Figure 1).

These authors also found a similar linear relationship between post-race rectal temperatures and the runners' body masses. Nevertheless they concluded that the level of dehydration alone was the most important factor determining the rectal temperature during exercise (Wyndham and Strydom, 1969; Wyndham, 1977). As a result, most authorities have been lured into the belief that the prevention of dehydration is the vital factor

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preventing heatstroke during prolonged exercise, especially marathon running (American College of Sports Medicine, 1985).

Two other features of Figure 1 were not discussed by Wyndham and Strydom (1969). First, the winners of the two races had the highest post-race rectal temperatures. This is a consistent finding (Maron and Horvath, 1978; Noakes et al. 1988) which might suggest that running velocity or a related variable may influence post-race rectal temperature. Unfortunately Wyndham and Strydom (1969) did not consider this variable in any of their analyses despite the fact (i) that their other studies had shown that metabolic rate, (which is proportional to the runner's mass and running velocity), determines the rectal temperature response during exercise (Wyndham et al. 1970) and (ii) they had already found a significant relationship between one component of the metabolic rate, body mass, and the post-exercise rectal temperature.

As will become apparent, the findings of Wyndham and Strydom (1969) can, with hindsight, be better explained if the exercising metabolic rate which determines the sweat rate (Greenhaff, 1989; Greenhaff and Clough, 1989; Noakes et al. 1990a) and therefore also the level of dehydration, is the real factor determining the rectal temperature during marathon running (Noakes et al. 1988; Noakes et al. 1990a). This postulate therefore holds that the relationship between dehydration and rectal temperature found by Wyndham and Strydom (1969) is spurious and can be explained by the co-dependence of these two variables on the third and determining factor, the exercising metabolic rate.

Second, if the level of dehydration does indeed determine the post-race rectal temperature, then the levels of dehydration needed to induce heatstroke are between 7-9% (Figure 1). This is an unrealistic proposal as such severe levels of dehydration are not found in marathon runners or other endurance athletes (Applegate et al. 1989; Faber et al. 1987; Noakes et al. 1988; Noakes et al. 1990a; Thomas and Motley, 1984; van Rensburg et al. 1986). Furthermore, it seems likely that at such high levels of dehydration, cardiovascular collapse would terminate exercise before heatstroke could develop.
Nevertheless, the end result of these studies is that the following has become established teaching in sports medicine:

(i) athletes collapse after exercise because they are dehydrated;

(ii) the dehydration causes hyperthermia and, if severe, heatstroke;

(iii) the only way to prevent the hyperthermia of marathon running and therefore to avoid post-exercise collapse is to ensure that all runners drink adequately during competition;

(iv) the correct way to treat post-exercise collapse is to correct the inevitable dehydration that causes it. This is especially important in the more severely

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affected runners who are clearly suffering from shock due to a reduced circulating blood volume;

(v) because severe dehydration occurs only in persons involved in very prolonged exercise, then it is only athletes involved in ultradistance events who are prone to heatstroke. Competitors in short distance events would be protected from heatstroke because they would not become sufficiently dehydrated to reach high level of hyperthermia.

These concepts are, to some extent, enshrined in the American College of Sports Medicine Position statement (1985) on the prevention of heat injuries in long distance races. But a growing body of evidence is not compatible with these conclusions.

First, observations in a number of field studies indicate that endurance athletes including those who collapse are not greatly dehydrated (Applegate et al. 1989; Berlinski et al. 1990; Faber et al. 1990a; Rogers et al. 1986; Thomas and Motley, 1984; van Rensburg et al. 1986) after competition nor are their post-race rectal temperatures particularly high (Maughan, 1985; Maughan et al. 1985; Noakes et al. 1989; Noakes et al. 1990a; Roberts, 1989; Sandell et al. 1988; Thomas and Motley, 1984). This conclusion is consistent with the historical data (Maron and Horvath, 1978).

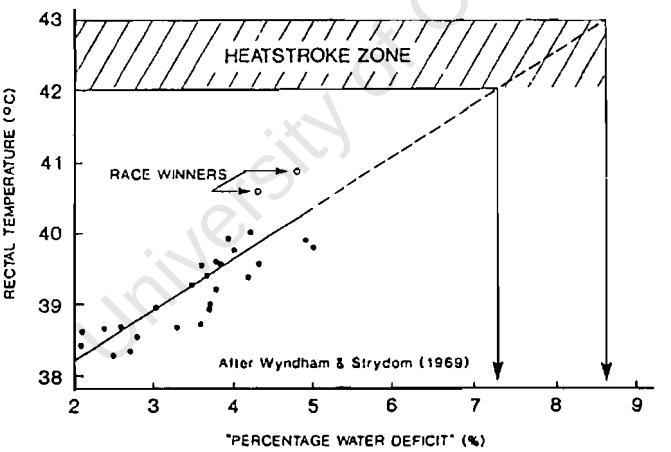

Figure 1

A linear relationship between rectal temperature after two 32 km foot races and percentage water deficit was reported by Wyndham and Strydom (22) in 1969. Note (i) that the highest rectal temperatures were found in the race winners, (ii) that heatstroke could only be expected in runners who were dehydrated by between 7 and 8.5%; (iii) that the highest levels of dehydration in these runners were 5% and (iv) that their rectal temperatures ranged between 38.3 and 41.0°C.

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Indeed the range of rectal temperatures in the vast majority of marathon and ultra-marathon runners who have been studied is the same as that reported by Wyndham, and Strydom (1969) and varies from 38.5 - 40.5°C (Figure 1). These temperatures are considerably lower than those found in patients with heatstroke (Figure 1). Interestingly, some runners competing in cold environmental conditions collapse because they are hypothermic (Maughan, 1985; Sandell et al. 1988).

The second finding that is incompatible with the belief that dehydration alone causes endurance athletes to collapse, is the reports of runners who developed hyponatraemia during prolonged exercise (Frizzell et al. 1986; Hiller at al. 1985; Hiller et al. 1986; Hiller et al. 1987; Noakes et al. 1985; Noakes et al. 1990b; O'Toole, 1988; Young et al. 1987). This condition is now known to be due to fluid retention in runners who ingest excessive volumes of fluid during very prolonged exercise (Irving et al. 1990a). Thus we must now confront the paradox that the group of collapsed runners who are the most seriously ill are those who have followed the instructions of the experts and have drunk the most during prolonged exercise!

Third, was the personal experience of treating seven cases of heat stroke during a single 12 km race (Noakes, 1982) - a number in excess of the total number of such cases that I had seen in two decades of marathon and ultramarathon running. This single event suggested that the speed of running or a related variable, rather than the level of dehydration, must be an essential component in the pathogenesis of heatstroke.

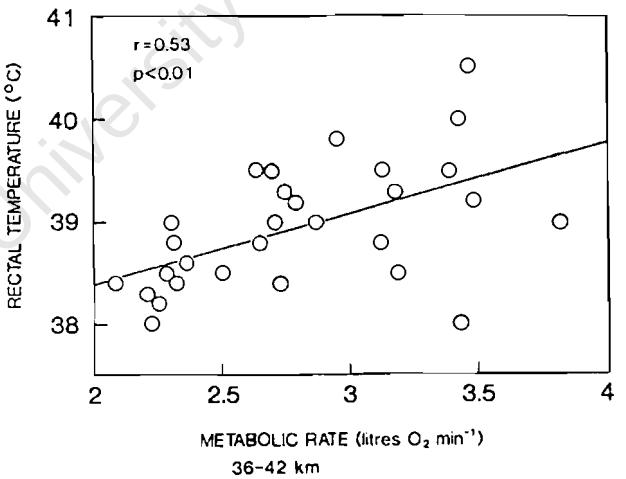

Figure 2

A significant relationship between metabolic rate for the last 6 km of a marathon race and the post-exercise rectal temperature was found in the study of Noakes et al. (1990).

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Fourth is the historical and modern evidence that the majority of patients who develop heatstroke, whether exercise-related or not, are not dehydrated as their haematocrits are within the normal range at the time of collapse (Austin and Berry, 1956; Barry and King, 1962; Beller and Boyd, 1975; Ferris et al. 1958).

Fifth, and most importantly, are the recent (Greenhaff, 1989; Noakes et al. 1990a - Figure 2) and historical (Davies, 1979; Davies et al. 1976; Wyndham et al. 1970 - Figure 3) findings that it is the metabolic rate, measured as the rate of oxygen consumption during exercise, which determines both the rectal temperature and the sweat rate (Greenhaff, 1989; Greenhaff and Clough, 1989; Noakes et al. 1990a) during exercise. Metabolic rate is a function of speed of movement and the mass moved; thus running speed has also been related to both the post-exercise rectal temperature and sweat rate during marathon races (Maughan, 1985; Maughan et al. 1985; Noakes et al. 1990a). In contrast, no relationship between rectal temperature and percentage dehydration has been found in all studies of runners postdating those of Wyndham and Strydom (Maron and Horvath, 1978; Maughan et al. 1985; Maughan, 1985; Noakes et al. 1988; Noakes et al. 1990a - Figure 4).

The finding that metabolic rate determines both the rectal temperature and the sweat rate would therefore explain why Wyndham and Strydom (1969) found a relationship between rectal temperature and percentage dehydration even though the two are not causally related. In a group of runners all of whom drink similar amounts of fluid, the runners with the highest metabolic rates would have the highest rectal temperatures. But they would also sweat the most and would become the most dehydrated.

However this does not mean that dehydration has no influence whatsoever on the rectal temperature response to exercise; simply that it is not the major determinant of the level to which the temperature will rise. As shown in Figure 5, the study of Gisolfi and Topping (1974) established that the rectal temperatures of subjects who did not drink during two hours of exercise at 75% VO_2 max and who became dehydrated by 5% were approximately $0.8^{o}C$ higher than they were when the same subjects performed the same exercise but drank sufficiently to avoid dehydration. Figure 5 also shows that even when these subjects exercised at 75% VO_2 max and became dehydrated by 5%, their rectal temperatures were still far below those normally measured in persons with heatstroke (Figure 1).

In summary, the conclusions from these studies would seem to be the following:

(i) An important determinant of the rectal temperature during exercise is the metabolic rate. Accordingly, the risk of heatstroke is greatest in those who compete the hardest and therefore have the highest metabolic rates during exercise. Thus heatstroke is more likely to occur in exercise of high intensity and short duration rather than in

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prolonged endurance exercise in which competitive speeds and therefore metabolic rates are substantially lower.

(ii) Dehydration plays only a permissive role in elevating the rectal temperature during exercise. Accordingly the maintenance of an adequate fluid intake will play only a small role in the prevention of heat injury during exercise.

(iii) Hyperthermia is an uncommon finding in persons with exercise-associated collapse (Roberts, 1989; Sandell et al. 1988) and can therefore not explain such collapses (Noakes, 1988a).

(iv) Dehydration does not occur more frequently than overhydration in collapsed runners (Berlinski et al. 1990). Thus dehydration alone cannot explain the vast majority of these collapses.

(iii) The role of overhydration in post-exercise collapse - the enigma of the hyponatraemia of exercise

The unlikely suggestion that it was possible to drink *too much* during prolonged exercise was prompted by the finding of exercise-induced hyponatraemia associated with acute pulmonary edema and grand mal epileptic seizures in athletes participating in very prolonged exercise (Noakes et al. 1985).

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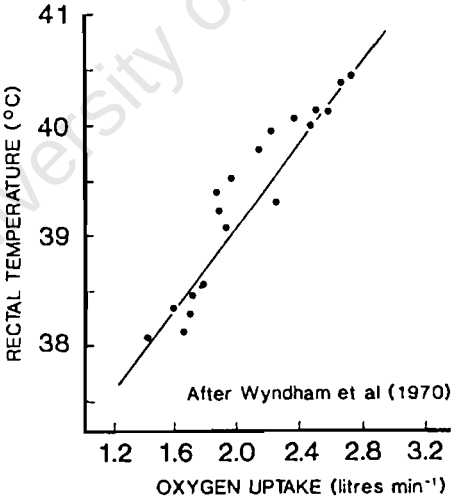

Figure 3

A significant relationship between oxygen uptake (metabolic rate) and rectal temperature during exercise was also reported by Wyndham et al. (1970).

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In the original description, we could only postulate that hyponatraemia resulted from an excessive fluid intake with abnormal fluid retention. Other workers concurred with this conclusion and reported very high rates of fluid intake in other runners who developed the hyponatraemia of exercise (Frizzell et al. 1986; Young et al. 1987). If this hypothesis is correct, it follows that those who are prone to develop the condition should limit their fluid intakes during prolonged exercise (Noakes et al. 1985).

However, a contrasting explanation is that the hyponatraemia of exercise results from the large sodium chloride losses that develop during prolonged exercise (Hiller et al. 1986; Hiller et al. 1987; Hiller, 1989; O'Toole, 1988). This proposal holds that runners who drink only hypotonic solutions with low sodium chloride content and who therefore fail to replace their sodium losses during exercise must develop a dilutional hyponatraemia. Alternatively, it is suggested that these runners are both sodium chloride deficient *and* dehydrated (Hiller, 1989). According to this hypothesis, runners at risk of developing hyponatraemia during exercise should be encouraged to ingest large volumes of fluids containing sodium chloride during exercise.

In order to distinguish between these two contrasting hypotheses, we studied 8 runners who developed hyponatraemia during the 1988 90 km Comrades Marathon (Irving et al. 1990a). Subjects were admitted to hospital and their renal function including fluid and electrolyte balance was studied exhaustively until their serum sodium concentrations had normalized.

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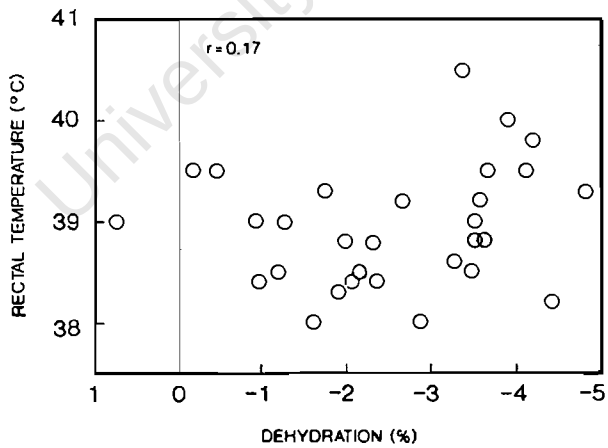

Figure 4

No significant relationship was found between the level of dehydration and the post-exercise rectal temperature of 30 marathon runners studied by Noakes et al. (1990a).

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The important findings of the study were that the rate of fluid intake of the hyponatraemic runners during exercise (1.3 1. hr^{-1}) was greatly in excess of rates found in runners who maintain normal serum sodium concentrations during prolonged exercise ($\pm$ 0.5 1.hr^{-1}) (Noakes et al. 1988). However the critical finding was that the hyponatraemic runners excreted an excess of 3 litres of fluid during recovery. In contrast, normonatraemic runners usually conserve water and gain weight during recovery (Irving et al. 1986; Irving et al. 1990a; Irving et al. 1990b). Furthermore renal function was enhanced in hyponatraemic runners whereas the sodium chloride deficit incurred by the hyponatraemic subjects during exercise (calculated as the net amount of infused sodium chloride retained by the subjects during recovery) was not greater than that of normonatraemic runners.

Accordingly we have concluded that the hyponatraemia of exercise results solely from abnormal fluid retention in runners who ingest excessive volumes of fluid during prolonged exercise. In contrast to the contentions of others (Hiller et al. 1986; Hiller et al. 1987; Hiller, 1989; O'Toole, 1988), large sodium chloride losses did not contribute to the pathogenesis of this condition, nor were the collapsed runners dehydrated. What currently remains to be explained is why the condition occurs only in certain athletes. Logic suggests that any fluid excess ingested by these athletes should simply be excreted during, rather than after exercise, thereby preventing the development of the hyponatraemia. Further work is needed to explain this anomaly.

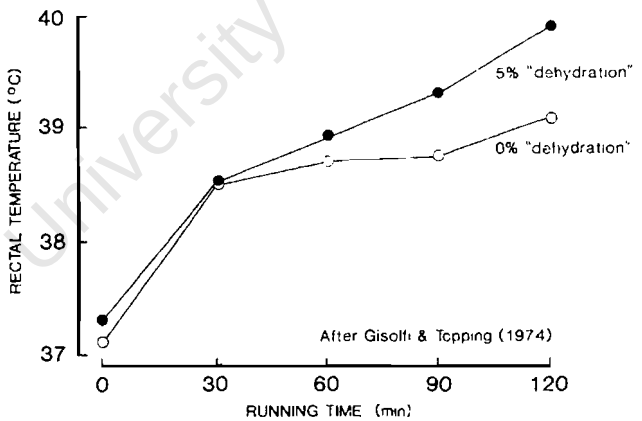

Figure 5

Time course of changes in rectal temperature during exercise in the same athletes when they either maintained euhydration or when they became dehydrated by 5%. From data of Gisolfi and Topping (1974).

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This finding does raise the important question of how is it possible for ultramarathon runners and triathletes to ingest fluid at rates greatly in excess of their sweat losses? The only answer must be that their rates of sweat loss are considerably lower than is generally believed.

Indeed another unfortunate effect of Wyndham and Strydom's (1969) work was to suggest that sweat rates can be very high during prolonged exercise like marathon running. They concluded that sweat rate was determined by body mass alone and predicted that an 80 kg person would sweat at a rate in excess of 2 litres per hour during marathon running. Such high sweat rates can probably not be replaced during exercise; the highest rates of fluid ingestion measured during running at high intensity in the laboratory are of the order of 800 ml hr (Costill et al. 1970). Accordingly if these assumptions were correct, severe dehydration must inevitably occur in all heavier runners during marathon and ultramarathon races.

In reality however, metabolic rate determines the sweat rate and heavier runners tend to run slower than lighter runners; thus the metabolic rates and sweat rates of heavier runners may be no higher than those of lighter runners. Thus no study has yet been able to confirm that sweat rates during marathon running are anywhere near as high as those predicted by Wyndham and Strydom (1969); most studies report sweat rates of up to 1.2 litres per hour in the fastest runners even in the severest environmental conditions (Noakes et al. 1988).

In contrast, an important characteristic of the runners who develop hyponatraemia are that they run very slowly and probably walk frequently; thus they must sustain low metabolic and sweat rates.

Yet they may continue to ingest fluid at rates necessary to balance the sweat losses they would incur if they were still running fast. Furthermore, because they are exercising at low intensity, their rates of fluid absorption from the intestine may be increased. In addition, the widespread belief that fluid ingestion prevents the development of fatigue and collapse, may encourage these runners to maintain these high rates of fluid intake. This is a natural extension of the beliefs described earlier in the article.

Thus runners who become fatigued during marathon races may well drink more the slower they progress, in the mistaken belief that an increased fluid intake will allow them to recover. Paradoxically because severe environmental conditions cause premature fatigue, runners competing in hot weather marathons will fatigue earlier and may therefore start drinking excessively, earlier in the race. In this way, severe environmental conditions may actually predispose to the development of overhydration, not dehydration, in the majority of runners who are not highly trained or competitive and who therefore fatigue early in the race. Indeed the highest incidence of hyponatraemia that we have

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encountered, occurred in the ultramarathon with the most severe environmental conditions (Berlinski et al. 1990).

(iv) The role of postural hypotension in post-exercise collapse

If the majority of collapsed runners are neither dehydrated, hyperthermic, hypothermic or hyponatraemic (Berlinski et al. 1990; Roberts, 1989; Sandell et al. 1988), why then do they collapse?

The overriding clinical impression is simply that collapsed runners show marked postural hypotension. When lying prone, although their blood pressures are low, their heart rates are not greatly elevated (Noakes, 1988a; Noakes, 1988c). Renal function also is not impaired and may even be enhanced (Irving et al. 1990a; Noakes, 1988c; Sandell et al. 1988). The observation that the athletes usually collapse *after exercise, when the demands on the cardiovascular system are reduced*, must indicate that neither cardiogenic nor hypovolaemic shock is present. Rather it seems likely that a redistribution of blood flow and blood volume after cessation of exercise must be a factor (Noakes, 1988a).

Figure 6 shows the expected cardiovascular responses at the onset of exercise. In this normal response, vasodilation occurs in the active muscles; this leads to a fall in total peripheral resistance which increases venous return and, by the Starling mechanism together with increased sympathetic stimulation of the heart, the cardiac output. Blood pressure which is proportional to the cardiac output and the total peripheral resistance, rises during exercise because the increase in cardiac output exceeds the fall in total peripheral resistance. In addition, sympathetically-mediated vasoconstriction of the arterioles in the inactive muscles and in the splanchnic circulation increases resistance in those organs. Furthermore, should the blood pressure begin to fall as might occur if, for example, the fall in total peripheral resistance exceeded the increase in cardiac output, a powerful sympathetically-mediated vasoconstrictor response is activated (Rowell, 1986). This response can cause vasoconstriction even of the arterioles in the active skeletal muscles. In this way a centrally-controlled vasoconstrictor response can be activated that will override the local vasodilator effects of increased tissue metabolism.

Figure 7 shows that upon cessation of exercise, the reduction in metabolic activity together with centrally mediated sympathetic stimulation will cause the arterioles in the previously active muscles to vasoconstrict. As a result, total peripheral resistance will rise and venous return, cardiac output and blood pressure will return to pre-exercise levels.

It follows that hypotension could develop on cessation of exercise if either the cardiac output fell too far or the total peripheral resistance failed to increase sufficiently. The fact that the hypotension shows a profound postural component indicates that venous blood pooling in the lower limb must be an important factor contributing to the collapse.

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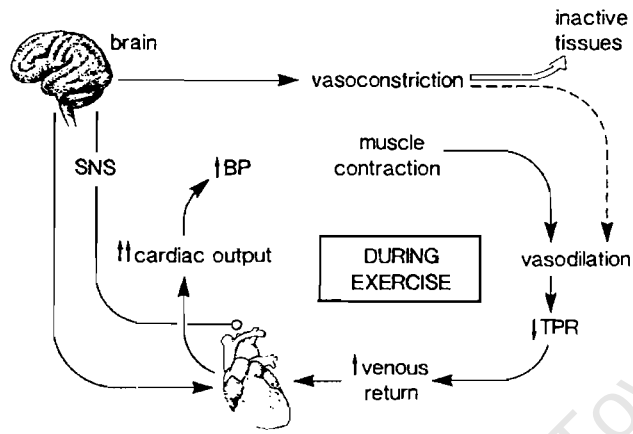

Figure 6

Cardiovascular changes at the onset of exercise. For details see text.

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Sudden pooling of blood in the veins of the legs on the cessation of exercise would cause a fall in central blood volume, in ventricular filling pressure and therefore in cardiac output and in blood pressure, leading to postural hypotension.

It therefore seems probable that on cessation of exercise, there is either persistent vasodilation of the arterioles in the previously active leg muscles or of the veins in the lower limbs, or both (Figure 8). Rowell (1986) has described how venous pooling in the lower limbs is controlled by two factors - the degree of venodilation and the activity of the calf muscles. Repetitive contraction of the calf muscles prevents blood pooling even in the dilated leg veins - the so-called "second heart" effect (Rowell, 1986; Figure 9). As venodilation is determined by both the core and skin temperatures, it follows that venous pooling will develop most rapidly when athletes suddenly stop exercising after prolonged exercise in the heat when their skin especially, but also their core body temperatures, are elevated. This would explain why the incidence of exercise-associated collapse increases with increasingly severe environmental conditions (Adner et al. 1988; Richards and Richards, 1984).

Whilst this hypothesis requires to be tested, it does suggest that the optimum treatment of this condition might simply be to keep the patients lying supine and possibly to elevate their legs. Cooling of the skin might also expedite the recovery of venoconstriction in the lower limbs.

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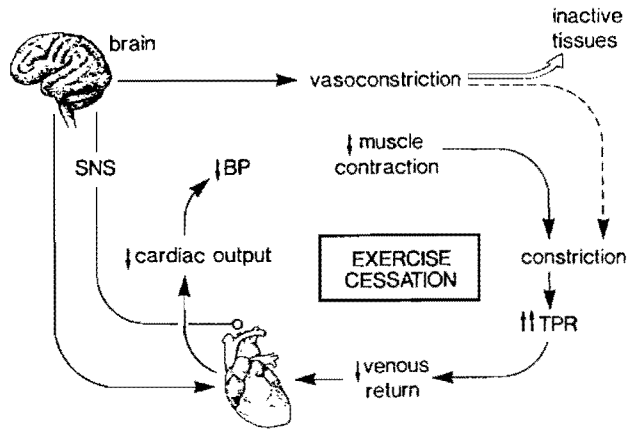

Figure 7
Cardiovascular changes immediately on cessation of exercise. (See text)
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Interestingly the observation that postural hypotension develops particularly in unacclimatized persons suddenly exposed to prolonged exercise in the heat is not new. Probably the first to observe this phenomenon was Eichna et al (1945) in a study of the patterns of acclimatization of soldiers to exercise in jungle heat. They showed that the single most characteristic feature of early exposure to exercise in jungle heat was the development of postural hypotension: "The cardiovascular instability of the unacclimatized state is brought out by the erect posture which induces tachycardia, a low systolic blood pressure and a narrow pulse pressure. Symptoms of cerebral ischaemia and syncope occur ... on returning to the supine position, the heart rate and blood pressure return to normal and the symptoms of cerebral ischaemia promptly disappear. Postural hypotension after working on the first day in 'jungle heat' is a common occurrence". This description faithfully describes all the features of exercise-associated collapse (Noakes, 1988a; Noakes, 1988c).

Interestingly, the postural hypotension disappeared within a few days of heat acclimatization. This suggests that inadequate heat acclimatization may be an essential component of exercise-associated collapse and would explain why undertrained athletes (who are much less likely to be heat acclimatized) are more prone to exercise-associated collapse (Sandell et al. 1988).

A final comment is in order. Eichna et al. (1945) labelled this syndrome of collapse in unacclimatized subjects exercising in jungle heat, as "heat exhaustion". Yet the rectal temperatures of these collapsed subjects were seldom, if ever greater than 39°C. Thus their definition referred not to the presence of hyperthermia in the collapsed subjects, but rather to the fact that the subjects became exhausted and collapsed *when*

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exercising in the heat. Thus the term "heat exhaustion" as used historically, does not refer in any way to the pathophysiological mechanisms causing collapse. As used by Eichna et al. (1945), the term "heat exhaustion" defines a syndrome of collapse during exercise in hot environmental conditions in subjects who are not heat acclimatized. The cause of the collapse is postural hypotension and not severe hyperthermia.

Proposed guidelines for the management of collapsed athletes

This review proposes that the aetiology of collapse frequently found in endurance athletes, runners and triathletes especially, is not simply due to dehydration-induced hyperthermia. Thus blindly treating collapsed runners for "dehydration" with intravenous fluids is not appropriate and may be life-threatening in persons with hyponatraemia (Noakes, 1988a; Noakes 1988c; Noakes et al. 1990b). Probably the most important point to emphasize is that the aetiology of the collapse may be multifactorial so that each patient deserves a reasonable clinical assessment and a working diagnosis before any treatment is instituted (Noakes, 1988a). It is no longer acceptable simply to assume that dehydration is the sole cause of the collapse.

To cope with the ever-increasing number of collapsed athletes after ultradistance events, we have adopted the following approach. All collapsed athletes are first assessed clinically and a decision on appropriate treatment is arrived at according to the following guidelines:

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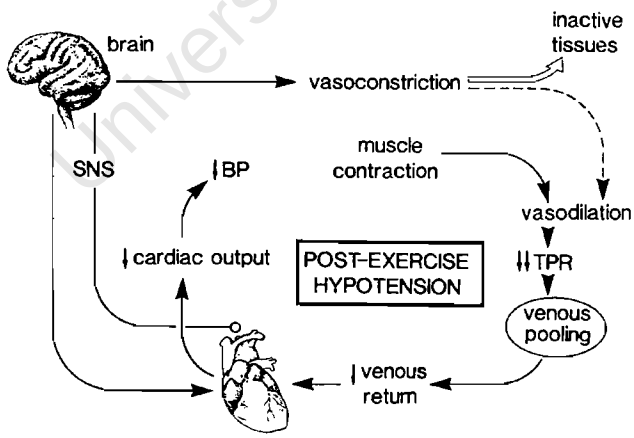

Figure 8
Cardiovascular changes shortly after exercise
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(i) Patients with impaired consciousness.

Athletes whose level of consciousness is impaired or who are unconscious receive priority treatment. Those with obvious medical emergencies such as cardiac arrest are immediately treated appropriately.

The remainder who constitute the overwhelming majority, have their blood pressures, heart rates and rectal temperatures measured. Blood is also drawn for measurement of serum sodium and blood glucose concentrations. Treatment is instituted on the basis of these results:

(a) If the rectal temperature is greater than 41^{o}C, the patient is actively cooled with icepacks, fanning and water sprays. The patient's condition, especially the rectal temperature, is monitored every 5-10 minutes. Patients in whom a firm diagnosis of heatstroke is made on the basis of marked hyperthermia (rectal temperature >42^{o}C and unconsciousness) are transferred to hospital as soon as the rectal temperature is less than 39^{o}C. Such patients require continued cooling during transfer to hospital in order to prevent a rebound of rectal temperature.

If belligerent, they may require intravenous valium to allow adequate medical management.

(b) Limited intravenous fluid is given if the serum sodium concentration is greater than 140 mmol l^{-1}. Intravenous glucose is also provided if the blood glucose concentration is less than 4 mmol l^{-1}.

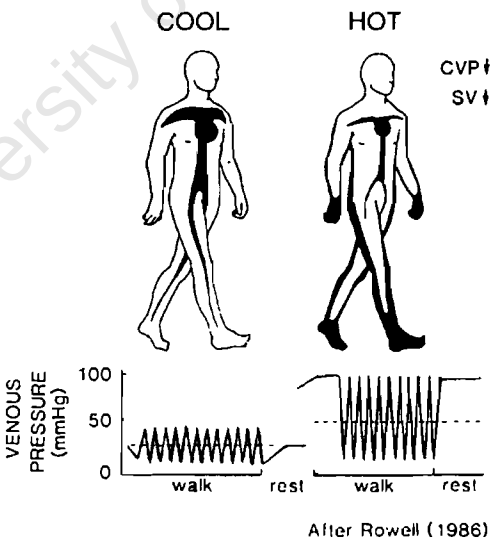

Figure 9

Repetitive contraction of calf muscles prevents blood pooling even in dilated leg veins

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(c) If the patient's level of consciousness is impaired, but the rectal temperature is less than 41°C and the blood glucose concentration is not below 4 mmol l^{-1}, it is likely that the patient's symptoms are due to hyponatraemia. Symptoms of hyponatraemia usually develop when the serum sodium concentration falls below 130 mmol l^{-1}; grand mal seizures and acute pulmonary oedema may develop at serum sodium concentrations below 120 mmol l^{-1}. A slow intravenous infusion of 0.9% sodium chloride may be started. If severe symptoms develop - acute pulmonary oedema or grand mal seizures - diuretics may be necessary. Patients with symptomatic hyponatraemia should be referred to hospital as the condition may worsen as, for reasons that are not clear, serum sodium concentrations tend to fall initially during recovery (Irving et al. 1990a).

(ii) Patients with normal levels of consciousness.

(a) If the patient is fully conscious and the rectal temperature is less than 41°C, the patient's cardiovascular status determines the treatment response. A heart rate below 100 beats per minute and a systolic blood pressure greater than 100 mmHg is not an immediate indication for active treatment. The patient's legs are elevated and the serum sodium concentration measured. Limited intravenous fluids may be given if the serum sodium concentration is greater than 140 mmol l^{-1}.

The normal response of these patients is to recover spontaneously within 60-90 minutes. We suspect that actively lowering the skin temperature with fans and direct cooling with icepacks may expedite recovery in this group of patients.

(b) Conscious patients with heart rates in excess of 100 beats per minute and blood pressures below 100 mmHg require close monitoring. Intravenous fluids may be given if the patients are not hyponatraemic and if leg elevation and skin cooling does not improve the cardiovascular status. A cardiogenic cause for hypotension should be considered in patients who fail to respond to these measures. Obviously the administration of fluids in excess to patients with impaired cardiac function must be avoided.

CONCLUSION

The main aim of this review has been to stimulate a fresh approach to the treatment of the collapsed endurance athlete. For too long, we have assumed that the condition can only be due to dehydration. By accepting this simple dogma, we have abused one of the most basic tenets of medicine - that a course of treatment should be prescribed only when some

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basic investigations have led to a diagnosis that has a reasonable probability of being correct. By failing routinely to make the most simple measurements including heart rate, blood pressure, rectal temperature, and serum sodium and blood glucose concentrations in collapsed athletes, we have overtreated many subjects, incorrectly treated others and produced iatrogenic, sometimes life-threatening, conditions in still others. The excuse that this has been justified because the athletes were treated under difficult conditions in the field is not acceptable. The collapsed athlete deserves optimum treatment based on the same clinical judgements, investigations and skills that should be applied to all medical problems.

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Collapsed Ultraendurance Athlete: Proposed Mechanisms and an Approach to Management

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Abstract:

Objective: To review the common conditions causing collapse in ultraendurance athletes, to propose appropriate treatment protocols for the more common medical conditions that are encountered, and to provide practical guidelines for the management of the medical facilities at these endurance events.

Data sources: Books published on the subject, abstracts of the American College of Sports Medicine Annual Congress dealing with the subject over the last 5 years, and electronic search of the Medline and Current Contents databases (last searched May 1995). German articles were included in the search criteria.

Study selection: Articles dealing generally with the management of medical facilities at endurance events were chosen. Articles dealing more specifically with the common medical conditions encountered at these events were then sourced and included in this review.

Data extraction: Multiple reader extraction of relevant data.

Data synthesis: A practical guideline to the management of the medical facility at an endurance event is detailed, expanding specifically on the nature of the conditions causing collapse during or after endurance exercise with a proposed classification of causes of collapse for optimizing immediate management and management protocols for specific conditions such as heatstroke, hyponatremia, hypoglycemia, exercise-associated collapse, and muscle cramps.

Conclusion: The most commonly encountered medical condition at endurance athletic events is collapse after the event. The popular view that all persons who collapse have dehydration-induced hyperthermia has been challenged. Here we extend that argument and provide diagnostic and management protocols and propose a triage system that considers the most common causes of collapse in ultraendurance athletes. These protocols can optimize the efficient and safe management of large numbers of collapsed ultraendurance athletes. It is proposed that these protocols can optimize the efficient and safe management of large numbers of collapsed ultra endurance athletes.

Key Words: Collapse—Ultraendurance.
Clin J Sport Med 1997;7(4):292–301.

There has been a large increase in the number of participants in ultraendurance sporting events in South Africa, as in many other countries, in the past 2 decades. The provision of competent medical care at such events has thus become a pressing need. But professionals who provide this medical care work in a discipline that is still relatively young and is consequently characterized by many uncertainties.

The aim of this article is to identify the common medical conditions that are encountered at these events, to suggest some appropriate protocols for the diagnosis and immediate management of those conditions, and to provide practical guidelines for the implementation and management of the medical facilities at which these services can best be provided. The information that we provide is based on our practical and research experience managing such facilities in competitive ultraendurance events in South Africa (13,14,17,29,30,36,47,50).

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CONDITIONS COMMONLY ASSOCIATED WITH COLLAPSE DURING OR AFTER EXERCISE

Table 1, compiled from various sources (1,5,41,42), includes the most common medical conditions that may be encountered in competitors who collapse during or after endurance sporting events. This list is not exhaustive but is practical. Certain conditions are more specific to the particular sport and the environmental conditions.

For example, hypothermia is likely in swim triathlons; the number of cases depend on the water temperature, the duration of the swim, and whether or not wetsuits are used. Drowning and near-drowning should also be anticipated in swim events. Cycling events invariably produce high-impact bony injuries to the skull and upper limb (34) after accidental falls from a bicycle at high speed. In this article, we focus more specifically on the conditions likely to be encountered in marathon and ultramarathon foot races and in ultratriathlons of the Ironman distance (226 km).

The most frequently encountered condition at these competitions is postexercise collapse. This has been

TABLE 1. *Conditions associated with collapse during or after prolonged exercise*

Exercise-associated collapse (heat syncope/exhaustion)
Muscle cramps
Heatstroke
Hypoglycemia
Hypothermia
Hyponatremia
Cardiac arrest
Other medical conditions
Orthopaedic conditions including stress and frank fractures

termed exercise-associated collapse (EAC; 42). The characteristics of this condition have been listed as the inability to walk unassisted with or without exhaustion, nausea, cramps, and normal, high, or low body temperatures. In the vast majority of subjects with EAC, the rectal temperature is not >39°C (14,42,43,47). The definition specifically excludes orthopaedic conditions, which are well described and for which treatment protocols are widely standardized.

Symptomatic hyponatremia (31), profound hypoglycemia, and exercise-induced hyperthermia (heatstroke) are the three serious emergencies likely to be encountered in long-distance footraces, especially in hot environmental conditions. In cold-weather conditions, hypothermia (14,25,47) should be anticipated. Contrary to general expectations, cardiac arrest is uncommon but is more likely in races that include large numbers of older participants.

Athletes who require treatment but who have not collapsed usually have minor medical or orthopaedic problems that do not constitute medical emergencies and are usually adequately handled according to well-established methods. This article restricts discussion to the management of collapsed athletes, some of whom represent real medical emergencies.

INITIAL MANAGEMENT OF COLLAPSED ATHLETES

Perhaps the major limitation in the management of collapsed athletes in the past has been that treatment was usually initiated before a rational differential diagnosis was considered (29,30,33). In part this has probably resulted from the (unrealistic) fear that any delay in the initiation of treatment will prejudice the patient's outcome. But the emergency treatment of life-threatening conditions, including heatstroke and hyponatremia, can safely be delayed for 1 or 2 minutes while the rectal temperature is measured and a reasonable working diagnosis is established. If the rectal temperature is >41°C, cooling should commence immediately after the rectal temperature has been measured.

The obvious exception to the rule is cardiac arrest, which, as indicated, occurs uncommonly, and the diagnosis of which is unambiguous.

Treatment is often initiated expeditiously because the rate of admission to the medical facility can be extremely high. For example, close to 50% of the 14,000 competitors in the 90-km Comrades Marathon complete the race in the last hour of the race. If 4% of those subjects collapse (Table 2), the average rate of admission during that period will exceed four patients per minute and is likely to be even faster in the last 10 minutes of the race when the rate of finishing accelerates further.

A third reason that treatment is often initiated without a diagnosis is because of the near-universal belief that dehydration is the major etiologic factor in all forms of athletic collapse (33,35). The belief has developed that all collapsed athletes will require intravenous fluid therapy and should therefore be initiated without delay (1,11,12).

But it is possible to manage such high rates of admission only if those selected patients who require urgent, sophisticated management receive such treatment. If all collapsed athletes are treated identically without differentiation on the basis of the nature and severity of the condition of each patient, it will never be possible to provide a medical staff sufficiently large to cope with the high rates of admission expected, especially in popular marathon and ultramarathon races.

Thus we propose that a triage system be established in which the severity and nature of each athlete's condition is rapidly assessed. The athlete can then be referred to the appropriate area of the medical facility for immediate treatment. The criteria that we have developed for determining the severity of collapse are described in Table 3. The initial assessment is made on the basis of the athlete's level of consciousness, assisted by knowledge of where in the race the athlete collapsed. It has been found that patients who are seriously ill will show alterations in the level of consciousness and will usually collapse before completion of the race (14), as discussed subsequently.

Thus level of consciousness and site of collapse are the initial criteria used for the immediate classification and early management of EAC. Additional helpful information is measurement of rectal temperature, blood pressure, and heart rate, which assist in further establishing the severity of the condition. In longer races (>25 km)

TABLE 2. *Percentage of starters with exercise-associated collapse in races of different lengths*

	Sun-City-to-Surf (Australia) 12 km	Boston Marathon (U.S.A.) 42 km	Two Oceans Marathon (South Africa) 56 km	Comrades Marathon (South Africa) 90 km
Cool, <24°C	0.2 (1984)	0.5 (1987)	0.7 (1990)	1.6 (1985)
Warm, >24°C	0.3 (1980)	1.3 (1985)	3.7 (1989)	3.6 (1987)

Data from references 1, 13, 24, 37, 41.

TABLE 3. *Guidelines for determining the severity of the collapsed athlete's condition*

Nonsevere	Severe
Immediate assessment	Immediate assessment
Conscious	Unconscious or altered mental state
Alert	Confused, disorientated, aggressive
Rectal temperature <40°C	Rectal temperature >40°C
Systolic blood pressure >100 mmHg	Systolic blood pressure <100 mmHg
Heart rate <100 beats/min	Heart rate >100 beats/min
Specialized assessment	Specialized assessment
Blood glucose 4–10 mmol/L	Blood glucose <4 or >10 mmol/L
Serum [sodium] 135–148 mmol/L	Serum [sodium] <130 or >148 mmol/L
Body weight loss 0–5%	Body weight gain or loss >10%

when hypoglycemia is more likely, the facility to measure the blood glucose concentration with a glycometer should also be provided. In mass events of much longer duration (>4 h), including ultramarathons and ultratriathlons, it is essential that there should be the capacity to measure the serum sodium concentration so that the potentially lethal condition of exercise-related hyponatremia can be diagnosed (12,31).

DIAGNOSTIC STEPS FOR THE OPTIMAL MANAGEMENT OF COLLAPSED ATHLETES WHO ARE UNCONSCIOUS

If the collapsed athlete is unconscious, then the initial differential diagnosis is between a medical condition not necessarily related to exercise (i.e., cardiac arrest, grand mal epilepsy, subarachnoid hemorrhage, or diabetic coma) and an exercise-related disorder, most especially heatstroke, hyponatremia, or severe hypoglycemia. The latter is an uncommon cause of exercise-related coma in nondiabetic subjects.

The emphasis in this review is not on the diagnosis of medical conditions unrelated to exercise, as the differentiation of these conditions does not usually present a problem to experienced clinicians. Rather the critical issue in the vast majority of cases of collapse is the rapid differentiation of the serious from the benign and the expeditious initiation of the correct treatment of the serious conditions.

If the patient is unconscious, the critical initial measurements are the heart rate, blood pressure, and especially the rectal temperature. If the rectal temperature is >41°C, the diagnosis is heatstroke, and the patient must be cooled immediately according to the techniques described subsequently. Patients with heatstroke are also hypotensive and have tachycardia.

If the rectal temperature is <40°C in an unconscious patient, the blood pressure and pulse are not grossly abnormal, and there is no other obvious medical condition to explain the unconsciousness, the probability is that the athlete has hyponatremia of exercise (31). This diagnosis can be confirmed only by measuring the serum sodium concentration. If the diagnosis is suspected, there is little risk in delaying the diagnosis, provided that any intravenous fluids the patient receives are of a high sodium content (3–5% saline) and given at a very slow rate (<50 ml/h), until a diagnosis is established. In most cases, the hyponatremia of exercise resolves spontaneously as soon as the patient begins to pass copious volumes of very dilute urine.

The critical measurements in conscious patients are heart rate and blood pressure in the supine position. During exercise, blood pressure and heart rate increase in proportion to the intensity of the effort. On cessation of exercise, heart rate and blood pressure initially decrease rapidly, but the heart rate may remain mildly elevated for some time, especially after prolonged exercise. The decrease in blood pressure is exaggerated when measured in the standing position.

Indeed, postural hypotension is likely after prolonged exercise in the heat (13) and may be the most important mechanism explaining the vast majority of collapses, which occur after the athlete has completed the event.

It would be helpful if the level of hydration could be accessed easily in all subjects, as this would assist in deciding the need for fluid-replacement therapy, but this is unfortunately not usually possible. In the past, this assessment has not been made; rather it has been assumed that dehydration is always present and is the principal etiologic factor explaining the athlete's collapse (33,35). Yet it seems likely that the levels of dehydration of 1–4% usually encountered in long-distance runners, although sufficient to impair their exercise performance, do not pose any significant health risks (13,32,33,35,37, 59). For example, studies performed during World War II showed that levels of dehydration of >8–10% are necessary to place the athlete's health at risk (2,32,33).

At present, the only reliable indicators of dehydration are an adequate history and clinical examination (Table 4) with special emphasis on the recognized clinical indicators of dehydration, including drying of the mouth caused by inhibition of parotid secretions, which occurs at dehydration levels of ≥5%, and loss of skin turgor. These signs have seldom been present in the collapsed endurance athletes we have treated. Furthermore, in our experience, changes in plasma volume and serum biochemical measures are poor indicators of the exact level of dehydration in runners (13).

In the absence of any absolute measure of the level of dehydration, persistent tachycardia and hypotension in subjects lying supine with feet and pelvis elevated above

TABLE 4. *Information required from each athlete admitted with collapse*

Pertinent history	Adequate examination
Amount of fluid ingested during the race	Level of consciousness/mental state
Amount of urine passed during the race	State of hydration
Presence of vomiting and/or diarrhea before and during the race	Rectal temperature
Amount of carbohydrate ingested before and during the race	Heart rate, supine and erect
Drugs taken during the race	Blood pressure, supine and erect
Recent intercurrent illness	Blood glucose concentration
Race preparation: heat acclimatization, training schedule, distance training	Serum sodium concentration

the level of the heart may indicate a reduced circulating blood volume and hence the possible need for fluid-replacement therapy (see the following).

MANAGEMENT PROTOCOLS FOR UNCONSCIOUS ATHLETES

Heatstroke

Rectal temperature is increased during exercise in proportion to the metabolic rate (37,62) and increases further in proportion to the degree of dehydration (26), as originally postulated by Wyndham and Strydom (61). When running, the metabolic rate is a function of running speed and body mass; thus the highest rectal temperatures are usually measured in the fastest runners competing in the shorter distance races of 8–21 km. In these runners, the rectal temperature may increase to ≥40.5°C without the athlete reporting symptoms or showing evidence of heat-related illness (16,25,37,40,44,61). Thus rectal temperatures of ≥40.5°C can be present in runners who are asymptomatic.

However, higher rectal temperatures are usually associated with a range of symptoms including dizziness, weakness, nausea, headache, confusion, disorientation, irrational behavior including aggressive combativeness, or drowsiness progressing to coma. The combination of an elevated rectal temperature with symptoms of an altered mental state confirms the diagnosis of heatstroke and is sufficient to warrant immediate initiation of cooling techniques to lower the body temperature, as the more rapidly the rectal temperature is reduced to 38°C, the better the prognosis.

The patient with heatstroke must be placed in a bath of ice-water for 5–10 minutes to expedite cooling (4,8,15, 22). The body temperature should decrease to 38°C within this time.

The theory that placing the hyperthermic athlete in a bath of ice water would delay cooling by inducing vasoconstriction in the subcutaneous vessels (56) should never have gained credence, given the clear observation that hypothermia develops rapidly in persons exposed to freezing water (20,28). Fortunately there is now firm evidence that cooling in a bath of ice-cold water is the most effective form of body cooling in exercise-induced hyperthermia (4,8) and rates of cooling close to 1°C/min can be achieved (4). Such high rates of cooling can induce hypothermia if sufficient care is not exercised. When body temperatures are changing rapidly, the rectal temperature lags behind the core (esophageal) temperature. Thus active cooling must be terminated before the rectal temperature reaches the normal body temperature. Shivering indicates that the core temperature has decreased to 37°C.

The physiologic changes in heatstroke include a large reduction in peripheral vascular resistance, caused by the elevated temperature. The observation that patients with heatstroke can continue to exercise vigorously almost to the moment of collapse implies that the vasomotor collapse occurs late in the evolution of heatstroke. One possibility is that the vasomotor collapse results from a sudden, dramatic vasodilation in the splanchnic circulation producing a hyperkinetic circulation characterized by a very low peripheral resistance, reduced central blood volume causing a low stroke volume, tachycardia, and systolic and diastolic hypotension (21,23,38). A rapid reduction in body temperature reverses the peripheral vasodilation and restores the central circulation with a reduction in heart rate and increases in central blood volume, stroke volume, and diastolic and systolic blood pressures.

But if the hypotension persists, myocardial damage exacerbated perhaps by absorption of endotoxins from the ischemic gastrointestinal tract, induces cardiac failure with ischemic necrosis of all the major body organs.

There is no published evidence showing that dehydration is a major factor in the etiology of heatstroke (35); the series of assumptions linking dehydration to heatstroke has been reviewed elsewhere (33). Intravenous fluids are given purely to correct the level of dehydration expected in the athlete and to assist in stabilization of the hyperkinetic circulation. Thus ≤1–1.5 L of 0.5 or 0.9% saline should be given initially. The mortality rate (10–80%) in heatstroke is directly related to the duration and severity of the hyperthermia, the presence of confounding medical conditions, and the rapidity with which cooling occurs (15). Mortality should be zero in healthy athletes who receive prompt and appropriate cooling (4,8).

Once the athlete's rectal temperature has been reduced to <38°C, the decision is whether or not to admit the patient to hospital for further observation. Factors influencing this decision are the known tendency for the rectal temperature to increase after cooling; this increase may not be noticed if the patient returns home without appropriate supervision. Any tendency for the rectal temperature to increase after the cessation of exercise and cooling indicates the presence of ongoing heat-generating biochemical processes in muscle unrelated to exercise and related perhaps to the biochemical abnormalities that initiate conditions like malignant hyperthermia (9,18).

Our experience is that hospital admission is always required if the patients fails to regain consciousness

within 20–30 minutes of appropriate therapy that returns the rectal temperature to 38°C. Patients who rapidly regain consciousness, whose cardiovascular system is stable, and whose rectal temperature does not increase in the first hour after active cooling ceases will not usually require hospital admission. Thus a decision of whether or not to admit the patients with heatstroke to hospital should be made within 30–60 minutes of admission to the medical tent.

Finally, heatstroke remains an uncommon complication during exercise, raising the possibility that individual factors may be operative. The possibility that persons who develop heatstroke may be genetically predisposed, perhaps by an inherited tendency for malignant hyperthermia, has been raised (9,18). Alternatively unique constitutional factors may be present only during that specific exercise bout that resulted in heatstroke. Such factors might include unaccustomed drug use or the presence of a subclinical viral infection.

Hyponatremia

Athletes who become unconscious during or after ultradistance running or triathlon races and whose rectal temperatures are not elevated should be considered to have symptomatic hyponatremia until the measurement of the serum sodium concentration establishes or refutes the diagnosis.

Current evidence is that all athletes with symptomatic hyponatremia are overhydrated by between 2 and 6 L (17,31). As a result, during recovery they pass a very dilute urine. The presence of a very dilute urine in a patient with an altered level of consciousness should alert the physician to the possible diagnosis.

Under no circumstances should large volumes of fluid be given to unconscious athletes and never to subjects with hyponatremia. Iso- or hypertonic saline (3–5%) solutions infused at a slow rate (<50 ml/h for a 5% saline solution) may be used. All unconscious hyponatremic patients in our series (31) recovered spontaneously without specific treatment other than fluid restriction and the occasional use of diuretics, the value of which is uncertain.

The responsibility of the medical care facility in the management of patients with hyponatremia is to ensure that such patients are transferred expeditiously, within 30 minutes, to a tertiary hospital for further management. The patient should not be left in the care of anyone who is not aware that symptomatic hyponatremia is caused by fluid overload and that uncontrolled fluid replacement must not, on the basis of our current understanding, be given to these patients. The race medical director must ensure that hospital physicians caring for athletes with hyponatremia are aware of correct management of this condition. Vigorously treating such patients with intravenous fluids for a perceived "dehydration" could have fatal consequences.

Hypoglycemia

Exercise-induced hypoglycemia occurs when liver glycogen depletion causes liver glucose production to lag behind the rate of muscle glucose uptake by muscle from the blood (7). Hypoglycemia occurs more commonly in long-distance events lasting ≥4 h, especially in athletes who fail to eat and drink sufficient carbohydrate before or during these events. During events of shorter duration, the higher exercise intensity increases the probability that factors other than hypoglycemia will initiate fatigue before the liver glycogen stores are depleted.

Persons who voluntarily restrict their intake of carbohydrates, usually young women with overt or covert eating disorders, are especially at risk. In our experience, the development of hypoglycemia in unusual circumstances should raise the possibility of an eating disorder with long-term carbohydrate restriction.

In most cases, the level of consciousness dictates that the glucose replacement be given intravenously as a 50% solution. Recovery is always rapid (within minutes) if hypoglycemia is the sole cause of collapse. Patients who are conscious can ingest a concentrated glucose solution orally.

MANAGEMENT PROTOCOLS FOR COLLAPSED CONSCIOUS ATHLETES

Exercise-associated collapse

Perhaps the most important recent observations are (a) that 85% of athletes who collapse in association with prolonged exercise do so after the cessation of exercise (14), and (b) that the vast majority of all collapses are not sufficiently serious to warrant hospital admission (43). Although the mechanisms causing postexercise collapse remain uncertain, it is clear that the syndrome is benign. In contrast, those athletes who collapse during exercise have identifiable medical conditions (14), some of which are serious.

In the absence of any clear diagnosis, this specific syndrome is defined as exercise-associated collapse (EAC; 42). It is in itself not a diagnosis as it gives no indication of the nature of the condition, but rather describes the major complaint, which is the inability to stand or walk unaided as a result of lightheadedness, faintness, or dizziness (47). The affected athlete may occasionally have syncope, which is rapidly reversed on lying down.

The diagnosis of EAC is made when other readily identifiable medical syndromes, already described, have been excluded (42). Although the origin of this syndrome remains uncertain, it has historically been assumed that EAC is caused by dehydration-induced hyperthermia with circulatory collapse (1,5,11,12,15,33,35,60,61), but a number of findings are not compatible with this explanation.

First, it is difficult to understand why dehydration-induced circulatory collapse should first appear after cessation of exercise, when the demands on the circulatory system are decreasing.

Second, most collapsed athletes have rectal temperatures that either are within the normal postexercise range of 38–41°C (5,14,42,51) or are subnormal (14,25,47,48). Thus the use of terms like "heat exhaustion" (15) or "heat strain" (48) are misleading, as the condition is

clearly not the result of a failure of thermoregulation, as is heatstroke (35), but must be caused by other mechanisms.

Historically, the condition of heat exhaustion was described in persons who collapsed during exercise but whose core temperatures were not greatly elevated (2,3, 10,57,58). All these authors concluded that the condition resulted from heat-induced peripheral vasodilation, causing cardiovascular instability (33).

Third is the finding that biochemical evidence for dehydration is no more common in collapsed than in noncollapsed runners (14,36), but more definitive studies are required to confirm this clinical impression.

One possibility is that EAC is an exaggeration of the normal reduction in standing blood pressure that occurs after prolonged exercise (10,13,21,52), exaggerated by the sudden cessation of exercise in persons who have exercised in the heat and in whom there is a substantial relocation of the central blood volume to the dilated capacitance vessels in the lower limbs.

We have suggested that the principal pathophysiologic change that explains EAC is a postural hypotension that develops as a result of three specific changes:

First is an increased blood flow to the cutaneous blood vessels to regulate body temperature. This response is increased in hot conditions and leads to a redistribution of the central blood volume to the periphery. As a result, the left atrial filling pressure and the stroke volume decrease; cardiac output is maintained by an increased heart rate (45,46). The higher the environmental temperature, the greater the cutaneous blood flow and thus the greater the peripheral location of blood volume in the capacitance cutaneous vessels, particularly on the cessation of exercise. This theory would explain why the number of collapsed athletes at any endurance event is linearly related to the ambient temperature (41; Fig. 1).

Second, the action of the calf-muscle pump helps to maintain the arterial pressure during exercise in the heat by reducing the volume of blood stored in the capacitance veins in the lower limb (45,46). With the cessation of exercise, this action of the calf-muscle pump ceases, and blood accumulates in the dilated capacitance veins of the lower limb, threatening the maintenance of an adequate arterial blood pressure (13).

Third, evidence shows that training-induced adaptations occur in the autonomic nervous system (39,49,53–55). These adaptations include an increased baseline parasympathetic (vagal) activity, associated with a resting bradycardia, and an attenuated sympathetic activity, associated with a blunted vasoconstrictor response to any hypotensive stress (27,53).

If this theory is correct, the most logical approach to the treatment of EAC would be to elevate and cool the athlete's legs and pelvis to reduce the skin blood flow and the volume of blood in the cutaneous veins. This is the treatment of choice in the medical tents that we direct. Subjects are encouraged to ingest fluids orally.

In our experience, few if any athletes with EAC are sufficiently dehydrated to show the usual clinical signs of dry mucous membranes, loss of skin turgor, sunken eyeballs, and an inability to spit. The presence of such signs might be used to justify the use of intravenous

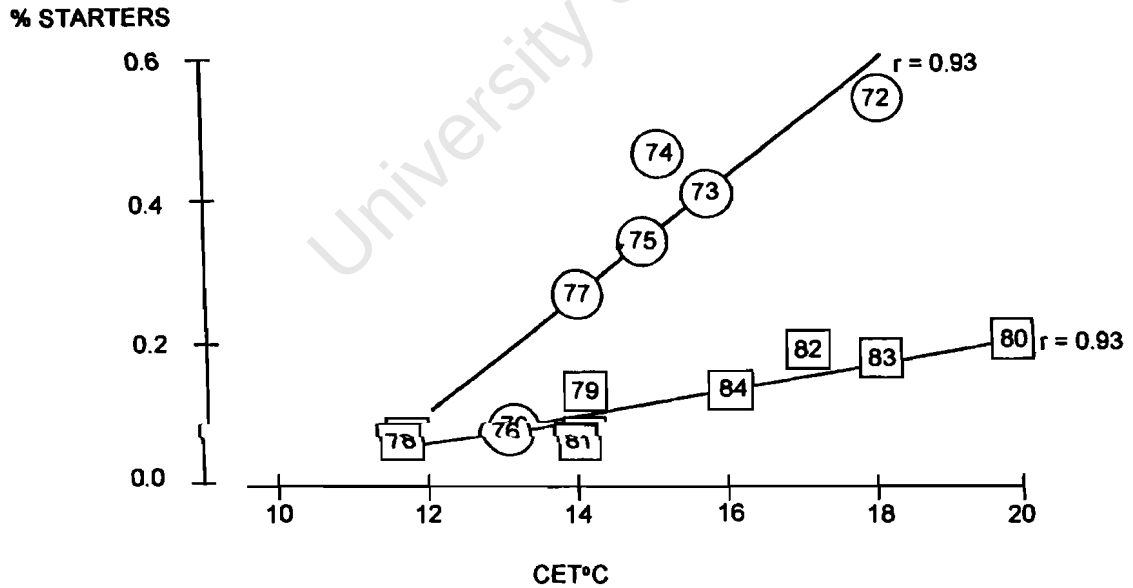

FIG. 1. Percentage of race starters with exercise-associated collapse expressed as a function of the corrected effective temperature (CET°C). Upper curve illustrates the regression for the years 1972–1977 inclusive; lower curve, for the years 1978–1984. Redrawn from Richards and Richards (41).

fluids. Rather we propose that intravenous fluid therapy should be saved for those athletes who continue to have increased heart rates (>100 beats/min) and hypotension (systolic blood pressure <110 mm Hg) when lying supine with the legs and pelvis elevated above the level of the heart.

Subjects with EAC can be encouraged to ingest fluids orally during recovery. Sports drinks containing both glucose (5–10%) and electrolytes (Na, 10–20 m*M*) can be advocated. Fluid retention is greatest from solutions with higher sodium contents (>80 m*M*), but such solutions are generally unpalatable and also unnecessary, as recovery from this condition, when correctly treated with elevation of the pelvis and legs, occurs within 10–20 minutes, before full rehydration could have occurred.

Most athletes with EAC will be able to stand and walk unaided within 10–30 minutes of the institution of appropriate treatment and can be encouraged to leave the medical facility within that time.

Muscle cramps

These are commonly seen and may show varying degrees of severity. The pathophysiology of muscle cramping is not determined, although a novel theory has recently been proposed (6,50). As a result there is, as yet, no uniform approach to treatment.

Maintaining the affected muscles in the lengthened position is the only therapy known to be effective (6,50). Icing and physiotherapy massage of the involved muscle groups are also used. The Boston Marathon medical team treat muscle cramps with normal saline given intravenously, but no clinical trials of the value of this treatment have yet been reported (1).

FACTORS INFLUENCING THE NUMBER OF MEDICAL CASUALTIES AT ENDURANCE EVENTS

Appropriate planning of the medical facility at an endurance event requires an estimation of the number of patients that are likely to require treatment, the nature of the medical conditions that will be encountered, and their severity. Available data allow the prediction of the expected number of casualties (1,41).

The total number of expected casualties is usually expressed as a percentage of the total number of race starters or entrants. It represents the predicted risk for the population involved and differs markedly according to the nature of the event. Table 5 lists these ranges for certain endurance events (42). When this figure is analyzed according to category of disorder, it is found that the proportion of certain conditions, for example, soft-tissue orthopaedic injuries, remains relatively constant and is essentially independent of the nature of the event.

However, the prevalence of EAC is dependent on the nature of the race, especially its length and whether it involves running, the nature of the participating population (in particular, their level of fitness and previous competitive experience), and the environmental temperature. Table 2, compiled from various sources (1,14,24, 36,41), indicates the effects of two of these factors, environmental conditions and race distance.

TABLE 5. *Ranges of the expected percentage of race starters likely to be admitted to the central medical care facility*

Activity	Percentage of race starters
Running	
42 km	2–20
21 km	1–5
Ultratriathlon >200 km	15–30
Cycling	5
Cross-country skiing	5

Data from Roberts, 1991.

It is clear that the longer the race and the higher the ambient temperature, the greater the proportion of casualties. It is also apparent that the detrimental effect of environmental heat increases substantially with increasing race distance. Whereas 50% more athletes will require treatment for collapse after a 12-km race run in hot than in cool conditions, this difference in a race of 90 km is 225% (Table 2).

Figure 1 shows the percentage of race starters treated for collapse at the medical facility at the Sydney City-to-Surf race for each year plotted against the prevailing environmental conditions during the race (41). There was a sharp reduction in the percentage of starters treated for collapse between 1978 and 1984, compared with that from 1971 to 1977. An intervention program, which encouraged the runners to improve their fitness and which explained how heat-related illnesses could be prevented during exercise, caused the lower prevalence after 1978. However, the annual prevalence, even in the fitter, more educated runners after 1978, was still related to the environmental temperature.

It is difficult to predict the exact number of medical personnel required to staff the medical facility at any particular race finish. This will depend on the predicted number of casualties, which is, in itself, strongly dependent on the environmental condition on race day (Table 2) and the proportion of more serious conditions that are likely to be encountered. Thus whereas a very large number of athletes with EAC can be comfortably managed by relatively few medical personnel, the opposite applies for the life-threatening medical conditions such as cardiac arrhythmias or the hyponatremia of exercise.

SUMMARY OF MANAGEMENT OF COLLAPSED ATHLETES

The probability is that the rate of admission of collapsed athletes to the medical facility at the finish of ultraendurance events lasting >4–6 h, and which include large numbers of competitors, will become too rapid for each new patient to receive a detailed medical examination before any specific treatment is initiated. For this reason, it is essential that some form of triage system should be introduced. Table 1 lists the different condi-

tions that may be expected in athletes competing in ultraendurance events; Tables 3 and 4 provide guidelines for how these conditions should be initially assessed, including the pertinent history that is required and adequate examination that should be performed.

Figure 2 depicts how the medical tent can be managed with admission and triage areas, green and red zones for nonsevere and severe cases, respectively, and areas for physiotherapy, medical supplies, toilets, and a diagnostic laboratory. An ambulance should be located next to the red zone to allow rapid evacuation of emergency cases. The activities that need to be completed in each of these areas also are indicated in Fig. 3.

Medical personnel required in the different designated areas include cardiologists, anesthetists, and intensive care nursing staff in the red area; physiotherapists would staff their own designated area. The green area, where most cases of EAC are treated, can be managed by sports physicians skilled in the management of fluid and electrolyte imbalances in endurance athletes.

Minimal diagnostic facilities would include equipment to measure blood pressure, rectal temperature, the electrocardiogram, and blood glucose concentrations. Equipment to measure serum electrolytes, especially sodium concentration, should be available at ultradistance events.

Equipment including one or more defibrillators and medications to treat cardiac arrest or serious arrhythmias and heatstroke must also be provided. When filled with ice-cold water, small, child-size, portable baths, each large enough to accommodate the torso of the collapsed athlete, are optimal for the treatment of heatstroke (5).

MANAGEMENT OF ATHLETES COLLAPSING ON THE COURSE (BEFORE THE RACE FINISH)

Provision needs to be made for the identification and management of athletes who collapse on the race course before the race finish. The probability is that these athletes will have one or more of the more serious medical conditions (Table 1) and can be more adequately managed in hospital without the delay of going first to the medical facility. It is necessary that the cooperation of the ambulance service and the local hospitals be obtained and coordinated to manage these eventualities.

CONCLUSION

The popular view that all persons who collapse after exercise have dehydration-induced hyperthermia has been challenged (33). Here we extend that argument and provide diagnostic and management protocols that, in our experience, cover the most common causes of collapse in ultraendurance athletes.

The use of these protocols can enhance the management of large numbers of collapsed ultraendurance athletes, providing optimal efficiency and improved safety.

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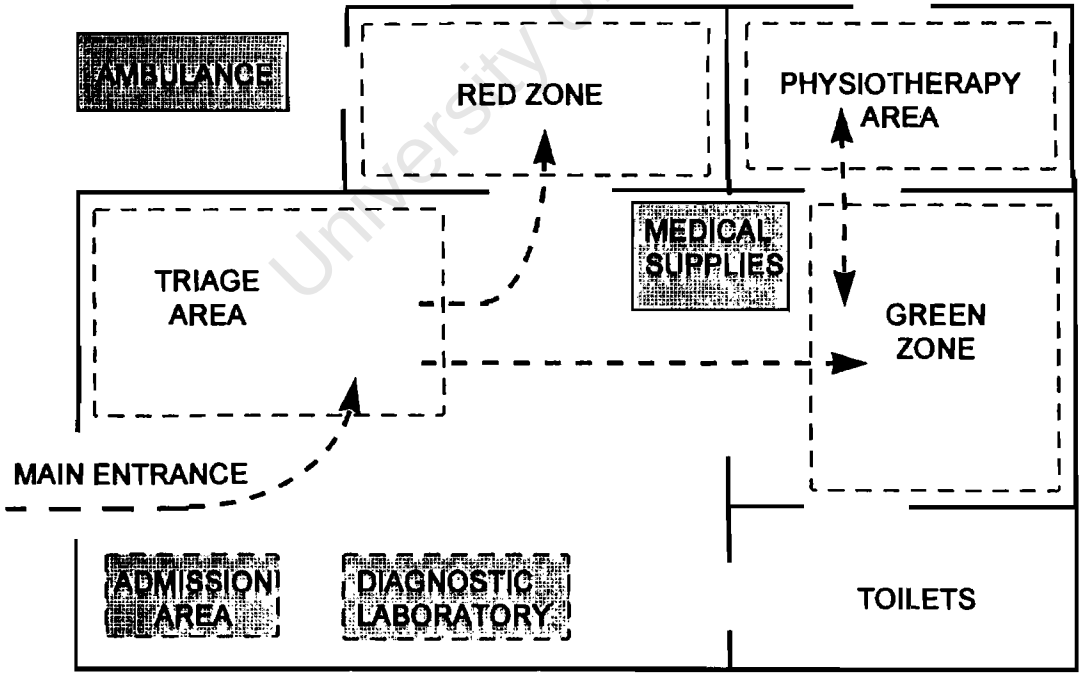

FIG. 2. Central medical care facility near the finish of an ultraendurance sporting event.

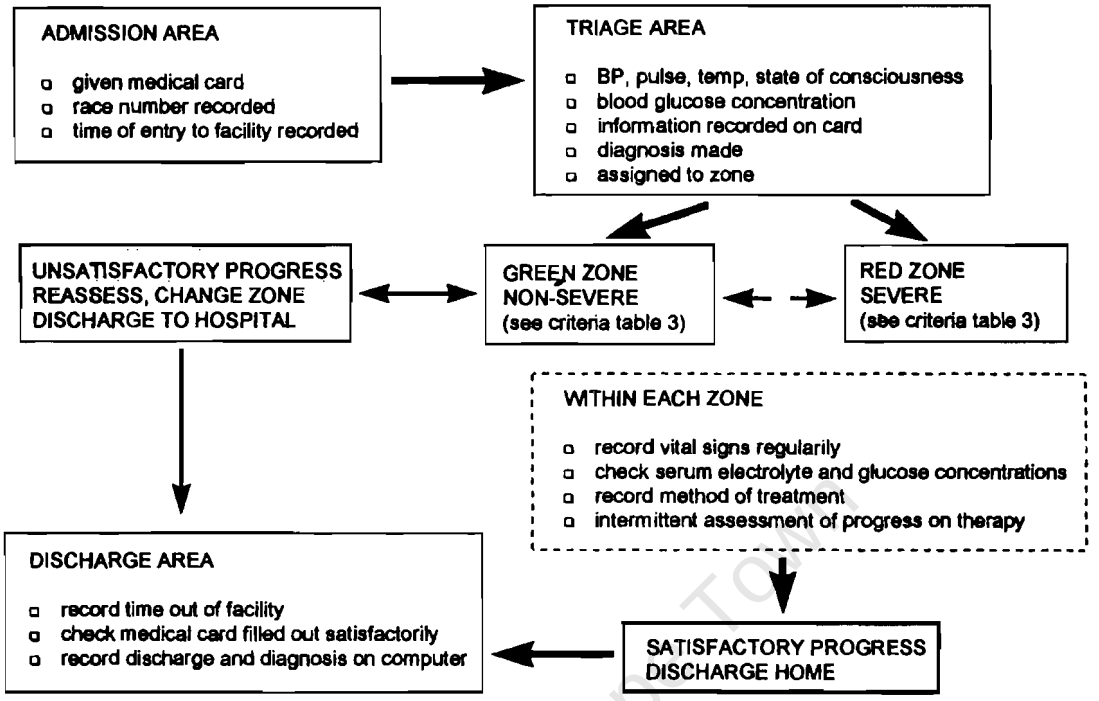

FIG. 3. Suggested flow chart for management of patients admitted to the central medical care facility (Fig. 2).

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Exercise-Associated Collapse

Postural Hypotension, or Something Deadlier?

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IN BRIEF: **Exercise-associated collapse (EAC) is the most common reason that athletes are treated in the medical tent following an endurance event. The pathophysiology of EAC is postural hypotension that results when the loss of muscle pumping action caused by the cessation of exercise is combined with cutaneous vasodilation. EAC usually occurs after an athlete crosses the finish line. If an athlete collapses *during* a race, then another serious medical cause is more likely. A brief assessment of the collapsed athlete should be carried out to obtain a working diagnosis. Prompt treatment of EAC includes elevating the legs and pelvis of the athlete.**

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Collapse following an endurance or ultra-endurance event is one of the most common reasons for an athlete to receive treatment at a race medical tent.[1-3] The cause in most cases is exercise-associated collapse (EAC), a benign condition related to postural hypotension on cessation of exercise.[4] Medical workers at the finish line of athletic events, who are often volunteers, need a sound understanding of EAC and a simple approach to the treatment of the collapsed athlete.

Definition of EAC

EAC is variably defined in the literature. Some authors[2,4] combine postural hypotension with the other medical causes for collapse (table 1), while others clearly differentiate EAC (presumed secondary to postural hypotension) from other causes.[1,3] Holtzhausen et al[4] have defined EAC as the "inability to stand or walk unaided as the result of light-headedness, faintness, dizziness, or syncope." This could be further defined by associating the collapse with completion of the race and a clearly demonstrable postural drop in

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TABLE 1. Conditions Associated With Collapse During or After Exercise

Exercise-associated collapse
Muscle cramping
Hyperthermia
Hypothermia
Hyponatremia
Hypoglycemia
Cardiac arrest
Other medical conditions
Musculoskeletal conditions

systolic blood pressure of greater than 20 mm Hg from standing to lying.[5]

EAC has previously been termed "heat syncope" or "heat exhaustion," but these terms are incorrect. No evidence shows that athletes who experience EAC have higher postrace rectal temperatures than do athletes who do not collapse after exercise.[6] Nor do athletes with EAC require the active cooling necessary for the treatment of heatstroke, the true heat disorder of exercise. As is the case in a great deal of research in this field, the absence of adequate control groups has led to the development and perpetuation of incorrect hypotheses.

Where and When

The prevalence of collapse in footraces is reported to be from 0.2% to 3.7%.[3,4,7-9] In 12 years at the Twin Cities Marathon in Minneapolis and St Paul, the incidence of EAC has been reported as 1.13% of race starters.[2] The 4-hour temperature range for these races was 41° to 68° F (5° to 20°C). Roberts[2] reported a medical encounter rate of of 25.3 per 1,000 finishers and that 59% of admissions to the medical facility were for EAC at the Twin Cities Marathon.

In ultradistance triathlon events, EAC has occurred in 17% to 21% of race starters.[1,10] When the stricter definition (which excludes other medical causes for collapse) was used, Speedy et al[1] reported that 27% of athletes seen in the medical tent after an Ironman Triathlon had EAC.

Postural Hypotension Explored

EAC is believed to be caused by postural hypotension brought on by the sudden cessation of exercise, especially if the exercise has been undertaken in the heat. Adolph[11] first suggested the role of postural hypotension in "heat exhaustion" after exercise. Similarly, Eichna et al[12] concluded that postural hypotension after exercise was caused by pooling of blood in the legs.

Holtzhausen and colleagues[4,5] reported that 85% of subjects with EAC collapsed *after* the cessation of a 56-km ultramarathon and not during the event, and that postural hypotension, often severe, could be demonstrated in virtually all the runners who completed the event. This evidence led them to suggest that Adolph and Eichna's hypotheses could explain the phenomenon of collapse immediately after exercise. The inactivation of the calf muscle pump immediately after cessation of endurance exercise results in blood pooling in the compliant veins of the lower limbs, causing a reduced atrial filling pressure and subsequent syncope. This circulatory decompensation is often exacerbated by heat-induced increases in muscle and cutaneous venous capacitance. Another factor may be a right atrial reflex that causes a paradoxical skeletal muscle vasodilation when the right atrial pressure falls dramatically (the Barcroft-Edholm reflex).[13]

In some cases, sources of extra fluid loss, such as sweating, diarrhea, and vomiting, may contribute to postural hypotension through a reduced blood volume. No evidence exists that athletes who have EAC are any more dehydrated than control athletes who finish the same race without collapsing. Indeed, levels of dehydration up to 5% do not alter cardiovascular function during exercise in the supine position, whereas such effects are measurable during exercise in the

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erect position.[14] This indicates that the position in which the exercise is performed, and not dehydration, is the primary cause for any cardiovascular instability that develops during exercise in healthy athletes.

The theory of postural hypotension on cessation of exercise is based on a study by Holtzhausen et al[4] who reported that 85% of athletes who required medical care in a 56 km ultramarathon collapsed *after* the race. Cessation of exercise was therefore considered important in the etiology. All of these runners had a postural drop in blood pressure immediately postrace that was not present when they were studied 24 hours later. Conversely, all runners who collapsed *during* the race had some identifiable medical condition that caused their collapse. Only 34% of runners who collapsed at the finish line were found to have some other medical condition responsible for their collapse—notably, hypoglycemia or heatstroke. The cardiovascular status of runners with EAC was normal when they were supine, in contrast to persisting hypotension and tachycardia in athletes who were in shock or had heatstroke. The distribution of rectal temperatures in runners who had EAC were not different from values measured in runners who did not collapse.[4] Similarly, others have reported that most runners who have EAC do not have rectal temperatures greater than 102.5°F (39°C).[2,3,15,16]

Training-induced adaptations to the autonomic nervous system have been postulated as contributing to the postural hypotension of EAC.[3] Exercise training induces adaptations, including a decreased vasoconstrictor response to hypotension.[17,18] Holtzhausen and Noakes[5] demonstrated an asymptomatic drop in postural systolic blood pressure of more than 20 mm Hg in 68% of runners who were studied immediately after an ultramarathon. Runners who had a postrace systolic blood pressure of less than 90 mm Hg experienced dizziness and nausea.

In the past, EAC has been attributed to dehydration-induced hyperthermia.[10] Holtzhausen et al[4] have argued against this theory on the grounds that if dehydration were a major contributing factor, athletes would be expected to collapse *during* exercise when the stress on the cardiovascular system is the greatest. Furthermore, they have reported similar levels of fluid losses in runners who collapsed and in controls who did not collapse, and similar levels of renin and arginine vasopressin in runners and controls.[4] The level of dehydration developed during the race has been shown to be unrelated to the degree of postural drop in systolic blood pressure.[5]

Differential Diagnosis

It is vital to differentiate serious causes of collapse from benign causes and to expedite treatment of those athletes who are seriously ill.[2,3] The first principle in the approach to the collapsed athlete is to establish a working diagnosis (see table 1). Holtzhausen and Noakes[3] and Noakes[19,20] have suggested that failure to consider a rational differential diagnosis prior to initiating treatment has been the major limitation to the management of collapsed athletes. They have also suggested this may stem from a fear on the part of the attending physician that delay in instituting treatment may prejudice the treatment outcome. However, the emergency treatment of severe medical conditions, such as hyperthermia and hyponatremia, can safely wait 1 to 2 minutes while a working diagnosis is established. The exception is cardiac arrest, which is an uncommon occurrence at ultradistance events and is an obvious diagnosis.

A further possible reason for initiating treatment without a diagnosis is the mistaken belief that dehydration is the major cause of collapse,[3,10,19] and that intravenous (IV) fluid replacement is often needed for athletes who collapse after ultradistance events.[10]

Assessment of the Collapsed Athlete

The initial clinical assessment (table 2) should be expedient but thorough, and it is beneficial to evaluate the collapsed athlete in the head-down position. Remember that athletes who collapse before reaching the finish line usually have a serious medical con-

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TABLE 2. Initial Assessment of the Collapsed Athlete

Mental status
Rectal temperature
Systolic blood pressure
Pulse rate
Hydration status
Site of collapse
Body weight change
Serum sodium concentration
Serum glucose concentration

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Figure 1: Courtesy of Timothy D. Noakes, MBChB, MD

FIGURE 1. Immediately placing a collapsed athlete in the head-down position is the first step toward correcting postural hypotension and restoring circulatory stability. The foot of the stretcher should be raised 6 in. (15 cm). Other assessments can be made and treatment can be initiated with the patient in this position.

dition that requires urgent attention.[4]

Mental status is the single most important clinical sign. If an athlete is unconscious or has an altered mental state when he or she is no longer in the erect position, the athlete is likely to have symptomatic hyponatremia, profound hypoglycemia, severe hyperthermia or heatstroke, or, paradoxically, hypothermia.

Core temperature is thus assessed first to rule out heatstroke as a cause of the altered mental state. It is crucial that the rectal and not oral, axillary, or aural routes be used, because only the rectal temperature accurately reflects core temperature in a field situation.[21] An unconscious athlete who has a rectal temperature higher than 107°F (41.6°C) has heatstroke, but an unconscious athlete whose rectal temperature is less than 104°F (40°C) and whose pulse and blood pressure are normal has hyponatremia until proven otherwise.

Pulse and blood pressure need to be measured in both the supine and erect position, if the athlete's condition allows. This gives some indication of the severity of the postural hypotension.

Signs of dehydration include a dry mouth, decreased skin turgor, and persisting hypotension and tachycardia despite elevation of the legs and pelvis. The inability to spit has also been found to be a useful clinical sign of dehydration,[3] but the most accurate method to determine the level of dehydration is by recording weight change over a race. Speedy et al[1] have recommended mandatory prerace weighing of all athletes participating in an ultradistance triathlon. Accurate data on weight change and hydration status are thus available if the athlete requires postrace medical care.

Signs of overhydration include an alteration of mental status caused by hyponatremia, weight gain during the race, and edema of the hands and fingers.[6] Increased tightness of rings, watches, or race registration wristbands is a useful sign of localized hand edema and possible fluid overload.

Serum sodium and glucose concentrations should be measured, if testing is available. A facility for on-site measurement of serum sodium concentration should be considered mandatory for ultradistance events, because hyponatremia is the major cause of serious illness following such events.[1] Serum sodium measurement is especially important when the official policy is that athletes should drink "as much as possible" during exercise; at such races the incidence of hyponatremia is especially high.[22] Of course, the most important preventive measure to ensure that athletes do not develop hyponatremia is simply to encourage athletes to drink "optimally but not maximally" during the race.[22]

A history made after the initial assessment should include an athlete's fluid and carbohydrate intake, urine output, presence of diarrhea or vomiting, drug intake, and concomitant illness. A general physical examination can follow the initial assessment after a working diagnosis has been achieved and any urgent treatment has been initiated.

Treatment of EAC

We[3,6] have recommended that athletes who have EAC be given oral fluids and have their legs and pelvises elevated by lifting the foot of the stretcher 6 in. (15 cm) (figure 1). The recovery of their cardiovas-

TABLE 3. Indications for Intravenous Fluid Therapy After Exercise-Associated Collapse

Intravenous fluid therapy is indicated *only* when the patient:
Shows signs of clinical dehydration (eg, dry mucous membranes, inability to spit, decreased skin turgor, sunken eyes)
Has dehydration that causes signs of cardiovascular instability or other medical problems
Cannot be treated with oral rehydration
Is unconscious and has serum sodium concentration >130 mmol/L

cular status is monitored every 15 minutes. IV fluids are not considered until response to the elevated lower-limb position is assessed. If the diagnosis is correct, the athlete's circulatory stability is almost instantly restored in the head-down position,[6] and the athlete can stand and walk unaided within 10 to 30 minutes.[2,3] Our clinical impression is that the quicker this form of treatment is initiated, the more rapidly the athlete recovers. In contrast, placing the patient in the supine position can occasionally worsen hypotension and delay recovery.

IV fluids administered to the athlete in the supine, unelevated lower-limb position are unlikely, on their own, to increase the venous return from dilated capacitance veins in the legs.[6,20] No study has demonstrated that treating collapsed athletes with IV fluids helps them to recover more quickly than nursing them in the head-down position.[6] Holtzhausen and Noakes[3] suggest that persistent tachycardia and hypotension, despite elevation of the legs and pelvis, could be an indication for IV fluid replacement. The indications for IV fluid therapy (table 3) following an ultradistance Ironman Triathlon are rare.[1,6,20] In the first 2 years of the South African Ironman Triathlon, it has not been necessary to give IV fluids to a single collapsed athlete. Rather, all have recovered rapidly with placement in the head-down position only.

Preventive measures for EAC include an appropriate cooldown after exercise (to avoid postural hypotension on sudden cessation of exercise) and the avoidance of hot showers immediately postrace. Collapse is also more likely when long queues develop in the race finishing area. When such queuing occurs, athletes who begin to feel faint should be encouraged to lie down and to elevate their legs and pelvises, if possible.

Other Common Conditions

In addition to postural hypotension, physicians in the medical tent are likely to see several other medical conditions.

Exercise-associated muscle cramping, the "painful, spasmodic, involuntary contraction of skeletal muscle that occurs during or immediately after muscular exercise,"[23] is also a common reason for visiting the medical tent following a race.[1-3,10] The cause has not yet been determined, and there is little support for abnormalities in either serum electrolyte concentrations or alterations in hydration status.[23] Schwellnus et al[23] have postulated that muscle cramping is caused by muscle fatigue, which alters alpha motor-neuron control at the spinal level. The treatment is to maintain the cramped muscle in a lengthened position with passive stretching.

Hyponatremia is defined as a serum sodium concentration of less than 135 mmol/L. Hyponatremia is more commonly seen in ultradistance races,[1] but it has also been described in marathon races[22,24] and in hik-

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The management of mild hyponatremia is 'masterly inactivity': awaiting a spontaneous diuresis of the excess fluid and observing the patient for a couple of hours. Alternatively, a low dose of diuretic may be used to initiate the diuresis.

ers.[25] Hyponatremia can either be symptomatic or asymptomatic. The cause of severe symptomatic hyponatremia is fluid overload.[22,26,27]

An endurance athlete who has an altered mental status and a normal rectal temperature should be considered to have hyponatremia until proven otherwise.[3] Other symptoms can include headache, incoordination, lightheadedness, seizures, and coma.[27] Edema of the hands and fingers is a useful physical sign of fluid overload. If athletes are stable with no symptoms or signs of cerebral or pulmonary edema, they can usually be managed in an on-site medical tent.[1]

The management of mild hyponatremia is "masterly inactivity": awaiting a spontaneous diuresis of the excess fluid. This normally requires observation for a couple of hours. Alternatively, a low dose of diuretic may be used to initiate the diuresis. Athletes with more severe hyponatremia need urgent transfer to a hospital, because seizures or coma may complicate this condition, and death may occur. A volunteer can quickly determine that immediate action is necessary if the athlete has a serum sodium level lower than 125 mmol/L, severe alterations in mental status, seizures, or pulmonary edema. These athletes should not be treated with oral or IV fluid since they are already suffering from fluid overload.[27] The exception is the judicious use of hypertonic saline if the athlete has severe central nervous system manifestations of hyponatremia, such as coma or seizures. Readers are referred to specific published guidelines on the use of hypertonic saline.[22,24,27]

Heatstroke is diagnosed when an athlete has a rectal temperature higher than 106.7°F (41.5°C) plus an altered mental status. Heatstroke requires immediate treatment to decrease body temperature. The simplest and most effective way to do this is to immerse the athlete in ice water for 5 to 10 minutes in a child's plastic bathtub with the arms and legs over the side.[3,6] Ice-water immersion should decrease the body temperature by 1.8°F (1°C) per minute, and after 5 to 10 minutes, the rectal temperature should have been reduced to 100.4°F (38°C). IV fluids may be given to correct any coexistent dehydration and to assist in stabilizing the circulation. Fluid overload, however, may induce myocardial failure and pulmonary edema in those with heatstroke, so IV fluids must be given with caution.

Hypothermia is diagnosed as "severe" when the rectal temperature is less than 86°F (30°C), "moderate" between 86° and 93.2°F (30° and 34°C), and "mild" between 93.2° and 96.8°F (34° and 36°C). Mild hypothermia is managed by replacing wet clothing with dry clothing, protecting the athlete from wind and rain, and insulating the athlete from the ground. If mental status is normal, athletes can be given warm fluids to drink. Athletes with moderate or severe hypothermia need to be gently wrapped in a blanket and transferred immediately to a hospital for passive heating. Ventricular fibrillation can occur with physical manipulation in severe hypothermia, so handling should be kept to a minimum.

Hypoglycemia is an unusual problem following an endurance event.[1,3] Athletes at risk are those involved in very long distance events who fail to consume adequate carbohydrate or who have an eating disorder.[3] Patients with type 1 diabetes are especially at risk if they fail to ingest adequate amounts of carbohydrate during exercise, particularly if they begin exercise with an excess of exogenous insulin from recent insulin injections. Management is with an IV infusion of 50% glucose.

Race Tent Expertise

The most common cause for EAC is postural hypotension caused by pooling of blood in the legs and pelvis. A sudden drop in the right atrial pressure that induces a reflex hypotension may also be a factor.[13]

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Collapsed athletes should be managed in the head-down position with the lower limbs elevated, while a simple assessment is made to determine if they have any other cause for collapse, such as heatstroke, hyponatremia, muscle cramping, or hypoglycemia. When a working diagnosis is achieved, specific treatment can be initiated.

The initial exam and triage system are the most important interventions that determine the efficacy of treatment of athletes who collapse during or after exercise. The foundation of a successful race-day medical facility is based on skilled clinicians who:

- Know that dehydration is not an acceptable clinical diagnosis for the conditions that typically occur in endurance athletes;
- Are aware that postural hypotension is the most common reason for admission to a medical tent at the finish of endurance events;
- Understand that the level of consciousness is the single most important clinical guide to the likely diagnosis; and
- Appreciate that some basic investigations will quickly establish a firm diagnosis for which the treatment is not usually especially demanding. **FSM**

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IMMDA-AIMS Advisory statement on guidelines for fluid replacement during marathon running

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by Tim Noakes, David E. Martin

ABSTRACT

During endurance exercise about 75% of the energy produced from metabolism is in the form of heat, which cannot accumulate. The remaining 25% of energy available can be used for movement. The rate of heat production increases as running pace increases and the larger the body mass, the greater the heat production at a particular pace. Sweat evaporation provides the primary cooling mechanism for the body, and for this reason athletes are encouraged to drink fluids to ensure continued fluid availability for both evaporation and circulatory flow to the tissues.

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Elite level runners could be in danger of heat illness if they race too quickly in hot/humid conditions, and may collapse at the end of their event. Most marathon races, however, are scheduled at cooler times of the year or day, so that heat loss to the environment is not excessive. Typically however, this post-race collapse is due simply to postural hypotension, caused by a decrease in the skeletal muscle massage of venous blood on its return to the heart, once the athlete has stopped. Elite athletes manage adequate hydration by ingesting about 200 – 800 ml per hour, and such a collapse is rare. Athletes "back in the pack," however, are moving at a much slower pace, with heat accumulation unlikely and drinking much easier to manage. They are often urged to drink "as much as possible," ostensibly to prevent dehydration from their hours out on the race course. Excessive drinking among these participants can lead to hyponatraemia severe enough to cause fatalities. Thus, a more reasonable approach is to urge these participants not to drink as much as possible but to drink as needed - no more than 400 – 800 ml per hour.

Historical Background: IMMDA and AIMS

The International Marathon Medical Directors Association (IMMDA) was formed in 1984 as the Consulting Medical Committee of the Association of International Marathons (AIMS). AIMS is a global organisation of marathons and other road races, formed in May, 1982. Starting with scarcely a dozen members, AIMS' current roster numbers approximately 150 events which are conducted on all 7 continents and which include the world's largest and most prestigious marathons. The purposes of AIMS are to:

1. Foster and promote marathon running throughout the world

2. Recognise and work with the International Association of Athletics Federations (IAAF) as the sport's world governing body on all matters relating to international marathons
3. Exchange information, knowledge, and expertise among its member events.

The purposes of the IMMDA are as follows:

1. Promote and study the health of long distance runners
2. Promote research into the cause and treatment of running injuries
3. Prevent the occurrence of injuries during mass participation runs
4. Offer guidelines for the provision of uniform marathon medical services throughout the world
5. Promote a close working relationship between race and medical directors in achieving the above four goals.

This "Advisory Statement on Guidelines for Fluid Replacement During Marathon Running" continues a series of periodic informational and advisory pieces prepared occasionally by IMMDA to provide timely, needed, and practical information for the health and safety of runners participating in AIMS events in particular, but applicable to other distance running races as well.

The changing nature of participation in marathon races

During the 1970s a major development in the worldwide fitness movement saw the creation of so-called "Big City Marathons," in which thousands of fitness enthusiasts joined elite athletes in the gruelling challenge of completing a 42.195 km (26.22 miles) trip on foot through city streets. The first of these occurred in 1976 when the New York City Marathon changed its course from several loops around Central Park to become a tour of the town, covering all 5 of its boroughs.

Prior to the early 1970s, relatively few marathons were staged around the world on an annual basis, and they were small, with participation numbering from the dozens into the hundreds. The competitors entered were talented athletes, well-trained and dedicated, including some hoping to earn berths on national teams travelling to major regional or world competitions such as the Olympics, Pan American and Commonwealth Games, European Championships and the like. The Boston Marathon was the largest of these, and so talented was the field that the race was finished within 3 hours. Women seldom participated until the mid 1970s.

The 1976 New York City Marathon thus added the element of a giant physical fitness participation spectacle to what previously was a purely athletic event, and its popularity gave it steady growth. Notice first the enormous size that can be attained by today's marathons; the New York City Marathon is often among the one or two world's largest such events. Secondly, notice the longer time required by the bulk of the runners in 2001 to complete the distance in comparison with 1978 - at least 60 minutes or more. Just the opposite might have been expected, i.e. the increasing popularity of marathon racing over the years ought to have produced faster rather than slower times for the participants. Indeed, this has occurred among the several dozen invited elite level runners up front, but it appears that the "back in the pack" marathon runners are delivering slower performances. They either have less inherent talent, or are doing less training, or both. Study of the race demographics does show among today's participants a large percentage who are engaging in "running tourism" or who are "running for a charitable cause," and thus for whom simply finishing is satisfaction enough.

This increased event size has of necessity resulted in an enormous expansion of medical support services for participants, especially during and immediately following these races. Much of this medical support has consisted of fluids (water plus electrolyte and energy-containing beverages) at so-called "aid stations" along the course. This is because the current approach to drinking, especially during the race, has become quite the opposite to that advocated in the 1960's and early 1970's. The current paradigm is that athletes should drink "as much as possi-

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ble" during lengthy endurance exercise such as marathon running (3-6).

The purpose of this IMMDA Advisory Statement is to provide a caution against this paradigm, due to the recent realisation that athletes – particularly the slower ones - can drink so much during prolonged exercise that potentially fatal consequences can result (7-14). The previously accepted guidelines for fluid replacement during more prolonged exercise thus require timely and meaningful revision. This Advisory Statement covers both social recreational running/racing as well as the more disciplined training done by elite level athletes and is also relevant for essentially sedentary people becoming military basic training recruits (12,13).

Perusal of the several revisions of published guidelines by the American College of Sports Medicine (ACSM) for fluid replacement during exercise (3-6), indicates that they are more laboratory-evidence-based than clinical-evidence-based (15,16). Although they indeed promote the wise doctrine that athletes do need to drink generously during exercise, a substantial and increasing body of evidence shows that harm can occur (7-9) from excessive drinking by endurance fitness enthusiasts requiring 4 or more hours to complete events such as a marathon footrace. This Advisory Statement briefly reviews the literature on the topic, describing how the interpretation of experimental data by itself has failed to adequately explain the physiological adjustments occurring in the body during exercise that cause heat gains and fluid losses.

Laboratory versus clinical observations regarding endurance exercise performance

Laboratory Studies

The logic for suggesting that athletes should drink copious amounts of fluids during prolonged exercise such as marathon running probably stems from the publication of laboratory research as early as 1969, which showed a relationship between the extent of dehydration that developed during exercise and the rise in rectal (core body) temperature (17-21). The sensible conclusion was that dehydration was the single greatest risk to the health of marathon runners because it would cause the body temperature to rise, leading to heat illness, including heatstroke (4-6,16-18). A related conclusion was that marathon runners who collapsed during or after races were suffering from dehydration-induced heat illness, the urgent treatment for which logically would include rapid intravenous fluid therapy (22). Further laboratory studies showed that the complete repletion of fluid losses during exercise maintained more normal cardiovascular function and lower rectal temperatures than did lesser levels of fluid replacement during exercise (20-21). Hence it was concluded that *complete* replacement of fluid losses during exercise was desirable and therefore all athletes should be encouraged to drink "as much as possible" during long lasting endurance exercise (4-6).

However, many of these studies lack practical relevance for advising such copious drinking because they were performed in laboratory temperature/humidity environmental conditions that exceed the typically cool-to-temperate spring or fall season climate under which most of today's city marathons are conducted (18-21). During these seasons, days with excessive heat production - and with it the risk of heat illness - are few and far between. Races contested in regions where the climate is consistently tropical – notably Pacific Rim locations - are held very early in the morning to alleviate any potential problems. Some experimental temperature conditions even exceeded the guidelines for safe exercise proposed by the ACSM in attempting to quantify the thermal challenge.

In addition, many of these studies were performed without adequate convective cooling caused by the movement of air over the body (16), which is another important difference when exercise is performed in the laboratory as opposed to out-of-doors (28). Inadequate convective cooling might explain why the high incidence of dehydration and elevated body temperature, reported in laboratory studies performed under these very

warm environmental conditions, has never been confirmed in out-of-doors competitive sport (26,27,29,30). Indeed, the logical conclusion from these studies is that when athlete subjects are allowed to choose their own pacing strategies as they do when participating in out-of-doors competitive sport, then their level of dehydration, as well as their drinking behavioural patterns, becomes a relatively unimportant determinant of the rectal temperature during exercise. A brief review of the physiological relationships between heat production and the development of heat injury is appropriate here.

Physiological Basis for Heat Stress and Heat Illness

The crucial factors that determine the risk of heatstroke are not the levels of dehydration reached during exercise but rather the rate at which the athlete produces heat and the capacity of the environment to absorb that heat. Perhaps the main reason why an incorrect doctrine (that dehydration *alone* causes heatstroke) has been allowed to achieve universal credence is because of the widespread ignorance of the multi-factorial aetiology of heatstroke and, especially, the relative importance of the different aetiological factors.

Several factors more important than dehydration combine together to determine when the rate of heat production exceeds the rate of heat loss. The rate of heat production is determined by the athlete's rate of energy expenditure (metabolic rate), which is a function of the athlete's mass and intensity of effort (running speed). Using this logic, the risk of heatstroke is likely to be greater in athletes who run 10 km races (42) than when they run marathons, because 10 km race pace is faster than 42.195 km race pace. Heavier athletes will also be at greater risk than lighter athletes when both run at the same speed (41), since they generate more heat when running at the same speed, which cannot accumulate. The reality is that heatstroke can only occur when the athlete's rate of heat production exceeds the rate at which the excess heat produced during exercise can be dissipated into the environment.

The capacity of the environment to absorb the heat generated by the athlete during exercise is determined by the environmental temperature and humidity, and by the rate at which the surrounding air courses over the athlete's body, producing cooling by convective heat losses. Thus, in summary, the risk of developing heat stroke is increased:

1. When the exercise intensity is highest, for example in shorter distance races (such as 10 km) rather than in longer distance races including the marathon
2. In athletes with greater body mass, who thereby generate more heat than lighter athletes who are running at the same pace
3. When the environmental temperature, and most especially the humidity of the air, is increased
4. When the potential for convective cooling is low as occurs under still wind conditions or in laboratory experiments in which there is inadequate convective cooling (16,28).

Practical Clinical Experience

Three compelling sets of clinical and field observations provide evidence against the recommended need for as much fluid replacement as possible during marathon competition. One set of data involves the marked rise in the number of athletes "back in the pack" suffering from fluid overload in marathon and ultramarathon races. More than 70 cases of this condition have been described (7-9) since it was first recognised in 1985 (23). The majority of these cases have occurred in athletes in the United States and many of the victims report that they followed the prevailing advice of drinking "as much as possible" during exercise (9).

During the same time period, it has been difficult to find any studies in which dehydration has been identified as the sole important causative factor for even a single case of exercise-related heatstroke.

In summary, it appears that the advice to drink copious amounts of fluid during prolonged exercise has generated an iatrogenic disease, the incidence of which has increased sharply in the past 15 years during the same

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period that this advice has been propagated with increasing enthusiasm. Furthermore, it appears that the medical risks associated with this novel iatrogenic condition exceed the risks associated with the condition for the prevention of which this (harmful) advice was originally formulated. This is particularly unfortunate since there is no credible evidence that high rates of fluid ingestion can influence the risk of heatstroke (22,24,25).

A second body of evidence mitigating against the need for drinking large volumes of fluids during marathon races comes from the observation that this behaviour does not appear to have reduced the number of people seeking medical care after marathon and ultramarathon races. Some medical directors have found that advocating a conservative rather than an aggressive drinking policy is associated with fewer than expected admissions to the race day medical facilities, if for no other reason than because the incidence of water intoxication is substantially reduced (26,27).

A third set of observations combines physiological estimates of dehydration with practical experience in working with elite athletes. It is well-known that the level of dehydration that develops during prolonged exercise like marathon running cannot be measured with certainty because it is not determined simply by the amount of weight loss during exercise. This is because the weight lost during exercise includes up to 1 kg of metabolic fuel that is irreversibly oxidised during exercise plus a variable amount of fluid that is stored with glycogen and released during exercise as the stored liver and muscle glycogen stores are oxidised. It has been calculated that an athlete who loses 2 kg of weight during a marathon race would, in fact, be dehydrated by only ~200 g (34) when allowance is made for the weight lost from those other sources.

Interestingly, the average weight loss during marathon races in which athletes drink as needed and not "as much as possible," is between 2-3 kg, suggesting that these athletes intuitively (and accurately) assess their needs for fluid replacement during exercise. This contrasts with the currently popular dogma which holds that thirst is an inadequate index of the fluid requirements during exercise, and thus athletes who drink only in response to their thirst will become sufficiently dehydrated during exercise, impairing their performance and placing their health at risk. On this basis, athletes have been urged to override their natural inclination and drink "as much as possible". This dogma may in fact not represent what competitive athletes ought to follow.

Athlete interview evidence suggests that world-class runners ingest minimal fluid volume during their competitive races, primarily because of the difficulty of such ingestion when racing at the high exercise intensities (~85% of maximum oxygen consumption) and fast running speeds necessary to achieve success in top-level races. To give an example for men, a 2:06:00 marathon represents a pace of 2:59 per km (4:48 per mile) or a velocity of 20.1 km per hour (12.5 miles per hour). For women, a 2:23:00 marathon represents a pace of 3:23 per km (5:27 per mile), or a velocity of 17.7 km/hr (11.0 miles per hour). Personal discussions with elite-level marathon runners suggests that they ingest about 200 ml per hour during marathon races. This value is similar to drinking amounts reported in the 1960s in slightly less talented athletes (17,35,36), but substantially less than the volume of 1.2 - 2 litres per hour that the ACSM guidelines recommend for elite athletes in competition. This practical information alone questions the dogma that only by drinking large volumes of fluids are athletes able to perform at a high level of competency.

Based upon the above review of literature, the practical information available from competing athletes, and experience in clinical settings gained at the finish lines of endurance races, several guidelines can be offered to assist medical personnel to manage better the population of patients who exhibit symptoms during or after their race.

Guideline # 1: *Be very careful to make accurate diagnoses, so that the treatment plan can be optimally effective rather than inappropriate.*

Perspective: To give a practical example, encouraging the slower runners/walkers in

marathon races to drink "as much as possible" is the incorrect treatment for the wrong group of athletes, since it is precisely this group of athletes who are essentially at no risk of developing heatstroke due to their low rate of heat production during exercise. It is the elite athletes who experience the greatest risk of heatstroke due to their much larger rate of heat production. Even they tend not to develop heat stroke despite drinking very little during such races, because they vary their pace according to existing conditions, delivering extraordinarily quick performance times in cooler weather and slowing the pace appropriately during hot summertime competitions such as occurs in major world championships.

Guideline # 2: *Considerable individual differences in responsiveness exist for tolerable fluid ingestion during exercise. The optimum rates of fluid ingestion during exercise depend on a number of individual and environmental factors. Therefore it is neither correct nor safe to provide a blanket recommendation for all athletes during exercise.*

Perspective: Several factors determine the rate of sweat loss and hence the necessary rate of fluid ingestion during exercise. These have been mentioned already, and include:

1. The rate of energy expenditure (metabolic rate), which is a function of the athlete's size and running speed
2. The environmental conditions, particularly the humidity and the presence or absence of convective cooling

In general, it has been found that the fastest athletes lose between 1 -1.5 kg of mass per hour during competitive marathon running. However, for reasons described earlier, this does not mean that this is the rate at which fluid must be replaced. This is because a portion of that weight loss is from oxidised metabolic fuels and another portion is from the release of water stored with muscle glycogen. Furthermore, there is no evidence that, during competition, elite athletes can drink at rates that even approach these rates of weight loss.

Guideline # 3: *A diagnosis of heat illness should be reserved only for those patients who have clear evidence of heatstroke, the diagnostic symptoms of which are described above, and the successful treatment of which requires active whole body cooling. When the rectal temperature is not elevated above 40 - 41 degrees C and the patient recovers fully without the need for whole body cooling, then a diagnosis of "heat illness" cannot be sustained and an alternate diagnosis must be considered (25,32,33).*

Perspective: Much of the confusion over the role of fluid balance in the prevention of heat illness arises because of the adoption of incorrect diagnostic categories for the classification of "heat illnesses" (16,25,32). Heatstroke should be diagnosed when rectal temperature in excess of 40-41 degrees C is exhibited in an athlete who shows an altered level of consciousness without any other cause, and who recovers only after a period of active cooling. This appears to be an extremely uncommon complication of marathon running since there are so few documented case reports in the medical literature. Even the boldly titled review article, "Heatstroke and Hyperthermia in Marathon Runners," (36) presented at the New York Academy of Sciences Conference on the Marathon that preceded the first 5 boroughs New York City Marathon in 1976, described anecdotal evidence of only one well-known case of heatstroke in a world class marathon runner. It is for this reason that these well remembered anecdotes - Jim Peters in the 1954 Empire Games Marathon (36); Alberto Salazar in the 1982 Boston Marathon; Gabrielle Andersen-Schiess in the 1984 Olympic Games Marathon - are frequently used to project the danger of heatstroke during marathon running and hence the need to drink adequately to prevent this condition in marathon races. In fact these anecdotes really only prove how extremely rare this condition is in modern marathon races run in reasonable environmental conditions.

Indeed the evidence from the 1996 Centennial Olympic Games held in "Hotlanta" was that "heat illness" was the most common diagnosis amongst spectators, accounting for 22% of medical visits, but was the least common diagnosis among the competitors, accounting for only 5% of

medical consultations (37). Furthermore of 10,715 persons treated by physicians during those Games, not one was treated for heat-stroke (37).

On the other hand, the number of athletes requiring medical care especially after marathon races has increased precipitously in the past 25 years, as reflected in the growth in provision of medical services at those races. However there is no evidence that the vast majority (> 99%) of the athletes treated in those medical facilities suffered from heat-related illnesses since they recovered without active cooling and their rectal temperatures were not higher than those of control runners who did not require medical care after those races (37-40).

In consequence, the prevention of heat-stroke in distance running requires that attention should first be paid to those factors that really do contribute to the condition in a meaningful way.

The true incidence of real heat illnesses *in marathon runners is unknown* but it *appears to be extremely low.* There are no studies showing that dehydration or its prevention plays any role in the cause or prevention of the so-called "heat illnesses" that are frequently diagnosed, on questionable grounds, in athletes seeking medical care after endurance events (22,24,25). In contrast, it has been suggested that postural hypotension, reversible by nursing the collapsed athlete in the head-down position (25,31-33), is the most appropriate and only necessary form of treatment for these incorrectly diagnosed as suffering from "heat illnesses".

Guideline # 4: *Athletes who collapse and require medical attention after completing long distance running events are probably suffering more from the sudden onset of postural hypotension (31,32) than from dehydration.*

Perspective: A crucial recent finding was that the majority (~ 75%) of athletes seeking medical care at marathon or ultra marathon races collapse only after they cross the finishing line (32,40). It is difficult to believe that a condition insufficiently serious to prevent the athlete from finishing a marathon, for example, suddenly becomes life-threatening only after the athlete has completed the race, at the very time when the athlete's physiology is returning to a state of rest. On the contrary, the evidence is that athletes who collapse before the race finish are likely to be suffering from a serious medical condition for which they require urgent and expert medical care (32,40).

The hypotension is more likely to be due to the persistence of a state of low peripheral vascular resistance into the recovery period, compounded by an absence of the rhythmic action of the skeletal muscles contracting in the legs (that earlier had been aiding blood return to the heart) as soon as the athlete completes the race and stops moving. Thus, there is a sudden fall in right atrial pressure which begins the moment the athlete stops exercising.

There is no published evidence that this postural hypotension is due to dehydration. Nor does logic suggest this as a likely explanation, since dehydration should cause collapse when the cardiovascular system is under the greatest stress, for example, during rather than immediately upon cessation of prolonged exercise. This has important implications for treatment of the common condition of post-exercise collapse in marathon runners.

Diagnosing this condition as a "heat illness" is intellectually risky not least because it leads to the false doctrine that "if only these athletes had drunk as much as possible during the marathon, they would not have required medical care after the race". In addition, there is evidence that a sudden fall in right atrial pressure can produce a paradoxical and sudden increase in skeletal muscle vasodilation. This leads to a sudden fall in peripheral vascular resistance, thereby inducing fainting. This was first identified by Barcroft et al. (43) in research undertaken during the Second World War (1944).

The assumption that athletes collapse after exercise because they are suffering from a dehydration-related heat illness has led to the widespread use of intravenous fluids as the first line of treatment for this condition of exercise-associated collapse. There are no clinical trials to show that

intravenous fluid therapy is either beneficial or even necessary for the optimum treatment of those athletes who collapse after completing marathon races and who seek medical care as a result.

If, however, the condition is really due to a sustained vasodilatation, perhaps in response to a dramatic reduction in right atrial pressure (43) that begins at the cessation of exercise, then the most appropriate treatment is to increase the right atrial pressure. The most effective method to achieve this is to nurse the collapsed athlete in the head down position. Since adopting this technique in the two races under our jurisdiction in Cape Town, South Africa, we have not used a single intravenous drip in the past 2 years. These are very long races with large numbers of participants. The 56 km Two Oceans Marathon had a total of ~ 16,000 runners in the last 2 years, and the 224 km Cape Town Ironman Triathlon had ~ 1,000 finishers in the last 2 years (26,27). We found no evidence that the management of these athletes was compromised in any way as a result of the adoption of this novel treatment method.

Guideline # 5: *Runners should aim to drink as needed between 400 - 800 ml per hour, with the higher rates for the faster, heavier runners competing in warm environmental conditions and the lower rates for the slower runners/walkers completing marathon races in cooler environmental conditions.*

Perspective: Published evidence indicates that rates of fluid intake during running races vary from 400 – 800 ml per hour (1, 29). Among those who develop the hyponatraemia of exercise, the rates of fluid ingestion during exercise are very much higher and may be as high as 1.5 litres per hour (7-9,44).

One can observe consistently that athletes who run fast in the present-day marathons with temperate environmental conditions appear to cope quite adequately despite what seem to be quite low levels of fluid intake during those races. Thus there does not appear to be any reason why elite athletes should be encouraged to increase their rates of fluid intake during marathon racing by drinking "as much as possible" (26, 27). What is even more important is that athletes who run/walk marathon races in 4 or more hours will have lower rates of both heat production and fluid loss, and must therefore be advised not to drink more than a maximum of 800 ml per hour during such races. They must be warned that higher rates of fluid intake can be fatal if sustained for 4 or more hours.

Several recent studies show that drinking as needed is as effective a drinking strategy during exercise as is drinking at the much higher rates proposed in the ACSM guidelines (45-47). Accordingly perhaps the wisest advice that can be provided to athletes in marathon races is that they should drink as needed and aim for ingestion rates that never exceed about 800 ml per hour.

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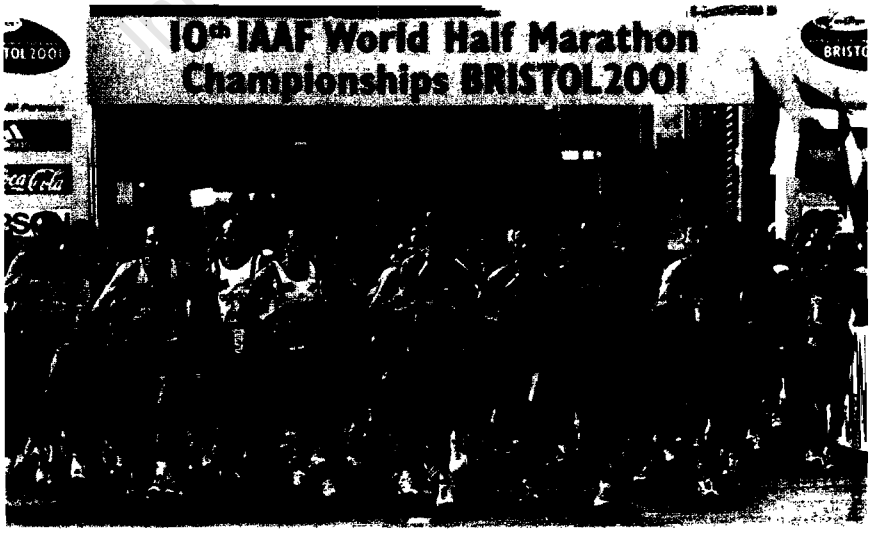

maintain priorities. Rewarming of the injured part in a water bath maintained precisely at 40 to 42°C (104 to 108°F) takes approximately 15 to 30 minutes. The process is complete when the skin changes to a red-purple color and becomes pliable. Another sign that rewarming is complete is the sudden onset of severe pain in the injured part. Dry heat is contraindicated and can lead to uneven warming and burn injury to the numb, fragile skin.

Blisters containing clear or milky fluid should be débrided, because this fluid is rich in inflammatory prostaglandins. Topical aloe vera (Dermaide Aloe), a potent antiprostaglandin agent, is applied every 6 to 12 hours. Ibuprofen should be administered orally at a dose of 12 mg per kg divided two to four times per day. It is a more potent inhibitor of thromboxane than other anti-inflammatory medications. Aspirin is not as useful because it blocks prostaglandin synthesis earlier in the cyclooxygenase pathway and limits the production of several beneficial mediators.

Penicillin, at a dose of 500,000 units every 6 hours, is administered empirically for the first 72 hours. During this period, a tissue edema makes the skin more susceptible to infection. Clindamycin (Cleocin), is the recommended alternative for penicillin-allergic patients. Antibiotic use after 72 hours is indicated only if there is evidence of infection.

Parenteral narcotics are used for analgesia for the intense pain associated with rewarming and early treatment. Morphine sulfate and meperidine (Demerol) are ideal in this setting. Almost all patients, except those with minimal tissue damage, should be admitted to the hospital. Daily hydrotherapy in water with hexachlorophene at 40°C aids débridement of devitalized tissue. Escharotomy or fasciotomy is performed if circulation is impaired or a compartment syndrome develops in the involved extremity. Definitive amputation of tissue should be delayed until 22 to 45 days after injury, when the demarcation between viable and nonviable tissue is clear.

Numerous adjuvant therapies for frostbite have undergone trials with varying degrees of success. Heparin, warfarin (Coumadin), and steroids have all failed to improve outcome. Hyperbaric oxygen and thrombolytics have had mixed success. At present, agents that inhibit the formation of free radicals, such as superoxide dismutase and PGE_1 analogues, and drugs that have antiplatelet activity, such as pentoxifylline (Trental), hold some promise as adjunctive agents. Future research will clarify their role in the treatment of frostbite.

DISTURBANCES DUE TO HEAT

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Traditionally, medical textbooks list three categories of heat illnesses resulting from exposure to heat, often with associated exercise: (1) minor medical conditions, including miliaria rubra and heat cramps; (2) heat exhaustion, which is considered a precursor of heatstroke; and (3) heatstroke. This classification, however, is illogical. Of these conditions, only heatstroke clearly fulfills the definition of a heat illness, which is "a state of thermoregulatory failure in which heat generation exceeds heat loss, causing heat retention within the body and a resultant increase in core temperature." There is no evidence that any of the other conditions are caused by a failure of thermoregulation. A more correct classification would be (1) heat illnesses occurring in persons exposed to a warm environment without evidence for thermoregulatory failure causing an elevated body temperature and (2) heatstroke, caused only by thermoregulatory failure.

HEAT ILLNESSES WITHOUT EVIDENCE FOR INTERNAL THERMOREGULATORY FAILURE

Included in this category are usually miliaria rubra, heat cramps, and heat exhaustion (heat syncope).

Miliaria Rubra

Miliaria rubra, also known as prickly heat or heat rash, is precipitated by keratin plugging of sweat gland pores, often with secondary bacterial infection. Management includes the use of skin cleansing agents, salicylic acid to promote skin desquamation, and antihistamines and antibiotics as required.

Heat Cramps

Heat cramps are involuntary, sustained, and painful contractions of skeletal muscle, usually of the calf, hamstring, or quadriceps muscles, most often occurring during or after unusually prolonged exercise such as marathon running. Although the cause of heat cramps is usually ascribed to severe dehydration accompanied by large sodium chloride losses that develop during exercise, especially in hot conditions, fluid balance studies have not shown that so-called "heat cramps" are (1) specific only to exercise in the heat; or (2) associated with fluid or electrolyte imbalances; or (3) caused by any failure of thermoregulation. Furthermore, clinical observation confirms that cramps can occur at rest or during or after exercise undertaken under any environmental conditions, including prolonged swimming in cold water, unlikely to cause heat retention. Hence, cramps are specific neither to exercise nor to exercise in the heat. The more recent hypothesis proposes that cramps result from alterations in spinal neural reflex activity activated by fatigue in susceptible individuals. According to this new understanding, stretching of the muscles both before and during exercise, and especially during an attack of cramp, is the only effective form of therapy and prevention. No controlled clinical trials have been conducted to establish the value of quinine, other medications, or electrolyte supplementation.

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Heat Exhaustion (Heat Syncope)

Heat exhaustion (heat syncope) is usually described as a condition in which the patient, usually an athlete, collapses during or after exercising in the heat. The condition is considered to be due to dehydration-induced heat retention insufficiently severe to cause heatstroke. Hence, heat exhaustion is described as a mild form of heatstroke caused by dehydration, which, unless correctly treated, must progress to heatstroke. However, heat exhaustion is *not* a true heat disorder, because there is no published evidence for thermoregulatory failure in this condition; nor is it caused solely by abnormal levels of dehydration; nor do patients with this condition experience heatstroke if managed incorrectly. Rather, the most important characteristic of heat exhaustion is that the condition usually develops in subjects who have already *stopped* exercising. This finding alone is incompatible with the belief that dehydration or hyperthermia are critical determinants of this condition. The more likely explanation is that the sudden cessation of exercise induces a postural hypotension by causing blood to pool in the dilated capacitance veins in the lower limbs when the "second heart" action of the lower limb musculature ceases on the sudden termination of exercise. In addition, there may be abnormal regulation of the splanchnic circulation with high rates of blood flow into the highly compliant splanchnic circulation. Accordingly, a more modern explanation is that heat exhaustion is caused by the sudden onset of postural hypotension on the cessation of exercise, caused probably by a precipitous fall in *central* (rather than circulating) blood volume and, hence, atrial filling pressure due to pooling of blood in the dilated capacitance veins in the lower limbs and, possibly, also in the splanchnic circulation.

On the basis of this theory, the most logical treatment of heat exhaustion is to elevate and cool the patients' legs and pelvises by nursing them in the head-down position. The twin goals are to reduce the skin blood flow and the volume of blood in the cutaneous and, perhaps, splanchnic veins and to increase venous return to the heart. Subjects considered to be dehydrated may ingest fluid orally, because no clinical trials have established either the need for, or the efficacy of, intravenous fluid therapy. Rather, injudicious intravenous fluid therapy has been associated with iatrogenic hyponatremia and occasional mortality in collapsed athletes treated inappropriately for an assumed dehydration. Using this form of treatment, we have dramatically reduced the need for intravenous fluid therapy in collapsed athletes, simultaneously improving the provision of medical care to those in greatest need because they have other potentially lethal exercise-related medical conditions such as heatstroke or hyponatremia.

HEATSTROKE

A diagnosis of (exercise-induced) heatstroke must be considered whenever, during exercise, a previously healthy athlete shows evidence of marked changes in mental functioning—for example, collapse with unconsciousness, a reduced level of consciousness (stupor, coma), or mental stimulation (irritability, convulsions)—in association with a rectal temperature in excess of 41°C. In nonexercising individuals, (classic) heatstroke occurs more commonly in elderly patients when the environmental heat load rises and in genetically predisposed individuals receiving anesthesia (malignant hyperthermia).

The factors that predispose to both exercise-induced and classic heatstroke are those that disturb the equilibrium between the rates of heat production and heat loss—for example, in athletes during exercise in hot and especially humid conditions or, during heat waves, in elderly persons with compromised cardiovascular function. The rate of heat loss is controlled by the air temperature and its humidity, by the rate of wind movement across the subjects' bodies, and by the rate at which they sweat; the rate of heat production is determined by the subjects' mass and work rates. Thus, in sport, *the rate of heat production and the risk of heatstroke is greatest in athletes who exercise the most vigorously and have the highest work rate—that is, usually in exercise of short duration and high intensity, not in the marathon footrace, as is commonly believed.* Thus, the most important factors causing heatstroke—especially during running—are the environmental conditions, the speed at which the athletes run, their body masses, and individual susceptibility. If short-distance running races (6–15 km) are held under extreme environmental conditions, heat injury will occur to a significant number of competitors *regardless* of whether or not they also become dehydrated.

In contrast, heatstroke occurs in the elderly with compromised myocardial function when they are unable to raise cardiac output sufficiently to increase heat loss under conditions of severe environmental heat stress.

Given the remarkably small number of athletes who experience exercise-induced heatstroke even when exercising in the heat, it seems probable that only certain individuals are predisposed to this condition during exercise. Thus, heatstroke occurs either because of acquired conditions that occur very rarely even in the large cohort of competitive runners or because affected athletes are susceptible perhaps because of hereditary abnormality of skeletal muscle metabolism similar to that which predisposes to the development of malignant hyperthermia. Thus, exercise may, perhaps, act as a trigger for (exercise-induced) malignant hyperthermia in some susceptible individuals.

Diagnosis and Management

The management of heatstroke is relatively simple provided the diagnosis is made early and treatment is initiated expeditiously. The problem is that the diagnosis is sometimes missed by those unfamiliar with the medical problems of sport.

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Rectal temperature increases during exercise in proportion to the metabolic rate and increases further if there is also dehydration. During vigorous exercise, the rectal temperature may increase to greater than or equal to 40.5°C in asymptomatic athletes involved in exercise of high intensity. The combination of an elevated rectal temperature (> 40.5°C) with symptoms of an altered mental state confirms the diagnosis of heatstroke and is sufficient to warrant immediate cooling to lower the body temperature. The more rapidly the rectal temperature is reduced to 38°C, the better the prognosis. The mortality rate (10–80%) in classic (non–exercise related) heatstroke is directly related to the duration and severity of the hyperthermia, to the presence of confounding medical conditions, and the rapidity with which cooling occurs. Mortality should be zero in healthy athletes who receive prompt and appropriate cooling. Indeed, it is unusual if an athlete, treated appropriately for exercise-induced heatstroke, has not recovered fully and is not ambulatory within 30 to 60 minutes of collapse. This excellent outcome requires that the correct treatment be initiated expeditiously.

Accordingly, the patient with heatstroke should ideally be placed in a bath of ice water for 5 to 10 minutes to expedite cooling. The body temperature should decrease to 38°C within this time.

The theory that placing the hyperthermic athlete in a bath of ice-cold water delays cooling by inducing vasoconstriction in the subcutaneous vessels should never have gained credence, given the clear evidence that hypothermia develops rapidly in persons exposed to freezing water. Fortunately, there is now firm evidence that cooling in a bath of ice-cold water is the most effective form of body cooling in exercise-induced hyperthermia, and rates of cooling close to 1°C per minute can be achieved. Such high rates of cooling can induce hypothermia if sufficient care is not taken. When body temperatures are changing rapidly, the rectal temperature lags behind the core (esophageal) temperature. Thus, active cooling must be terminated before the rectal temperature reaches the normal body temperature. Shivering indicates that the core temperature has decreased to 37°C or below.

There is no published evidence to establish that dehydration is an important etiologic factor in heatstroke. Intravenous fluids should be given purely to correct the level of dehydration expected in the athlete and to assist in stabilization of the hyperkinetic circulation. Thus, 0.5 or 0.9% saline (≥ 1–1.5 L) can be given initially, in part to ensure rapid venous access, should that be required.

Once the athlete's rectal temperature has been reduced to 38°C, the decision is whether or not to admit the patient to the hospital for further observation. Factors influencing this decision are the known tendency for the rectal temperature to increase after cooling; this increase may pass unnoticed if the patient returns home without appropriate supervision. Any tendency for the rectal temperature to increase after the cessation of exercise and cooling indicates the presence of ongoing heat-generating biochemical processes in muscle unrelated to exercise and related, perhaps, to the biochemical abnormalities that initiate malignant hyperthermia.

Our experience is that hospital admission is always required if the patient fails to regain consciousness within 30 minutes of appropriate therapy that returns the rectal temperature to 38°C. A patient who rapidly regains consciousness, whose cardiovascular system is stable, and whose rectal temperature does not increase in the first hour after active cooling ceases, does usually not require hospital admission. Thus, the decision whether or not to admit the patient with heatstroke to the hospital can usually be made within 30 to 60 minutes of the initiation of active cooling. Absolute indications for hospital admission are a failure to achieve cardiovascular stability or a fully conscious state during that time. A persisting tachycardia and hypotension in the lying position suggest a developing cardiogenic shock that requires hospital management.

Elderly patients who experience classic heatstroke during periods of severe environmental heat stress require hospitalization for management of the associated medical complications such as renal, cardiac, or hepatic failure, disseminated intravascular coagulopathy, or adult respiratory distress syndrome. These complications should not occur in healthy athletes treated immediately and effectively for exercise-induced heatstroke.

SPIDER BITES AND SCORPION STINGS

method of
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SPIDER BITES

Approximately 60 species of spiders in North America have been implicated in human bites of medical importance. Most bites are by female spiders. Deaths occur rarely and only with brown recluse and black widow envenomations. Mechanisms of injury from spider bites include dermonecrosis, development of secondary infection, neuromuscular damage, and allergic reactions (including urticaria). Children may be more likely to have greater morbidity and mortality. Hands and cutaneous areas with ample subcutaneous tissue develop more serious lesions, and individuals with underlying skin disorders may develop more extensive cutaneous reactions.

The diagnosis of spider bite is frequently very difficult to make, especially when the spider has not

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the physician and sportsmedicine

New Hydration Recommendations

Risk of Hyponatremia Plays a Big Role

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University of Cape Town

Concerns about overhydration and hyponatremia among endurance athletes were once discussed only in sports medicine circles. In May, USA Track & Field, the national governing body for track and field and race walking, issued new hydration recommendations[1] that urge runners to hydrate based on individual needs, rather than drinking as much as they can tolerate. Since then, the message has trickled down to mainstream medicine and even the lay press.

Hyponatremia is a hot topic among marathon medical experts and military physicians, because the condition is one of several causes of exertion-related collapse. Though experts agree that successful identification and treatment of hyponatremia depends on distinguishing the condition from heat illness and other diagnoses, disagreements flare about what level of hydration is optimal for the health and performance of athletes.

Two recent reports[2,3] in the medical literature seem to confirm a trend that marathon medical experts have observed: Hyponatremia has become more common as greater numbers of less competitive athletes participate in endurance events. A postrace blood study[2] done on 481 participants who ran the 2002 Boston Marathon found that 13% experienced hyponatremia. Risk factors included female gender, slower finishing times, and excess fluid consumption. An observational, retrospective, case-controlled study[3] of medical care at the 2000 Houston Marathon found that 21 runners (0.31% of entrants) presented to the medical area with hyponatremia. Risk factors among participants included slower race times and excess fluid consumption.

What Led to New Recommendations?

Douglas J. Casa, PhD, ATC, assistant professor in the department of kinesiology at the University of Connecticut in Storrs, Connecticut, wrote USA Track & Field's hydration advisory. He says the organization's intent was to acknowledge hyponatremia concerns that were expressed in a hydration advisory issued by the International Marathon Medical Directors Association (IMMDA) in 2002[4] and to educate athletes about determining their own individualized fluid needs. "Athletes should understand the risks of both hyponatremia and dehydration," Casa says. "This document gets people involved in finding a middle ground between the two."

The IMMDA advisory challenges the conventional wisdom, contained in, for example, the 1996 American College of Sports Medicine hydration recommendations,[5] that endurance athletes should drink as much as they can tolerate during exercise. Instead, the IMMDA advisory states that blanket hydration recommendations for athletes are incorrect and unsafe, and that they should drink as needed, but not to exceed 800 mL per hour.

Casa says that some level of dehydration is inevitable in some endurance activities and that USA Track & Field advises participants to at least replace what they are losing during activity. The USA Track & Field advisory teaches athletes how to calculate their individual sweat rates and how to monitor their hydration status with a urine color chart. "The biggest point we want to get across is that athletes have different sweat rates based on environment, exercise intensity, equipment, and body weight," he says.

Practical Considerations

Casa says he worries that the public may misconstrue the hydration recommendations. He points to a recent *New York Times* headline[6] that says "New Advice to Runners: Don't Drink the Water." He's particularly concerned about athletes in other sports getting the wrong information about hydration. "Runners have a longer time to overhydrate. But in soccer or football, dehydration is more common, because activity is more intense and is often performed in the summer," he says.

William O. Roberts, MD, associate professor in the Department of Family Practice and Community Health at the University of Minnesota in St Paul, says hyponatremia is mostly a problem among slower participants in long-distance or duration events and is not usually an issue in sports such as football, as long as players ingest adequate sodium. When patients ask about the new hydration advisories, Roberts, medical director of the Twin Cities Marathon, emphasizes that they should learn how to calculate and replace their sweat losses.

Roberts predicts that marathon groups will educate runners about the new hydration recommendations and that race volunteers will less aggressively push fluids on runners. Hydration stations will likely be fewer. "The Houston Marathon dropped from 30 to 15, and I'm pressing to go back to 12 for the Twin Cities Marathon," he says.

Timothy Noakes, MB ChB, MD, professor of exercise and sport science at the University of Cape Town and the Sports Science Institute of South Africa in Newlands, South Africa, who wrote the IMMDA recommendations and was the first to describe exercise-related hyponatremia along with the role of fluid overload, say he advises his patients to heed their thirst and to employ the same individualized hydration strategies in competition as they do in training. "I think that's where some of the problems have arisen," he notes.

Future Directions, Debate

Though IMMDA and USA Track & Field's hydration recommendations have generally been well received, Roberts says that some in the sports medicine field believe allowing thirst to guide hydration automatically puts athletes behind with fluid replacement--not dangerously, but enough to affect peak performance. "This should make for some heated and healthy debate," Roberts says.

Noakes says confusion still remains about the real dangers of dehydration. He contends that there is no evidence showing that dehydration levels during competition (2% to 8%) impair health or performance. "There is an urgent need to do properly controlled trials of the effects of weight loss (dehydration) during exercise on performance during weight-bearing activities like long-distance running," Noakes says. "Similarly, there is a need to determine what levels of dehydration carry health risks."

More research is also needed to determine the effects of convective cooling on heat balance during exercise, Noakes says, alluding to his belief that earlier lab studies that suggested the need to drink as much as possible did not match environmental conditions that athletes encounter during competition.

Lisa Schnirring
Minneapolis

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Position Statement

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Fluid Replacement during Marathon Running

Tim Noakes, MBChB, MD, DSc, FACSM

Summary

During endurance exercise, about 75% of the energy produced from metabolism is in the form of heat, which cannot accumulate. The remaining 25% of energy available can be used for movement. As running pace increases, the rate of heat production increases. Also, the larger one's body mass, the greater the heat production at a particular pace. Sweat evaporation provides the primary cooling mechanism for the body, and for this reason athletes are encouraged to drink fluids to ensure continued fluid availability for evaporation and circulatory flow to the tissues. Elite level runners could be in danger of heat illness if they race too quickly in hot/humid conditions and may collapse at the end of their event. Most marathon races are scheduled at cooler times of the year or day, however, so that heat loss to the environment is adequate. Typically, this postrace collapse is due simply to postural hypotension from decreased skeletal muscle massage of the venous return circulation to the heart on stopping. Elite athletes manage adequate hydration by ingesting about 200–800 mL/hour, and such collapse is rare. Athletes "back in the pack" are moving at a much slower pace, however, with heat accumulation unlikely and drinking much easier to manage. They are often urged to drink "as much as tolerable," ostensibly to prevent dehydration from their hours out on the race course. Excessive drinking among these participants can lead to hyponatremia severe enough to cause fatalities. A more reasonable approach is to urge these participants not to drink as much as possible but to drink *ad libitum* (according to the dictates of thirst) no more than 400–800 mL/hour.

Key Words: fluid replacement, heat stress, marathon running

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The International Marathon Medical Directors Association (IMMDA) was formed as the Consulting Medical Committee of the Association of International Marathons (AIMS). AIMS is a global organization of marathons and other road races, formed in May 1982. The purpose of AIMS is to (1) foster and promote marathon running throughout the world; (2) recognize and work with the International Association of Athletics Federations (IAAF) as the sport's world governing body on all matters relating to international marathons; and (3) exchange information, knowledge, and expertise among its member events. Starting with scarcely a dozen members, AIMS' current roster numbers approximately 150 events, which are conducted on all seven continents and which include the world's largest and most prestigious marathons.

The purpose of IMMDA is to (1) promote and study the health of long distance runners, (2) promote research into the cause and treatment of running injuries, (3) prevent the occurrence of injuries during mass participation runs, (4) offer guidelines for the provision of uniform marathon medical services throughout the world, and (5) promote a close working relationship between race and medical directors in achieving the first four goals. This Advisory Statement on Guidelines for Fluid Replacement During Marathon Running continues a series of periodic informational and advisory pieces prepared occasionally by IMMDA to provide timely, needed, and practical information for the health and safety of runners participating in AIMS events in particular, but applicable to other distance running races as well.

CHANGING NATURE OF PARTICIPATION IN MARATHON RACES

During the 1970s, a major development in the worldwide fitness movement saw the

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creation of "Big City Marathons," in which thousands of fitness enthusiasts joined elite athletes in the grueling challenge of completing a 42.195 km (26.22 mile) trip on foot through city streets. The first of these occurred in 1976, when the New York City Marathon changed its course from several loops around Central Park to become a tour of the city covering all five of its boroughs. Before the early 1970s, relatively few marathons were staged around the world on an annual basis, and they were small, with participation numbering from the dozens into the hundreds. The competitors entered were talented athletes, well trained and dedicated, including some hoping to earn berths on national traveling teams to major regional or world competitions, such as the Olympic, Pan American, and Commonwealth Games; European Championships; and the like. The Boston Marathon was the largest of these, and as shown in Table 1, so talented was the field that the race was finished by 3.5 hours. Women seldom participated until the mid-1970s.

The 1976 New York City Marathon added the element of a giant physical fitness participation spectacle to what previously was a purely athletic event, and its popularity gave it steady growth. Table 1 shows the numbers of finishers sorted by 30-minute time groupings for the 1978 and 2001 editions of this race as a means for comparing its changing participatory dynamics over time. Notice first the enormous size that can be attained by today's marathons; the New York City Marathon is often among the one or two world's largest such events. Second, notice the longer time required by the bulk of the runners in 2001 to complete the distance compared with that in 1978—at least 60 minutes or more. Just the opposite might have been expected (ie, the increasing popularity of marathon racing over the years ought to have produced faster times for participants rather than slower). This has occurred among the several dozen invited elite level runners up front, but it appears that the "back-in-the-pack" marathon runners are delivering slower performances. They have less inherent talent or are doing less training or both. Study of the race demographics does show among today's participants a large percentage who are engaging in "running tourism" or who are "running for a charitable cause" and for whom simply finishing is satisfaction enough.

This increased event size of necessity has resulted in an enormous expansion of medical support services for participants, especially during and immediately after these races. Much of this medical support has consisted of fluids (water plus electrolyte and energy-containing beverages) at so-called "aid stations" along the course. This is because the current approach to drinking, es-

TABLE 1. Difference in Finish Time Distribution Among Marathons 1975–2001

	Boston, 1975	New York City, 1978	New York City, 2001
Men's winning time	2:09:55	2:12:11	2:07:43
Total no. finishers	1818	8588	23,651
<3 hr	48.8%	9.4%	2.4%
3–3.5 hr	51.2%	21.1%	8.4%
3.5–4 hr		29.3%	19.4%
4–4.5 hr		21.0%	24.4%
4.5–5 hr		12.2%	22.4%
5–5.5 hr		5.1%	11.9%
5.5–6 hr		1.5%	6.1%
6–6.5 hr		0.4%	2.6%
6.5–7 hr		0.03%	1.4%
7–7.5 hr		0.05%	0.6%
7.5–8 hr			0.3%
8–8.5 hr			0.1%

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pecially during the race, has become quite the opposite to that advocated in the 1960s and early 1970s.[1,2] The current paradigm is that athletes should drink "as much as tolerable" during lengthy endurance exercise such as marathon running.[3–6]

The purpose of this IMMDA Advisory Statement is to provide a caution against this paradigm, due to the recent realization that athletes—particularly slower ones—can drink so much during prolonged exercise that potentially fatal consequences can result.[7–25] The previously accepted guidelines for fluid replacement during more prolonged exercise require timely and meaningful revision. This Advisory Statement covers social recreational running/racing and the more disciplined training done by elite level athletes as well as essentially sedentary people becoming military basic training recruits.[20–23] Perusal of the several revisions of published guidelines by the American College of Sports Medicine (ACSM) for fluid replacement during exercise[3–6] indicates that they are more laboratory evidence-based than clinical evidence-based.[24,25] Although these guidelines promote the wise doctrine that athletes do need to drink generously during exercise, a substantial and increasing body of evidence shows that harm can occur[7–25] from excessive drinking by endurance fitness enthusiasts requiring 4 or more hours to complete events such as a marathon footrace. This Advisory Statement briefly reviews the literature on this topic, describing how the interpretation of experimental data by itself has failed to explain adequately physiologic adjustments occurring in the body during exercise that causes heat gains and fluid losses.

LABORATORY VERSUS CLINICAL OBSERVATIONS REGARDING ENDURANCE EXERCISE PERFORMANCE

Laboratory Studies

The logic for suggesting that athletes should drink copious amounts of fluids during prolonged exercise such as marathon running likely stems from publication of laboratory research beginning in 1969 that showed a relationship between the extent of dehydration that developed during exercise and the rise in rectal (core body) temperature.[26–30] The sensible conclusion was that dehydration was the greatest risk to the health of marathon runners because it would cause the body temperature to rise, leading to heat illness, including heatstroke.[4–6,26–28] A related conclusion was that marathon runners who collapsed during or after races were experiencing dehydration-induced heat illness, the urgent treatment of which logically would include rapid intravenous fluid therapy.[2,31] Further laboratory studies showed that the complete repletion of fluid losses during exercise maintained more normal cardiovascular function and lower rectal temperatures than did lesser levels of fluid replacement during exercise.[29,30] It was concluded that *complete* replacement of fluid losses during exercise was desirable. All athletes should be encouraged to drink "as much as tolerable" during long-lasting endurance exercise.[4–6]

Many of these studies lack practical relevance for advising such copious drinking because they were performed in laboratory temperature/humidity environmental conditions that exceeded the typically cool-to-temperate spring or fall season climate under which most of today's city marathons are conducted.[25,27–31] During these seasons, days that are excessively hot and humid and, with it, the risk of exercise-induced heat illness are minimal. (Races contested in regions where the climate is consistently tropical—notably Pacific Rim locations—are held early in the morning.) Some experimental temperature conditions even exceeded the guidelines for safe exercise proposed by the ACSM in attempting to quantify the thermal challenge.

In addition, many of these studies were performed without adequate convective cooling[25] (facing wind speed), which is another important difference when exercise is performed in the laboratory as opposed to outdoors.[32] Inadequate convective cooling

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might explain why the high incidence of dehydration and elevated body temperature, reported in laboratory studies performed under these warm environmental conditions, has never been confirmed in outdoors competitive sport.[33-36] The logical conclusion from those studies is that when athletic subjects are allowed to choose their own pacing strategies as they do when participating in outdoors competitive sport, their level of dehydration and their drinking behavioral patterns become relatively unimportant determinants of the rectal temperature during exercise.[31,33-36] A brief review of the physiologic relationships between heat production and the development of heat injury is appropriate here.

Physiologic Basis for Heat Stress and Heat Illness

The crucial factors that determine the risk of heatstroke are not the levels of dehydration reached during exercise, but rather the rate at which the athlete produces heat and the capacity of the environment to absorb that heat. Perhaps the main reason why an incorrect doctrine (that dehydration *alone* causes heatstroke) has been allowed to achieve universal credence is because of the widespread ignorance of the multifactorial etiology of heatstroke and especially the relative importance of the different etiologic factors.

Several factors more important than dehydration combine their influence to determine when the rate of heat production exceeds the rate of heat loss. The rate of heat production is determined by the athlete's rate of energy expenditure (metabolic rate), which is a function of the athlete's mass and intensity of effort (running speed). Using this logic, the risk of heatstroke is likely to be greater in athletes who run 10-km races[37] than when they run marathons because 10-km race pace is faster than 42.195-km race pace. Heavier athletes also would be at greater risk than lighter athletes when both run at the same speed[38,39] because they generate more heat when running at the same speed, which cannot accumulate. ***The reality is that heatstroke can occur only when the athlete's rate of heat production exceeds the rate at which the excess heat produced during exercise can be dissipated into the environment.***

The capacity of the environment to absorb the heat generated by the athlete during exercise is determined by the environmental temperature and humidity and by the rate at which the surrounding air courses over the athlete's body, producing cooling by convective heat losses. In summary, the risk of developing heat stroke is increased:

1. When the exercise intensity is highest, for example, in shorter distance races (eg, 10 km) rather than in longer distance races including the marathon
2. In athletes with greater body mass, who generate more heat than lighter athletes who are running at the same pace
3. When the environmental temperature and especially the humidity of the air are increased
4. When the potential for convective cooling is low as occurs under still wind conditions or in laboratory experiments in which there is inadequate convective cooling[25,32]

Practical Clinical Experience

Three compelling sets of clinical and field observations provide evidence against the recommended need for as much fluid replacement as tolerable during marathon competition. One set of data involves the marked rise in the number of athletes "back in the pack" having fluid overload in marathon and ultramarathon races (Table 2).[7,9,11-19,40,41] More than 250 cases of this condition have been described[7-25] since it was first recognized in 1985.[10] Most of these cases have occurred in athletes in the United States, and many of the victims reported that they followed the prevailing advice of drinking "as much as tolerable" during exercise.[11,13,16-19,21-23,41] During the same time period, it has been difficult to find any studies in which dehydration has been identified as

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TABLE 2. Symptoms and Serum Sodium Concentrations in 77 Nonfatal Cases of Exercise-Related Hyponatremia: 1985–2001

Main presenting symptoms	%	Mean Serum [Na] (mmol/L)	Serum [Na+] Range (mmol/L)
Disorientation	43	125	117–131
Pulmonary edema	16	121	115–127
Respiratory arrest	1	118	113–123
Seizure	28	117	108–124
Coma	12	113	107–117

the sole important causative factor for a single case of exercise-related heatstroke.

It seems that the advice to drink copious amounts of fluid during prolonged exercise has generated an iatrogenic disease, the incidence of which has increased sharply in the past 15 years during the same period that this advice has been propagated with increasing enthusiasm. It seems that the medical risks associated with this novel iatrogenic condition exceed the risks associated with the condition for the prevention of which this (harmful) advice originally was formulated. This is particularly unfortunate because there is no credible evidence that high rates of fluid ingestion can influence the risk of heatstroke.[24,25,31,35,36,42–44]

A second body of evidence mitigating against the need for drinking large volumes of fluids during marathon races comes from the observation that this behavior does not seem to have reduced the number of people seeking medical care after marathon and ultramarathon races. Some medical directors have found that advocating a *conservative* rather than an aggressive drinking policy is associated with fewer than expected admissions to the race day medical facilities, if for no other reason than because the incidence of water intoxication is substantially reduced.[12,35,36,44,45]

A third set of observations combines physiologic estimates of dehydration with practical experience in working with elite athletes. It is well known that the level of dehydration that develops during prolonged exercise such as marathon running cannot be measured with certainty because it is not determined simply by the amount of weight loss during exercise. This is because the weight lost during exercise includes up to 1 kg of metabolic fuel that is irreversibly oxidized during exercise plus a variable amount of fluid that is stored with glycogen and released during exercise as the stored liver and muscle glycogen stores are oxidized. It has been calculated that an athlete who loses 2 kg of weight during a marathon race would be dehydrated by only approximately 200 g[46] when allowance is made for the weight lost from those other sources.

The average weight loss during marathon races in which athletes drink *ad libitum* (according to the dictates of thirst) and not "as much as tolerable" is 2–3 kg,[1] suggesting that these athletes intuitively (and accurately) assess their needs for fluid replacement during exercise. This is in contrast to the currently popular dogma that holds thirst is an inadequate index of the fluid requirements during exercise, and athletes who drink only in response to their thirst will become sufficiently dehydrated during exercise that their performances will be impaired and their health placed at risk. They are urged to override their natural inclination and rather to drink "as much as tolerable." This dogma may not represent what competitive athletes ought to follow.

Athlete interview evidence suggests that world-class runners ingest minimal fluid volume during their competitive races, primarily because of the difficulty of such ingestion when racing at the high exercise intensities (approximately 85% of maximum oxygen consumption) and fast running speeds necessary to achieve success in top-level races. For men, a 2:06:00 marathon repre-

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sents a pace of 2:59 per km (4:48 per mile) or a velocity of 20.1 km/hr (12.5 mph). For women, a 2:23:00 marathon represents a pace of 3:23 per km (5:27 per mile), or a velocity of 17.7 km/hr (11.0 mph). Personal discussions with elite level marathon runners suggest that they ingest about 200 mL/hr during marathon races. This value is similar to drinking amounts reported in the 1960s in slightly less talented athletes[1,26,47,48] but is substantially less than the volume of 1.2–2 L/hr that the ACSM guidelines recommend for elite athletes in competition. This practical information alone questions the dogma that only by drinking large volumes of fluids are athletes able to perform at a high level of competency.

GUIDELINES

Based on the above review of literature, practical information available from competing athletes, and experience in clinical settings at finish lines of endurance races, several guidelines can be offered to assist medical personnel better manage patients presenting with symptoms during or after a race.

Guideline 1

Be careful to make accurate diagnoses so that the treatment plan can be optimally effective rather than inappropriate.

Perspective

Encouraging slower runners/walkers in marathon races to drink "as much as possible" is the incorrect treatment of the wrong group of athletes because it is precisely this group of athletes who are at essentially no risk of developing heatstroke due to their low rate of heat production during exercise. Elite athletes experience the greatest risk of heatstroke due to their much faster *rate* of heat production. Even they tend not to develop heatstroke despite drinking very little during such races because they vary their pace according to existing conditions, delivering extraordinarily quick performance times in cooler weather and slowing the pace appropriately during hot summertime competitions, such as occurs with major world championships.

Guideline 2

Considerable individual difference in responsiveness exists for tolerable fluid ingestion during exercise. The optimal rates of fluid ingestion during exercise depend on many individual and environmental factors. It is neither correct nor safe to provide a blanket recommendation for all athletes during exercise.

Perspective

Several factors determine the rate of sweat loss and the necessary rate of fluid ingestion during exercise. These have been mentioned already and include (1) the rate of energy expenditure (metabolic rate), which is a function of the athlete's size and running speed, and (2) the environmental conditions, particularly the humidity and the presence or absence of convective cooling (facing wind speed).

In general, it is found that the fastest running athletes lose 1–1.5 kg of mass per hour during competitive marathon running. For reasons described earlier, this does not mean that this is the rate at which fluid must be replaced. A portion of that weight loss is from oxidized metabolic fuels, and another portion is from the release of water stored with muscle glycogen. There is no evidence that during competition elite athletes can drink at rates that even approach these rates of weight loss.

Guideline 3

A diagnosis of heat illness should be reserved only for patients who have clear evidence of heatstroke, the diagnostic symptoms of which are a clear alteration of mental function, either confusion or loss of consciousness, associated with a body temperature >41°C, and the successful treatment

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of which requires active whole body cooling. If the rectal temperature is not elevated to >40–41°C so that the patient recovers fully without the need for whole body cooling, a diagnosis of heat illness cannot be sustained, and an alternative diagnosis must be entertained.[42,43,49–51]

Perspective

Much of the confusion of the role of fluid balance in the prevention of heat illness arises because of the adoption of incorrect diagnostic categories for the classification of heat illnesses.[24,43,49] True heatstroke is diagnosed as a rectal temperature >40–41°C in an athlete who shows an altered level of consciousness without other cause and who recovers only after a period of active cooling; this seems to be an extremely uncommon complication of marathon running because there are few documented case reports in the medical literature. Even the boldly titled review article, "Heatstroke and Hyperthermia in Marathon Runners,"[48] presented at the New York Academy of Sciences Conference on the Marathon that preceded the first five-boroughs New York City Marathon in 1976, described anecdotal evidence of only one well-known case of heatstroke in a world class marathon runner. It is for this reason that well-remembered anecdotes—Jim Peters in the 1954 Empire Games Marathon,[48] Alberto Salazar in the 1982 Boston Marathon, Gabrielle Andersen-Schiess in the 1984 Olympic Games Marathon—are frequently used to project the danger of heatstroke during marathon running and the need to drink adequately to prevent this condition in marathon races. These anecdotes only prove how extremely rare this condition is in modern marathon races run in reasonable environmental conditions.

The evidence from the 1996 Centennial Olympic Games held in "Hotlanta" was that heat illness was the most common diagnosis among spectators, accounting for 22% of medical visits, but was the least common diagnosis among the competitors, accounting for only 5% of medical consultations.[52] Of 10,715 persons treated by physicians during those Games, not one was treated for heatstroke.[52]

The number of athletes requiring medical care especially after marathon races has increased precipitously in the past 25 years, as evidenced by the growth in the provision of medical services at those races. There is no evidence, however, that most (>99%) of the athletes treated in those medical facilities are suffering from heat-related illnesses because (1) they recover without active cooling and (2) their rectal temperatures are not higher than are those of control runners who do not require medical care after those races.[51,53–55] As a result, the prevention of heatstroke in distance running requires that attention first be paid to the factors that really do contribute to the condition in a meaningful way.

The true incidence of the real heat illnesses in marathon runners is unknown but appears to be extremely low. There are no studies showing that dehydration or its prevention plays any role in the cause or prevention of the so-called heat illnesses that are frequently diagnosed, on questionable grounds, in athletes seeking medical care after endurance events.[51,42,43] Rather it has been suggested that postural hypotension, reversible by nursing the collapsed athlete in the head-down position,[43,49–51,56] is the most appropriate and only necessary form of treatment of these incorrectly diagnosed as cases of heat illness.

Guideline 4

Athletes who collapse and require medical attention after completing long distance running events probably are suffering more from the sudden onset of postural hypotension[49,51,56] *than from dehydration.*

Perspective

A crucial recent finding was that most (approximately 75%) athletes seeking medical care at marathon or ultramarathon races collapse only *after* they cross the finishing

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line.[49,51,55,56] It is difficult to believe that a condition insufficiently serious to prevent the athlete from finishing a marathon suddenly becomes life-threatening only *after* the athlete has completed the race, at the time when the athlete's physiology is returning to a state of rest. Rather, the evidence is that athletes who collapse *before* the race finish are likely to have a serious medical condition for which they require urgent and expert medical care.[49,51,55]

The hypotension is likely due to the persistence of a state of low peripheral vascular resistance into the recovery period, compounded by an absence of the rhythmic action of the skeletal muscles contracting in the legs (that earlier had been aiding blood return to the heart) as soon as the athlete completes the race and stops moving. There is a sudden fall in right atrial pressure that begins the moment the athlete stops exercising.

There is no published evidence that this postural hypotension is due to dehydration. Logic does not suggest this as a likely explanation because dehydration should cause collapse when the cardiovascular system is under the greatest stress, for example, *during* rather than immediately on cessation of prolonged exercise. This has important implications for treatment of the common condition of postexercise collapse in marathon runners.

Diagnosing this condition as a heat illness is intellectually risky not least because it leads to the false doctrine that "if only these athletes had drunk 'as much as possible' during the marathon, they would not have required medical care after the race." In addition, there is evidence that a sudden decrease in right atrial pressure can produce a paradoxical and sudden increase in skeletal muscle vasodilation. This leads to a sudden fall in peripheral vascular resistance, inducing fainting; this was first identified by Barcroft et al[57,58] in research undertaken during World War II in 1944.

The assumption that athletes collapse after exercise because they are suffering from a dehydration-related heat illness has led to the widespread use of intravenous fluids as the first line of treatment of this condition of exercise-associated collapse. There are no clinical trials to show that intravenous fluid therapy is either beneficial or even necessary for the optimal treatment of athletes who collapse *after completing marathon races* and who seek medical care as a result.

If the condition is due to a sustained vasodilation, perhaps in response to a dramatic reduction in right atrial pressure[57,58] that begins at the cessation of exercise, the most appropriate treatment is to increase the right atrial pressure. The most effective method to achieve this is to nurse the collapsed athlete in the head-down position. Since adopting this technique in the two races under our jurisdiction in Cape Town, South Africa, we have not used a single intravenous drip in the past 4 years. These are long races with large numbers of participants. The 56-km Two Oceans Marathon had a total of approximately 33,000 runners in the last 4 years, and the 224-km Cape Town Ironman Triathlon had approximately 1000 finishers in 2000 and 2001.[35,36,44] We found no evidence that the management of these athletes was compromised in any way as a result of the adoption of this novel treatment method.

Guideline 5

Runners should aim to drink ad libitum ***400–800 mL/hr, with the higher rates for the faster, heavier runners competing in warm environmental conditions and the lower rates for the slower runners/walkers completing marathon races in cooler environmental conditions.***

Perspective

Published evidence indicates that rates of fluid intake during running races vary from 400–800 mL/hr.[1,33] Among persons who develop the hyponatremia of exercise, the rates

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of fluid ingestion during exercise are much higher and may be 1.5 L/hr.[7,12,15,16,41,44,45]

One can observe consistently that athletes who run fast in the present-day marathons with temperate environmental conditions seem to cope adequately despite what appear to be low levels of fluid intake during the races. There does not seem to be any reason why elite athletes should be encouraged to increase their rates of fluid intake during marathon racing by drinking "as much as tolerable."[35,36] Perhaps the even more cardinal point is that athletes who run/walk marathon races in 4 or more hours have lower rates of heat production and fluid loss and must be advised *not* to drink more than a maximum of 800 mL/hr during such races. They must be warned that higher rates of fluid intake can be fatal if sustained for 4 or more hours.

Several studies show that drinking *ad libitum* is as effective a drinking strategy during exercise as is drinking at the much higher rates proposed in the ACSM guidelines.[59-64] Perhaps the wisest advice that can be provided to athletes in marathon races is that they should drink *ad libitum* and aim for ingestion rates that never exceed about 800 mL/hr.

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THE FACTS ABOUT OVER-HYDRATION

Hyponatremia Can Pose a **Serious Threat** to Runners

For years, the mantra among runners and exercise enthusiasts has been: "Drink as much water as possible." But a condition called hyponatremia shows that, like many things, too much of a good thing can be unhealthy.

- **Hyponatremia** is a condition that can occur when fluid overload throws off the balance between the body's water and sodium levels. Basically, the water dilutes the body's salts and washes them away. When the blood has too much water and too little sodium, brain cells absorb too much water and the brain swells, pushing against the skull.
- **Hyponatremia** may lead to nausea, fatigue, vomiting, weakness, sleepiness, changes in sensorium and in the most severe instances, seizures, coma and even death.
- Those at risk for hyponatremia include:

1. **Women:** Women may be at risk for hormonal reasons or because they may tend to be overly conscientious about drinking water.
2. **Runners with slower finishing times who attempt to drink as much as possible.** Running a marathon in more than four hours give athletes more time to drink and to lose large amounts of sodium through prolonged sweating. Runners who are hyper-vigilant about increasing their water intake before and during a race are at risk for hyponatremia without even realizing it. Runners must learn how to optimize rather than maximize fluid intake during extreme exercise.
3. **Those who use NSAIDs before a race.** A recent study conducted by Runner's World indicates that 74% of marathon runners take analgesics, and over 88% report use of NSAIDs . However, runners who use NSAIDs such as Advil® or Aleve® for pain relief before or during endurance events may be at additional risk for hyponatremia, according to a few published reports. If a marathoner plans to take a pain reliever, Tylenol® 8 Hour is a safe over-the-counter choice during endurance sports activity..

1 "Too Much Fluids as Bad as Too Little; Drink Wisely During Exercise, Athletes Warned," by Daniel DeNoon, *WebMD Medical News,* July 17, 2003. Quote from Leslie Bonci, MPH, RD, director of sports nutrition at the University of Pittsburgh Medical Center

2 "Marathons: Blood, sweat, and cheers," Harvard Health Letter, Volume 28; Issue 6, 1 April 2003 Copyright 2003 Gale Group Inc. Copyright 2003 by President and Fellows of Harvard College.

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TIPS ON PREVENTING HYPONATREMIA

Hyponatremia occurs when fluid intake exceeds fluid loss during exercise, throwing off the balance between the body's water and sodium levels

For years, the mantra among runners has been: "Drink as much water as possible." But a condition called exercise-related **hyponatremia** shows that, like many things, too much of a good thing can be unhealthy.

Hyponatremia occurs when fluid intake – including sports drinks – exceeds fluid loss during exercise, throwing off the balance between the body's water and sodium levels. When the blood has too much water and too little sodium, brain cells absorb too much water and the brain swells, pushing against the skull. This condition can lead to nausea, fatigue and vomiting and in the most severe instances, seizures, coma and even death.

All endurance athletes who over-drink are at risk for hyponatremia, but those most prone to the condition include females and people with marathon times over 4 hours who are hyper-vigilant about their water intake. Additionally, runners who use nonsteroidal anti-inflammatory drugs (NSAIDs) like Advil® and Aleve® for pain relief in close proximity to race time may be at additional risk.

Some Do's and Don'ts on Avoiding Hyponatremia:

- **DO** drink moderately during races as recommended in Guidelines developed by The American Medical Athletic Association and the USA Track & Field.
- **DON'T** drink more than 16-24 ounces of fluid, including sports drinks, one to two hours before running a race.
- **DO** figure out personal intake and output levels by weighing yourself before and after a training run:

  * If you lost weight, you should drink more the next time.
  * If you gained weight, you should drink less.

- **DON'T** take NSAIDs like Advil® and Aleve® before or during endurance events because, according to a few published reports, these over-the-counter pain relievers seem to increase the risk for hyponatremia. Do take acetaminophen, such as Tylenol® 8 Hour, as a safe over-the-counter choice for your muscle aches and pains.
- **DO** stop all fluid intake if you experience weight gain with progressive symptoms such as swollen hands and feet, confusion, throbbing headache, dizziness and nausea.

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University of Cape Town

RUNNERS BEWARE

Up to 27% of athletes seeking medical attention during a long race exhibit warning symptoms of hyponatremia

Some Do's and Don'ts on Avoiding Hyponatremia:

October 8, 2003 - The more than 200,000 runners approaching the starting line of major marathoners this fall must be warned about a recently identified, potentially life-threatening hazard that may be caused by drinking too much water, hyponatremia.

"While the dangers of dehydration are common knowledge amongst amateur and experienced endurance athletes alike, there is something much more dangerous than not enough water: too much water," said Dr. Arthur Siegel, a physician at Harvard-affiliated McLean Hospital in Belmont, Mass., and leading researcher on hyponatremia who has run 20 marathons. "We must educate runners to optimize rather than maximize fluid intake during extreme exercise to avoid water intoxication."

Exercise-related hyponatremia may occur during prolonged sports activity such as marathons, triathlons, long-distance hiking or bicycling when fluid intake, including water and sports drinks, exceeds fluid loss. When water dilutes the body's salts, the blood has too much water and too little sodium, causing brain cells to absorb too much water, swell and push against the skull. This can result in nausea, severe fatigue, disorientation, vomiting and, in the most severe cases, seizures, coma and even death.

All endurance athletes who over-drink are at risk for hyponatremia, but those most prone to the condition include females and people with slower marathon finishing times (more than 4 hours) who are hyper-vigilant about their water intake . A recent study conducted by Runner's World indicates that 74% of marathon runners take analgesics, and over 88% report use of NSAIDs. However, runners who use nonsteroidal anti-inflammatory drugs (NSAIDs) for pain relief in close proximity to race time may be at additional risk.

Katherine "KC" Guevara experienced the horrors of hyponatremia first hand at the Boston Marathon this past April, only one year after the condition caused the collapse and subsequent death of 28-year-old Cynthia Lucero after collapsing at the 22-mile mark.

Water Intoxication a Potentially Life-Threatening Medical Crisis

"Even though I increased my salt intake the week before the race, I also drank almost three liters of water beforehand and drank more throughout. I knew at mile seven that something was wrong and I was in trouble," said Guevara, a 27-year-old running enthusiast from Centerville, VA. "In the medical tent, I was woozy and slurring my speech and once someone took my sodium levels, they realized I had hyponatremia and gave me some hot, salty broth. The scary thing is, a few years ago, I may have been treated for dehydration - with more water."

Despite new hydration guidelines and educational materials developed by the USA Track & Field Association, the American Medical Athletic Association and marathon race directors, many runners have not gotten the word about hyponatremia.

Siegel said there are several simple steps runners can take to prevent hyponatremia.

"Runners should weigh themselves before and after their next long training run to determine if their body tends to retain fluid during endurance exercise," said Dr. Siegel. "If they gain weight, they are at risk for the condition and should take precautions during the marathon."

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During a race, Dr. Siegel said it is vital that runners avoid over-drinking. Runners who develop progressive headache, nausea or vomiting should stop all fluid intake, including sports drinks, and seek medical assistance immediately. If a marathoner plans to take a pain reliever, take Tylenol® 8 Hour as a safe over-the-counter choice during endurance sports activity.

For more information about hyponatremia, please visit www.marathonfirsttimers.com, a web site designed to educate runners of all ages and abilities on the crucial aspects of running a marathon, including nutrition, apparel, injury prevention and pain treatment.

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University of Cape Town

Managing Triathlon Competition

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Medical coverage of endurance events requires knowledge of conditions that are specific to, or present differently in, endurance athletes. Serious conditions such as hyponatremia and rhabdomyolysis, and heat illnesses such as hypo- and hyperthermia, need to be accurately and quickly separated from more benign conditions such as exercise-associated collapse.

Introduction

The rapid interest and growth in triathlons has resulted in an increased requirement for sport-specific medical knowledge in those medical professionals that provide race-day coverage. Although a majority of race-day injuries are minor and self-limiting, it is important to quickly and accurately diagnose and treat those athletes with more serious medical problems, such as hyponatremia, rhabdomyolysis, and heat illnesses.

Staffing of the triathlon medical tent requires coordination, cooperation, and communication between the race director, the physician medical director, volunteer medical and paramedical staff, and local emergency medical systems and hospital personnel. Typically, an average of two to three physicians and seven to eight nurses and other paramedical volunteers for every 100 athletes is sufficient to meet the medical needs of the participants [1].

The main medical tent is typically situated close to the finish line, because most visits to the medical tent occur after completing, not during, the race. The medical tent should be equipped with a cardiac monitor/defibrillator or automated external defibrillator and advanced cardiac life support cardiac emergency medications, with trained personnel in the event of a cardiac emergency. Additional medical equipment may include nebulizers for administration of albuterol, and laboratory services for determination of glucose, sodium, potassium, and hemoglobin levels.

It is also appropriate to have medical teams and equipment at the swim-to-bike and bike-to-run transition areas. The availability of mobile medical staff is important in longer races, in which athletes requiring medical care may be some distance or transport time from the medical tent. Protocols for patient transfer from the race course and medical tent to a local hospital should be established in advance, and should follow local, state, and federal guidelines for patient transfer, including Emergency Medical Treatment and Active Labor Act laws.

A prerace medical questionnaire should be completed by all athletes; a compiled list of athletes with significant medical conditions should also be available in the medical tent and to medical staff. Documentation of athletes who receive treatment in the medical tent is important, and should include name, race number, and time entering and leaving medical tent. Additionally, the form should include a brief medical history, examination, diagnosis, treatment, and final disposition of the athlete.

Event-specific Injuries

Swim

Triathlons combine three sports in sequence (typically swimming, road cycling, and running), but some triathlons may have different events, such as mountain biking or canoeing as a portion of the race. The length of the triathlon can also differ, but several standards have been established. In a sprint triathlon, the swim is approximately 0.25- to 0.5-mile, the bike portion 5 to 15 miles, and the run 2 to 5 miles. An Olympic-distance triathlon includes a 0.9-mile (1.5 km) swim, 24-mile (40 km) bike, and a 6.2-mile (10 km) run. Ironman-distance triathlons consist of a 2.4-mile swim, 112-mile bike, and a 26.2-mile (marathon) run.

The swim segment of the triathlon may have the highest potential for injury, but accounts for less than 3% of medical visits at the Hawaii Ironman triathlon [1]. Traumatic injuries to the face, such as contusions, corneal abrasions, and mild concussions, due to the close proximity of other competitors and the kicking of feet and freestyle swim stroke, are the most common injuries seen. The type of swim start may affect the number of injuries also. The swim portion of the triathlon may be a "mass start," in which all competitors (over 2000 at larger events) start at the same time, or the competitors may be started in smaller groups based on age-group ("wave start"), with each group starting at a specific time interval from the next group.

Adverse weather and water conditions, such as high waves or cold temperatures, may also cause other problems, such as hypothermia, or increase the risk of drowning. Many athletes wear wet suits to prevent hypothermia and help with floatation. The guideline for wet suit use in triathlons is

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based on water temperature before the race. Wet suits are permitted for age group athletes in water temperatures under 78°F, whereas professional triathletes are permitted to use them in water temperatures below 74°F.

Bike

The cycling portion of the race results in approximately 10% of injuries requiring medical evaluation in Ironman-distance races [1]. Most injuries in this portion are traumatic, due to falls from the bike, and may be self-limiting, such as abrasions ("road rash"), contusions, or lacerations. More serious injuries include head injuries, fractures, and internal organ injuries from a high-speed fall or collision.

Run

Most visits to the medical tent occur from the finish line (71%) [1]. The most common reason for medical care from the finish line is exercise-associated collapse, followed by musculoskeletal complaints and dehydration [2,3].

Medical Problems

Overall, the medical tent visits and the injury rates for triathlons are dependent upon the length of the race, the weather conditions, and the difficulty of the course; these rates may also be somewhat higher than those of other endurance events. The Twin Cities Marathon (Minneapolis, MN) has recorded a medical tent visitation rate of 1.9% for entrants and 2.5% for marathon finishers, and only 0.1% of finishers requiring a higher level of medical care at the emergency department or hospital [3].

Data from the Hawaii Ironman triathlon demonstrate a higher percentage of medical tent visits, with approximately 25% to 30% of the starters receiving medical attention. Despite the length of the race and extreme temperature conditions, on average only one to four athletes each year require transport to the local hospital for a higher level of medical care (Laird, Personal communication, 2002).

The collapsed athlete

The collapsed athlete is one of the more common conditions that the medical staff will be called upon to evaluate in an endurance event such as a triathlon [3,4•]. It is important to quickly and accurately determine if the collapse is a minor and self-limiting condition, or if evidence of a more serious and potentially life-threatening medical problem exists. Most athletes will collapse after crossing the finish line, and this exercise-associated collapse (EAC) has been reported as the most common medical problem experienced at the finish line [2].

Traditionally, the collapse was attributed to dehydration-induced hyperthermia; however, more recently, the concept of EAC has evolved [4•]. A common finding in EAC is significant postural systolic hypotension with secondary tachycardia. Studies of EAC in ultra-marathoners have found only modest changes in rectal temperature and supine heart rates. Postrace serum sodium concentrations, and changes in plasma volume and mass during recovery, were not significantly different from values in control runners [5]. Not all athletes with significant systolic hypotension (> 20 mm Hg change from standing to supine) will be symptomatic [6]. The treatment of EAC consists of elevating the legs of the athlete to help increase central blood flow and pressure. EAC can be prevented in some athletes by encouraging them to continue walking, and not standing or sitting, immediately after finishing the race.

Hyponatremia

Hyponatremia (serum sodium < 135 mg/dL) has been recognized as a serious problem in the endurance athletes, and may occur in 10% to 40% of ultra-endurance athletes [7,8]. Most cases above 130 mg/dL are asymptomatic, but severe cases (serum sodium < 125 mg/dL) may present with altered mental status, lethargy, confusion, or seizures, and can be fatal if not diagnosed quickly.

One cause of hyponatremia in endurance events was thought to be due to overhydration [7] secondary to excessive free water intake prior to and during the race. Noakes [9] has suggested three possible pathologies for the development of symptomatic hyponatremia, including inappropriate antidiuretic hormone secretion (causing increased fluid retention), an abnormal regulation of the extracellular fluid volume, and "third spacing" of sodium and fluid. However, a recent study of 90 Ironman athletes in the Hawaii Ironman triathlon found that athletes with documented hyponatremia (serum sodium < 135 mg/dL) were more likely to be either dehydrated or euhydrated [10]. An earlier study at Ironman New Zealand found 58 of 330 (18%) of finishers with some degree of hyponatremia, with 18 athletes requiring medical care. In the severe hyponatremic group, there was a significant increase in weight gain, whereas the mildly hyponatremic group had a more variable weight gain or loss [7].

Athletes with hyponatremia secondary to overhydration typically have a significantly smaller body weight, have slower race times, and lose less weight during the race [11••]. Hyponatremic triathletes also have shown no significant difference in estimated sodium deficit compared with eunatremic athletes [11••].

Treatment

The treatment of hyponatremia in the endurance athlete is typically one of close observation in the medical tent, or transfer to the hospital if the athlete displays more serious signs such as mental confusion, lethargy, or seizures. The administration of hypertonic intravenous fluids is rarely indicated in the medical tent. In most cases of hyponatremia, the serum sodium levels will correct once the athlete begins diuresis of excess fluid. Currently, no research supports the routine use of diuretics in the treatment of athletes with hypervolemic hyponatremia. Overhydrated

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hyponatremic athletes will excrete a larger amount of fluid during postrace recovery (1346 mL excess vs 521 mL fluid deficit) and experience more weight loss than eunatremic athletes [11••]. Athletes with hypovolemic hyponatremia can receive normal saline intravenous fluids if indicated by their level of dehydration.

Prevention

Prerace education of triathletes concerning excessive fluid intake and hyponatremia is common at longer-distance triathlons. Additionally, measurement of prerace body weight is a requirement at some races, so that weight change during and after the race can be determined [2].

Dehydration

Prevention of dehydration during exercise is important for performance. Fluid loss during exercise is a combination of sweat rate, respiratory water loss, and urine output. Studies of ultradistance triathletes has found that the fluid intake during competition is less that fluid output, resulting in an average weight loss of 2.5 kg for pre- and postrace weights [12].

The American College of Sports Medicine recommends that athletes drink about 500 mL of fluid approximately 2 hours prior to exercise, and encourages regular ingestion of fluid during exercise to replace what is lost through sweating. Races longer than 1 hour should offer a carbohydrate/electrolyte drink for fluid replacement [13].

Treatment

Most cases of dehydration can be treated conservatively with slow oral hydration as tolerated by the athlete after the race. In cases where the athlete is nauseated or has significant dehydration with a normal sodium level, intravenous fluid may be appropriate.

Initial intravenous fluid management at races lasting longer than 2 hours is a liter of 5% dextrose solution with normal saline (D5NS) followed by normal saline (NS) if necessary. In shorter races, a more hypotonic solution such as 1/2NS may be used.

Heat illnesses

Exercise-induced heat stroke (core body temperature > 41 °C) is a serious and life-threatening condition that requires rapid diagnosis and treatment to prevent a catastrophic and fatal outcome [14]. Heat stroke may be seen with or without significant dehydration, and is more common in shorter-duration events, due to the higher rate of exercise in comparison with ultradistance triathlons. A life-threatening presentation is a rectal temperature greater than 41 °C (105.8 °F) and an altered mental status (*eg*, lethargy, confusion, seizures, or unconsciousness). Immediate treatment should focus upon rapid cooling, either with ice-packing or immersion in a cold-water tub, until the core body temperature can be lowered to 38 °C (100.4 °F). Initial treatment should be started before transport to a medical facility.

Rhabdomyolysis

Rhabdomyolysis is a rare but serious complication of prolonged or intense exercise. The diagnosis should be considered in the differential diagnosis of acute muscle weakness or pain. The athlete may also present with anuria, oliguria, or dark urine, as well as an altered level of consciousness. Measurement of an elevated creatine kinase level (> 500 U/L) and a urine dipstick positive for blood without obvious hematuria may confirm the diagnosis. The management of rhabdomyolysis requires rapid intravenous fluid replacement to maintain a high urine output and avoid acute renal failure.

Muscle cramps

Surveys of marathon runners and Ironman triathletes have reported a prevalence of muscle cramps of 30% to 50%, and 67%, respectively [15], and is a common complaint during and after competition.

Many theories regarding the etiology of muscle cramps including electrolyte disturbances of sodium, potassium or magnesium, but many of these studies are based on patients with renal failure on dialysis, cancer, or during pregnancy [16], and may be difficult to relate to endurance athletes. Limited studies looking at electrolyte disturbances in athletes in endurance events have not found significant differences between serum electrolyte levels and reports of muscle cramping. There have been case reports of athletes with significantly high sodium sweat rates who have exercise-associated muscle cramps that improve with ingestion of saline drinks, but no studies to date have proven the sodium deficit hypothesis on a larger scale. Several authors have proposed mechanisms for exercise-associated muscle cramps [15,17,18•].

Exercise-associated muscle cramps may be the result of muscle fatigue and an altered or abnormal spinal reflex activity. As the muscle fatigues, the amount of relaxation time in between muscle contractions lengthens. If the relaxation time is too long, or a high rate of muscle contraction is required (such as during running), muscle cramping may result. Cramping may also be a protective mechanism to prevent further injury to fatiguing or damaged muscle tissue.

Treatment

Initial treatment of muscle cramps focuses on passive stretching of the affected muscle groups. Athletes with excessive muscle cramping should be assessed for significant electrolyte abnormalities. Cramping refractory to passive stretching may be treated by intravenous magnesium (2–4 g) or diazepam (5 mg).

Pulmonary disorders

Exercised-induced asthma is one of the more common pulmonary conditions found in endurance athletes, and most athletes are well controlled on long-acting β-agonist inhalers. Treatment of acute asthma exacerbations in the medical tent should follow standard treatment protocols,

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Table 1. Guidelines for determining the severity of a collapsed triathlete's condition

Immediate assessment	Not severe	Severe
Mental state	Conscious Alert	Unconscious or altered Confused, disoriented, or aggressive
Rectal temperature	< 40°C (104°F)	> 40°C (104°F)
Systolic blood pressure	> 100 mm Hg	< 100 mm Hg
Heart rate	< 100 beats/min	> 100 beats/min
Blood glucose	4–10 mmol/L	< 4 mmol/L
Serum sodium	135–148 mmol/L	< 130 mmol/L or > 148 mmol/L
Body weight loss	0%–5%	> 10%
Body weight gain	< 2%	> 2%

(*Adapted from* Mayers and Noakes [20••].)

including providing albuterol, oxygen, and steroids as medically indicated. More severe cases that do not respond to initial treatment in the medical tent may be transported to the hospital for further care.

Cardiac disorders

Cardiac emergencies are rare during endurance events. The incidence of cardiac fatalities during marathons is approximately one in 50,000 [19]. Most events occur during the competition [20••]. Sudden cardiac death may be due in part to ventricular premature beats (VPB) leading to ventricular fibrillation. There is a higher incidence of VPB in triathletes than in the general population [21]. Triathletes and other endurance athletes have several cardiac adaptations that occur as the result of their training, including mixed eccentric and concentric hypertrophy of the left ventricle with normal function [22,23]. Other studies have demonstrated reversible ventricular abnormalities of left ventricular function on echocardiogram, and transient elevation of troponin-T and troponin-I immediately after completing an Ironman-distance event [24].

Gastrointestinal disorders

Dietary intake may play a role in the symptoms experienced during competition. Rehrer *et al.* [25] found that triathletes who had eaten within 30 minutes of the start of the race vomited during the swim. The type of prerace meal was also found to have an effect upon the incidence of gastrointestinal complaints. A high-fat or -protein diet before the race, or drinking hypertonic beverages, resulted in a higher incidence of nausea or vomiting. Abdominal cramping is also more common in athletes who have consumed a high-fiber prerace meal [25].

Serious gastrointestinal (GI) complications may also occur during or after triathlon competition. Several cases of bowel ischemia and infarction in triathletes have occurred in ultradistance triathlons; similar cases have also been documented in marathons [26].

Gastrointestinal bleeding has also been reported at a rate between 8% to 30% of marathon runners [27]. Studies looking at prerace medicating with 400 mg of cimetidine has not proven effective for decreasing the incidence of occult GI bleeding, suggesting that the cause of bleeding may not be related to gastric acid levels [27]. The incidence of GI bleeding also appears to be independent of GI symptoms, age, or race duration [28].

Infectious diseases

Two extensive outbreaks of leptospirosis have been reported in triathletes as a result of exposure during the fresh-water swimming portion of races in Wisconsin and Illinois [29]. Most affected athletes presented with an acute febrile illness several days after completing the race, although some of the more seriously ill athletes developed acute renal failure. Out of 876 triathletes in one race, 120 required medical care and 22 were hospitalized [30]. Isolated cases have also been reported in triathletes training in contaminated fresh water [31].

Dermatologic injuries

Prolonged sun exposure occurs at most events [32]. Although sunburn can develop, the acute injury is usually self-limiting, and treatment should focus primarily on prevention of long-term problems of prolonged sun exposure. The use of waterproof sun block (sun protection factor 15 or greater), and clothing such as hats or visors and longer-sleeved shirts can limit exposure.

Blisters and chaffing are other common skin problems caused by excessive rubbing or ill-fitting shoes. Initial treatment of blisters should be limited to needle drainage where appropriate. Moleskin or other types of occlusive dressings may provide comfort.

Conclusions

Coverage and management of medical issues at a triathlon requires precise planning and coordination between medical staff, the race director, other race volunteers and staff, as well as local medical facilities, such as ambulance services and nearby hospitals and emergency departments. The USA Triathlon Federation recommends that the race medical staff be able to evaluate, adequately treat, stabilize, and possibly transport athletes to a higher level of medical care (Table 1).

Acknowledgment

Dr. Laird is the Medical Director of the Ironman Triathlon World Championships, Kona, HI.

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ORIGINAL INVESTIGATIONS

Implications of exercise testing for prediction of athletic performance: a contemporary perspective

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ABSTRACT

NOAKES, T. D. Implications of exercise testing for prediction of athletic performance: a contemporary perspective. *Med. Sci. Sports Exerc.*, Vol. 20, No. 4, pp. 319–330, 1988. One of the most fundamental beliefs in exercise physiology is that performance during maximum exercise of short duration is limited by the inability of the heart and lungs to provide oxygen at a rate sufficiently fast to fuel energy production by the active muscle mass. This belief originates from work undertaken in the 1920's by Hill and Lupton. A result is that most, if not all, of the studies explaining the effects of exercise *training* or *detraining* or *other interventions* on *human physiology* explain these changes in terms either of central adaptations increasing oxygen delivery to muscle or of peripheral adaptations that modify the rates of oxygen or fuel utilization by the active muscles. Yet a critical review of Hill and Lupton's results shows that they inferred but certainly did not prove that oxygen limitation develops during maximal exercise. Furthermore, more modern studies suggest that, if such an oxygen limitation does indeed occur during maximal exercise, it develops in about 50% of test subjects. Thus, an alternative mechanism may need to be evoked to explain exhaustion during maximal exercise in a rather large group of subjects. This review proposes that the factors limiting maximal exercise performance might be better explained in terms of a failure of muscle contractility ("muscle power"), which may be independent of tissue oxygen deficiency. The implications for exercise testing and the prediction of athletic performance are discussed.

MAXIMUM OXYGEN CONSUMPTION, RUNNING ECONOMY, MAXIMUM WORKLOAD, MUSCLE CONTRACTILITY, MUSCLE POWER, PERFORMANCE PREDICTION.

Probably the single most commonly used procedure in exercise physiology is the test for maximum oxygen consumption ($\dot{V}O_{2max}$). Judging by the frequency with which the topic is discussed in lay publications, it would seem that the vast majority of runners, swimmers, triathletes and cyclists implicitly believe that the $\dot{V}O_{2max}$ is the single best predictor of athletic potential.

This article will review the historical development of the $\dot{V}O_{2max}$ concept in order to show that the popular interpretation of $\dot{V}O_{2max}$ test results may be simplistic and is based on a fundamental misinterpretation of the historical studies. A more modern interpretation of the meaning of this test will be proposed, and alternative tests for predicting athletic performance will be reviewed.

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HISTORICAL OVERVIEW OF TESTING FOR MAXIMUM OXYGEN CONSUMPTION

The concept that oxygen consumption plateaus during maximal exercise of progressively increasing intensity—the "$\dot{V}O_{2max}$ plateau" phenomenon. Probably the first scientists to measure oxygen consumption during exercise in athletes were Lindhard at the University of Copenhagen (43, 44), Liljestrand and Stenstrom at the Karolinska Institute in Stockholm (41, 42), and Herbst (31) in Berlin.

These studies, reported in German, established that oxygen consumption increased with running (31, 41) or swimming speed (42) and that the fastest runners had the highest values for oxygen consumption during running (31). Herbst (31) also showed that the rate of oxygen consumption when running on the spot was greatest at 280 steps per minute and did not increase further at 320 steps per minute, analagous to the concept of a plateau in oxygen consumption with increasing exercise intensity.

The work of Hill, Long, and Lupton. The first English-speaking scientist to study oxygen consumption during exercise in some detail was Nobel laureate Archibald Vivian Hill, Professor of Physiology at University College, London. Hill wrote the following in his monograph on Muscular Activity (32):

> In running the oxygen requirement increases continuously as the speed increases, attaining enormous values at the highest speeds; the actual oxygen intake, however, reaches a maximum beyond which no effort can drive it ... The oxygen intake may attain its maximum and remain constant merely because it cannot go any higher owing to the limitations of the circulatory and respiratory system.

In the scientific paper on which this work was based (33), this interpretation is emphasized:

> However much the speed be increased beyond this limit, no further increase in oxygen intake can occur: the heart, lungs, circulation and the diffusion of oxygen to the active muscle-fibres have attained their maximum activity. At the higher speeds the requirement of the body for oxygen ... cannot be satisfied ... lactic acid accumulates, a continuously increasing oxygen debt being incurred, fatigue and exhaustion setting in.

This interpretation has been perpetuated in a number of popular texts of exercise physiology (2, 4, 8, 9, 26, 45, 47, 48) and review articles (24, 57).

Clearly it is important to scrutinize the experimental data of Hill and Lupton (33) to determine exactly how they established 1) that oxygen consumption reached a maximum during running "beyond which no effort can drive it" and 2) that the oxygen debt increased at high exercise intensities causing "lactic acid" to accumulate in muscle and blood, particularly as their explanations for the biochemical basis of the "oxygen debt" are now known to have been seriously in error (28).

The basic experimental protocol used by Hill and his colleagues (33–35) was to have the test subjects run for three minutes at different speeds on a circular grass track 85 m in circumference. Oxygen consumption was measured with a Douglas bag every thirty seconds for each of the three minutes that the subject ran. Some of the data reported by Hill and Lupton (33) and Hill et al. (34, 35) were measured in Hill when he was 35 years old. The data for their first study (33) of Hill have been redrawn in Figure 1. Their interpretation of these data was the following:

> When muscular exercise is taken in man at a constant speed, the lactic content of his active muscles increases gradually from its resting minimum at the start. The rise in lactic acid content increases the rate of oxidation, so that finally, if the oxygen supply be adequate, a "steady state" is reached in which the rate of lactic acid production is balanced by the rate of its oxidative removal, and its concentration remains constant in the muscle as long as exercise at that speed is maintained. The lower three curves represent a genuine steady state, the uppermost curve *only an apparent steady state* in which the oxygen intake is at its maximum and the oxygen debt is rapidly increasing.

Hill and Lupton concluded that the constant oxygen consumption they measured at the fastest running speed (16 km·hr^{-1} in Figure 1) represented an apparent, not a *true* steady state on the basis 1) of Hill's feelings of fatigue during the run and 2) their interpretation of the meaning of the "oxygen debt," which they knew to increase after exercise of increasing intensity.

Specifically, from his feelings of fatigue, Hill concluded that he would be unable to maintain that pace for even 10 min. Consequently, he surmised that his real rate of oxygen consumption must have exceeded that which was measured during that specific exercise bout. This was a circular argument; Hill used his belief that oxygen limitation explained his fatigue as the basis for his argument that an oxygen limitation was indeed present.

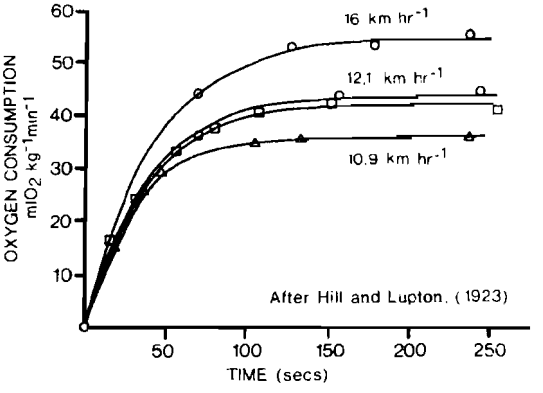

Figure 1—Time course of the rise in oxygen consumption at three different running speeds for A. V. Hill, from Hill and Lupton (33).

As Hill and Lupton (33) had previously established that the excess post-exercise oxygen consumption, termed the "oxygen debt" by them, increased with increasing severity of the preceding exercise, they also concluded that Hill's "oxygen debt" and, therefore, his blood lactate levels must have been greatest after his run at the fastest speed. Based on these reasonings, they (34) proposed the following:

> ... if human muscles be similar in their general oxidative capacity to frogs' muscles, the recovery process in a human muscle should be complete in 2 or 3 minutes. ... The recovery process is indeed complete in about that time, after an effort so gentle, that the oxygen supply is completely adequate (during the exercise—author's addition). The extreme prolongation of the recovery process after very severe exercise cannot be explained simply by considerations of a deficient oxygen supply (during exercise). Something has happened, in the first few minutes of recovery, or during the exercise itself, while the oxygen supply was still inadequate, which has rendered subsequent recovery slow. ... If the oxygen supply is adequate, as it is after very mild exertion, the lactic acid formed rapidly passes through the recovery mechanism, and reappears in a minute or two as glycogen. ... After severe exercise, the oxygen supply is at first inadequate to allow the whole of the lactic acid present to pass immediately through the recovery mechanism (to glycogen); the acid ... diffuses slowly into the blood stream ... causing the phenomena of objective and subjective fatigue ... (from) the bloodstream its oxidative removal is prolonged and constitutes the second phase of recovery. In such severe exercise the lactic acid is continuously accumulating in the muscles, the maximum oxygen intake (depending upon the capacity of the heart and lungs) being inadequate to ... cope with the production of lactic acid. ... Considering the case of running, ... there is clearly some critical speed for each individual ... above which, the maximum oxygen intake is inadequate, lactic acid accumulating, a continuously increasing oxygen debt being incurred, fatigue and exhaustion setting in.

Hill and Lupton (33) provide no evidence that they actually measured concurrently either the oxygen debt or muscle or blood lactate levels during these or subsequent studies. To have shown that the oxygen uptake they measured in Hill at 16 km·hr^{-1} was indeed maximal, they would have had to run Hill at a higher speed, probably 18 km·hr^{-1}, and to have measured either the same or a lower oxygen consumption as that measured at 16 km·hr^{-1}.

Technical limitations would seem to be the reason why they failed to undertake these additional, critical experiments:

> Greater speeds were not comfortable on our small track, and in any case much higher speeds cannot be maintained long enough to allow us sufficient foreperiod and collection interval. The form however of the oxygen uptake curve ... approaching a constant level of 4 litres/min, makes it obvious that no useful purpose would be served by investigating higher speeds in this way (35).

However, as they did not repeat these experiments at higher running speeds (33), they could not conclude that oxygen consumption was indeed maximal at 16 $km \cdot hr^{-1}$. Thus, their major conclusion that oxygen consumption reaches a plateau during exercise of progressively increasing intensity was not proven.

The data shown in Figure 2 confirm that during these experiments Hill did not reach a plateau in his rate of oxygen consumption with increasing running speed. The data show a linear relationship between Hill's mean rate of oxygen consumption and his running speed at three different speeds. There is no evidence that a plateau in oxygen consumption developed at the highest running speeds. Interestingly, the values for oxygen consumption measured in Hill are similar to those in the modern literature (40), indicating the remarkable accuracy of Hill and Lupton's measurements.

Additional data for Hill's oxygen consumption at different running speeds published in a subsequent paper (35) also fail to show a plateau in oxygen consumption with increasing running speed (Figure 3). These data do show a clear ventilation turnpoint, as first noted by Bainbridge (3) and Douglas et al. (23) and subsequently by Owles (49), who first described the lactate turnpoint.

In summary, the sole conclusion that can be drawn from Hill, Long, and Lupton's work is that they considered the maximum oxygen consumption to be that

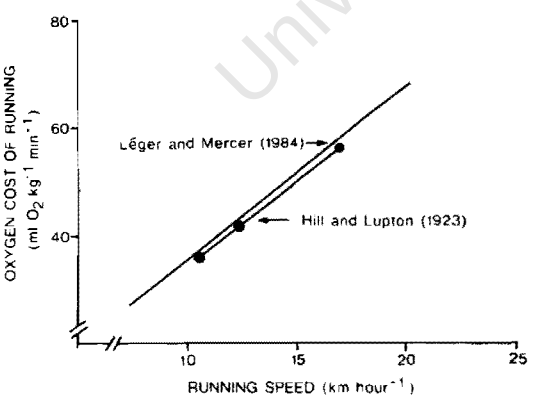

Figure 2—Average steady-state oxygen consumption of A. V. Hill at three different running speeds, from Hill and Lupton (33). Also shown is the linear regression equation for oxygen consumption and running speed from Leger and Mercer (40).

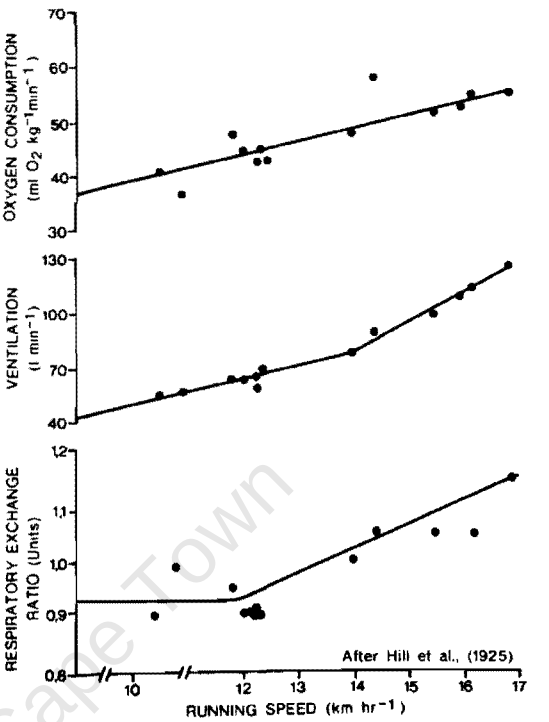

Figure 3—Oxygen consumption, ventilation, and respiratory exchange ratio for A. V. Hill when running at different speeds (note the clear ventilation turnpoint at 14,5 $km \cdot hr^{-1}$), from Hill and Lupton (33).

value of oxygen consumption measured 2 to 3 min after the athlete had started exercising at an intensity that he could maintain for about 10 min. They did *not* establish that the rate of oxygen consumption plateaus during exercise of increasing intensity. They were amongst the first to record the ventilation turnpoint or "respiratory anaerobic threshold," although they did not describe this phenomenon in detail.

Early research after Hill, Long, and Lupton. Wyndham et al. (67) were amongst the first to reinvestigate this phenomenon in detail. They began their article with the following statement:

> In a classic study of the physiology of exercise, Hill and Lupton noted a) that each individual has a maximum level of oxygen intake per minute, b) that the level varies from one individual to another and c) that the extra work done above the maximum level of O_2, intake is by means of "anaerobic" metabolism, i.e. the oxygen requirement comprises O_2 intake plus an "O_2 debt."

The evidence showing that Hill and Lupton did not establish any of these has been presented.

The study of Wyndham et al. (67) is important because it remains one of the few detailed studies that have attempted to determine whether a true plateau in oxygen consumption occurs during interrupted exercise

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of progressively increasing intensity. These workers measured the rate of oxygen consumption at a number of different workloads of increasing intensity in four subjects. They repeatedly determined the oxygen consumption at the highest workloads the subjects were able to sustain. As is shown in Figure 4, in none of the subjects was there a true plateau in oxygen consumption at the highest workloads; rather, the values showed an asymptote of varying degrees of steepness. In two subjects (B and C), the asymptote was less evident than it was in subjects A and D. Wyndham et al. (67, 68) proposed that the $\dot{V}O_{2max}$ value should be taken as the mean of three values falling on the asymptote, provided they did not differ by more than 0,15 $l \cdot min^{-1}$.

The interpretation of these findings is influenced by the different protocol used to measure oxygen consumption at low and high workloads. At the low workloads, expired air was sampled for 3 minutes starting after 3 and 10 min of exercise. However, at the highest workloads, a single sample of expired air was collected from 2 to 3 min. Thus, it is not impossible that the asymptote in oxygen consumption observed by Wyndham et al. (67) could be an artefact of the testing procedure.

For example, it is not established that the blood flow distribution and muscle fibre recruitment patterns are the same during maximal exercise lasting 3 min as they are during more prolonged exercise at low intensity. It is likely that, during maximal exercise of short duration, a majority of the high glycolytic fast-twitch muscle fibres with low oxidative capacity (Type IIB fibres) are recruited in addition to the slow-twitch oxidative and fast-twitch oxidative (Type IIA) fibres (63). Activation of the Type IIB fibres might occur during exercise of near maximal intensity without a further linear increase in oxygen utilization, not because an oxygen limitation is present but because maximum exercise activates oxygen-independent metabolism in these fast-twitch muscle fibres.

Changes in muscle and blood pH levels during maximal exercise could also influence oxygen transport at high workloads. Furthermore, the economy of movement might improve at high workloads, causing an apparent plateau in oxygen consumption. Thus, the asymptote in oxygen consumption found at high exercise workloads could be a result either of 1) an altered muscle fibre recruitment pattern at peak exercise, 2) pH-dependent changes in oxygen transport, or 3) improved economy of movement, rather than indicating a true state of oxygen limitation.

In their article, Wyndham et al. (67) also referred to the criteria for maximum oxygen consumption developed by other workers active at that time. They noted that Robinson and his colleagues (52, 53) at the Harvard Fatigue Laboratory avoided the issue of the oxygen plateau by defining the $\dot{V}O_{2max}$ as the highest value for oxygen consumption measured during exercise that was severe enough to exhaust the subject in less than 5 min. Their analysis of Astrand's (1) published figures was that these failed to show a plateau in oxygen consumption with increasing exercise intensity and that the oxygen consumption of his subjects was "in fact, still increasing" at the highest workloads. They also concluded that the definition of a plateau used by Taylor et al. (62) was not appropriate as those workers considered that the first value on the asymptote was the

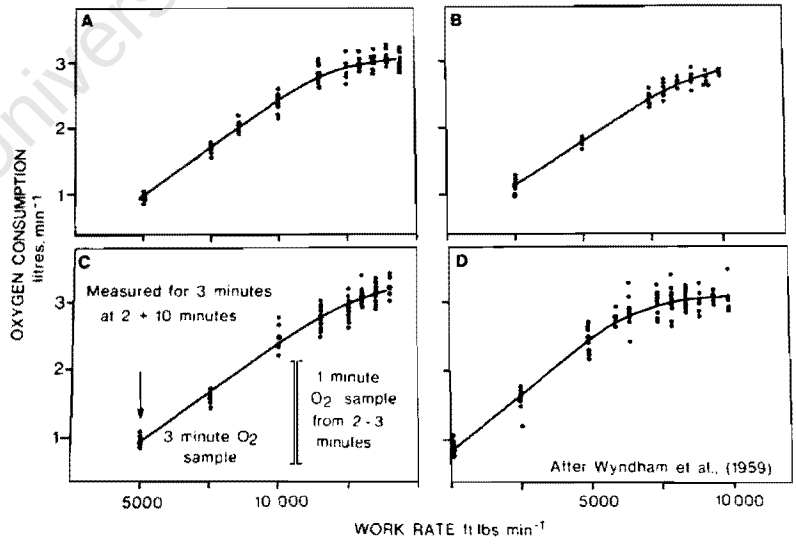

Figure 4—Oxygen consumption at different work rates in four subjects studied by Wyndham et al. (67). Note the absence of a clear plateau in oxygen consumption with increasing workload in subjects B and C.

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$\dot{V}O_{2max}$ and did not study higher workloads at which, as shown by the work of Wyndham et al. (67), oxygen consumption was still increasing.

Taylor et al. (62) also used the protocol subsequently adopted by Wyndham et al. (67) with all its potential limitations; in particular, they sampled expired air for 1 min starting after 1 min 45 s of exercise. It is certainly not established that a true steady state is reached after only 1 min 45 s of maximal exercise. Thus, the conclusion of Taylor et al. (62) that they were able to identify a plateau in oxygen consumption in 108 of 115 subjects during uphill treadmill running must, according to the argument of Wyndham et al. (67), also be treated with circumspection.

The final historic paper that deals with the oxygen plateau concept is that of Mitchell et al. (46). They too opened their article with a quotation from Hill (32): "Oxygen intake attains ... its maximum and remains constant ... owing to the limitation of the circulatory and respiratory system." They used essentially the same testing procedure as that adopted by Taylor et al. (62) except that they began measuring oxygen consumption even earlier (one and a half minutes) after the onset of exercise. In contrast to the findings of Taylor et al. (62), they did not show a plateau in oxygen consumption in 28% of subjects. Their published figure (Figure 1 in their article) also fails to show a plateau in oxygen consumption with increasing exercise intensity in the total group of subjects.

More recent studies. A number of modern researchers have commented on the frequency with which they have been able to identify a plateau in oxygen consumption during maximal exercise.

Cumming and Borysyk (17) showed that, whereas between 54 and 78% of 65 men aged 40–65 reached values of blood lactate (>8 mmol·l^{-1}), respiratory exchange ratio (>1.12), and heart rate (within 5 beats·min^{-1} of average for age) that were considered maximal or near maximal, only 43% showed the equivalent of a plateau phenomenon (an oxygen uptake at the maximum workload 10% below the expected for that work rate). They also noted that there was no correlation between these four criteria for maximum work, a finding which they could not explain: "To some extent, they are all indicators that the oxygen transport system is fully taxed and exercise is increasingly being carried out anaerobically." They concluded: "The plateau is theoretically exact, in practice it is much less so."

Cumming and Friesen (16) and Cunningham et al. (18) reported a plateau in less than 50% of young boys, similar to the finding of Astrand (1). Sidney and Shephard (58) demonstrated a plateau in approximately 75% of elderly subjects. On the basis of these studies, Shephard (57) has concluded that it is difficult to determine an oxygen plateau in children and in older persons. Despite this, Shephard begins the same article with the statement: "During treadmill exercise, maximum effort is halted by central circulatory failure." These two opposing statements can only be reconciled if one assumes that the failure to demonstrate the $\dot{V}O_{2max}$ plateau phenomenon indicates that the tested subject was not sufficiently motivated to exercise to the intensity at which a central limitation to exercise performance would become apparent.

However, this conclusion would be valid only if the alternative possibility that maximal exercise might be limited by factors other than the central circulation were shown not to be true. In a similar vein, it should be noted that the results of blood doping studies, which are frequently cited as proof that maximum exercise performance is limited by tissue oxygen deficiency, cannot be interpreted unless there is good evidence that maximal exercise performance in the pre-doping test was limited by the failure of the central circulation to maintain adequate tissue oxygenation. In the most frequently cited of such studies (5, 60), no attempt was made to determine this; in fact, there is no evidence that the subjects in that study reached a plateau in oxygen consumption during any of the maximal exercise tests. Thus, in retrospect, the authors may have been guilty of a circular argument similar to that of Hill and Lupton.

Furthermore, whereas the increase in $\dot{V}O_{2max}$ induced by blood doping lasted 16 wk in the study of Buick et al. (5), enhanced running performance was present for only 1 wk, indicating a dissociation between changes in maximal running performance and in tissue oxygen delivery.

The interpretation of this research method and of those studies in which the effects of hyperoxia (64) or induced anemia (6) on exercise performance and $\dot{V}O_{2max}$ have been reported is further complicated by the finding that all of these procedures also alter either acid-base balance (64) or whole-body lactate kinetics as shown by reduced blood lactate levels during submaximal (60) or maximal (60) exercise, including a shift in the lactate turnpoint (6). Indeed, Welch (64) has concluded that the ergogenic effect of hyperoxia is not likely due to improved oxygen delivery to muscle but is more likely a result of altered acid-base and respiratory responses to exercise. It remains the onus of those undertaking future studies of blood doping to prove that the same does not apply to their work.

Finally it should be noted that, in all the studies in which the appropriate parameters have been measured, it has been found that the increase in tissue oxygen delivery following induced erythrocythemia exceeds the measured increase in tissue oxygen utilization (60). A possible explanation for this which was not considered by these authors (60) is that oxygen supply to muscle

was not limiting either before or after induced erythrocythemia. Thus, the active muscles had no use for the surplus oxygen provided after blood doping.

The final study relevant to the plateau phenomenon is that of Freedson et al. (27). They found that less than 40% of 301 adults undergoing maximal exercise testing showed a plateau in oxygen consumption according to the criteria of Mitchell et al. (46) and Taylor et al. (62).

In summary, the evidence presented to date does not prove conclusively that oxygen uptake reaches a plateau during maximum exercise in all subjects. Furthermore, a plateau value does not by itself indicate that a limitation in oxygen delivery or utilization is present at maximal exercise but could result from the other factors detailed previously. Thus, it has not been disproved that, when present, the plateau phenomenon might be an artefact of the testing protocol. It would seem that the minimal criteria for identifying a true plateau phenomenon would be a failure of oxygen consumption to rise during exercise of progressively increasing intensity lasting at least 5 min or during interrupted testing in which the maximum workloads are sustained for at least 3 to 5 min.

Finally, it is the author's contention that, unless studies of induced erythrocythemia establish either that oxygen limitation was present during maximal exercise in the pre-doping condition or that the principal effects of this procedure are not to alter either skeletal muscle "contractility," lactate kinetics, acid-base balance, or the ventilatory response to exercise, they cannot be interpreted. At present it is not clear that the presence of an oxygen limitation in skeletal muscle can be inferred from the respiratory gas exchange data. It would seem that, even when the plateau phenomenon has been identified in any subject, biochemical evidence of tissue hypoxia will also need to be gathered to prove that an oxygen limitation is present.

IMPORTANCE OF THERE BEING OR NOT BEING A PLATEAU IN OXYGEN CONSUMPTION DURING EXERCISE OF INCREASING INTENSITY

A conclusion that has naturally been drawn from the conventional interpretation that a hypoxia-induced failure of mitochondrial ATP production explains exhaustion during maximal exercise (Figure 5) is that the improved exercise tolerance that develops with training or other interventions must be a result solely of adaptations that enhance whole-body oxygen utilization capacity. Thus, improvements in $\dot{V}O_{2max}$ that result from physical training or other interventions have been explained on the basis either of central adaptations enhancing oxygen delivery to the tissues or of peripheral adaptations including increased muscle capillarization and an increased mitochondrial oxidative capacity (29, 36).

Yet this explanation clearly ignores the possibilities that 1) tissue oxygen deficiency may not have been the factor limiting maximal exercise in the untrained state and 2) even if tissue oxygen deficiency had been present, it might have limited performance during maximal exercise by acting on factors other than the rate of mitochondrial ATP production. Indirect evidence for this latter possibility is the finding that 1) maximal exercise at extreme altitude does not appear to be limited by high blood lactate levels or by indications of central limitations in cardiac or respiratory function (61, 66), 2) exhaustion during maximal exercise occurs at a *lower* oxygen consumption during cycling than during running in the same subjects (24), and 3) blood lactate levels at exhaustion during progressive treadmill exercise testing are lowest in the very best athletes (Noakes et al., unpublished data).

The alternative possibility is that maximal exercise performance is determined by other factors, for example the development of progressive dyspnea (see below) or skeletal muscle factors, in particular those controlling the rate and force of myofibrillar cross-bridge cycle activity (Figure 6), and which include myofibrillar ATPase activity and the amount of calcium bound by troponin-C during contraction. It is possible that a failure of either intracellular calcium transport or an alteration in myosin ATPase activity or both might occur during maximal exercise either on the basis of pH-dependent changes in the active muscles or because of a fall in tissue PO_2 that is insufficient to influence mitochondrial oxidative metabolism.

It is clear that we need to consider that any increase in exercise capacity that results either from training or from other interventions may act *primarily* by altering muscle cross-bridge activity rather than by increasing mitochondrial oxidative capacity or by altering the respiratory response to exercise, thereby delaying the onset of progressive dyspnea. There will always be an increase in maximum oxygen consumption with any increase in maximum work capacity, provided the efficiency of movement does not change (Figure 11—see below). However, this increase in oxygen consumption

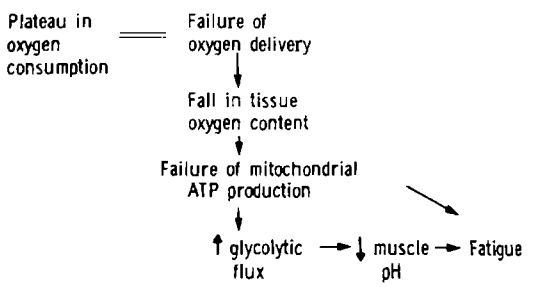

Figure 5—The traditional interpretation of how a plateau in oxygen consumption during maximal exercise leads to fatigue.

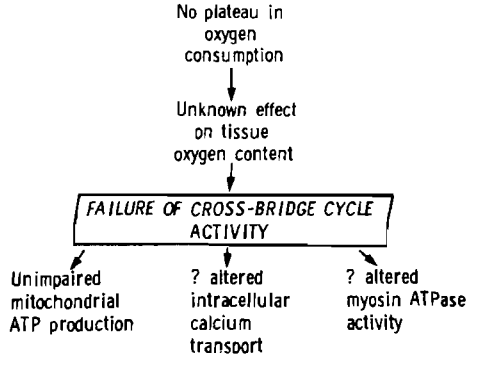

Figure 6—Proposed mechanism for the failure of muscle cross-bridge cycle activity during maximal exercise.

may be the result, not the cause, of changes in either muscle cross-bridge activity or the ventilatory response to exercise.

HOW ARE $\dot{V}O_{2max}$ TEST RESULTS INTERPRETED IN THE ABSENCE OF THE PLATEAU PHENOMENON?

If one accepts uncritically that each $\dot{V}O_{2max}$ test is always limited by tissue oxygen deficiency, then inappropriate conclusions may be drawn in those tests in which no plateau in oxygen consumption develops, as might have occurred in some of the blood doping studies.

An example of this potential error is shown in our own studies of renal transplant patients (Kempeneers et al., unpublished data). These patients have usually been physically inactive for prolonged periods and have been treated with corticosteroid agents; both of these factors are likely to induce muscle weakness.

We found that training produced significant increases in both the $\dot{V}O_{2max}$ and in the maximum run time to exhaustion of these subjects. However, in the initial maximal exercise test, the subjects showed evidence for a peripheral, not central, limitation to their exercise tolerance as their values for "maximal" heart rate, maximal ventilation and respiratory quotient and peak blood lactate levels were low. In addition, none showed evidence for a plateau in oxygen consumption with increasing exercise workload.

During retesting after training, the subjects exercised for longer and reached higher values for maximum heart rate, ventilation, respiratory quotient, and blood lactate levels without a change in the lactate turnpoint, principally because they were more powerful and were therefore able to exercise to higher workloads. Thus, the increase in $\dot{V}O_{2max}$ that developed in these subjects with training resulted from peripheral changes in muscle power and were not likely due to central cardiovascular changes increasing oxygen delivery to the active muscles. This example shows that care must be exercised in the interpretation of $\dot{V}O_{2max}$ test results in persons who initially have muscle weakness which is likely to alter with training.

Similar care must be taken in the interpretation of $\dot{V}O_{2max}$ test results in athletes undergoing either pure sprint training or detraining. For example, the anomalous finding that strength training in humans (65) and sprint training in rats (22) increases $\dot{V}O_{2max}$ without increasing muscle oxidative capacity (13, 22, 36) can be explained on the basis of training-induced increases in muscle power analogous to those found in our renal transplant patients. Thus, during exercise testing after training, the sprint- and strength-trained athletes achieve higher maximum workloads and therefore higher $\dot{V}O_{2max}$ values due to peripheral, not central, adaptations.

The training study of Daniels et al. (20) and other studies of detraining provide additional indirect support for the belief that factors other than mitochondrial oxidative capacity explain changes in exercise capacity. Thus, Daniels et al. (20). showed that changes in running performance with training occurred without equivalent changes in $\dot{V}O_{2max}$. They concluded that "physiological adaptations not integrated in the test of $\dot{V}O_{2max}$ ... contribute to training-induced improvements in running performance."

Similarly, the work of Costill et al. (14, 15) demonstrates a clear dissociation of exercise performance, muscle power, and muscle oxidative capacity with detraining in swimmers. This is depicted in Figure 7 which shows that the swimmers' performances improved with a week of detraining, whereas muscle oxidative capacity fell by up to 50% during the same period.

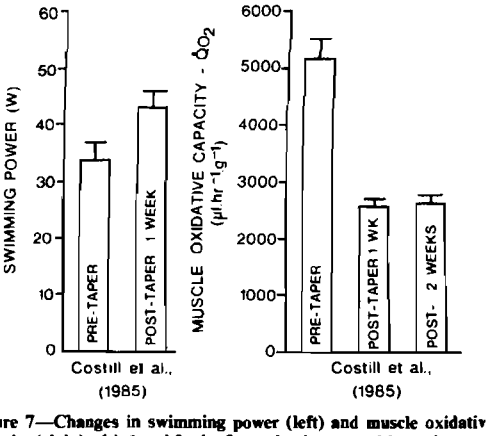

Figure 7—Changes in swimming power (left) and muscle oxidativ capacity (right) with 1 and 2 wk of tapering in competitive swimmers. Data are from Costill et al. (14, 15). Note divergent effects o swimming power aud on muscle oxidative capacity with tapering.

This is a particularly important study as it shows that performance under these experimental conditions was linked to muscle power, not to muscle oxidative capacity, and that an increase in performance can occur despite a fall in muscle oxidative capacity. Therefore, the effects of training and detraining on exercise performance cannot always be predicted solely on the basis of changes in muscle oxidative capacity.

$\dot{V}O_{2max}$ AS A PREDICTOR OF ATHLETIC POTENTIAL

The very earliest studies established that the $\dot{V}O_{2max}$ expressed relative to body weight was highest in the best runners (1, 31, 53). Thus, credence was given to the belief that the $\dot{V}O_{2max}$ would always be a good predictor of athletic potential (10, 12, 21, 25, 39, 69).

However, a more critical interpretation shows that, whereas the $\dot{V}O_{2max}$ is a good predictor of athletic performance when a heterogenous group of athletes with quite different athletic abilities is studied, it is a relatively poor predictor when athletes of similar ability are evaluated (7, 11, 47, 50). The key to the interpretation of this finding was provided first by Costill and Winrow (11) and later by Daniels (19).

Costill and Winrow (11) showed that, when two athletes with the same $\dot{V}O_{2max}$ values but with different running abilities were compared, the running economy of the faster runner was superior (Figure 8). Although not reported by these authors, the faster and more economical runner must also have achieved a higher maximum workload at $\dot{V}O_{2max}$, as predicted by their data and reproduced in Figure 8. Thus, the faster runner was characterized by being both more "economical" and more "powerful."

Daniels (19) reported the converse finding of two runners with quite different $\dot{V}O_{2max}$ values but with the same running ability. The feature of similarity shared by these runners was that they reached the same peak treadmill running speed during maximal exercise. Their different $\dot{V}O_{2max}$ values at the same peak running speed resulted from their marked differences in running economy as shown in Figure 9.

Taken together, these studies indicate that, for the prediction of athletic performance, the $\dot{V}O_{2max}$ cannot be interpreted without reference to the economy of movement of the different athletes. Furthermore, they suggest that the factor predicting athletic performance is neither the absolute $\dot{V}O_{2max}$ value nor the running economy but may be related to a factor of muscle "power" measured as the peak workload reached during the maximum treadmill running (54; Noakes et al., unpublished data) or swimming (30) test or isokinetic muscle power measured in swimmers (55). The failure of the majority of (21, 38, 59), but not all (7), studies to show a significant relationship between running economy and athletic performance indicates that running economy cannot be the principal factor predicting athletic performance.

Data from some of our own studies support these findings. Figure 10 (top) shows the oxygen cost of running, the $\dot{V}O_{2max}$, and the peak treadmill running speed achieved by three runners with best standard marathon times falling in a narrow range of 2 h 30 min to 2 h 35 min. It is clear that the only variable that is similar in these runners is the peak treadmill running speed. In common with the finding of Daniels (19—Figure 9), the $\dot{V}O_{2max}$ and running economy of these athletes are quite different.

Figure 10 (bottom) shows the same variables for runners with similar $\dot{V}O_{2max}$ values of 65–71 $ml \cdot kg^{-1} \cdot min^{-1}$ but whose best 42,2-km standard marathon performances range from 3 h 12 min to 2 h 8 min. In this group, the most dissimilar variable is the peak treadmill running speed. It should be noted that, at a running

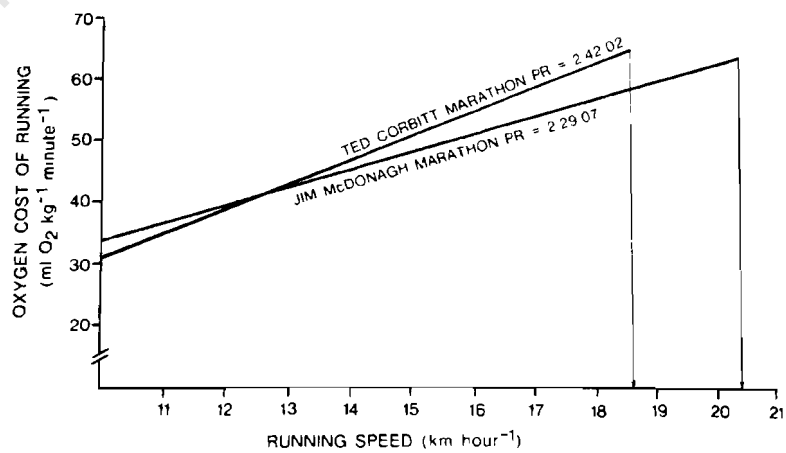

Figure 8—Relationship of oxygen cost and running speed for two athletes with similar $\dot{V}O_{2max}$ values but with different best standard 42, 2 km standard marathon times and different running economies, from Costill and Winrow (11). Note that peak treadmill running speed also differs between the two athletes.

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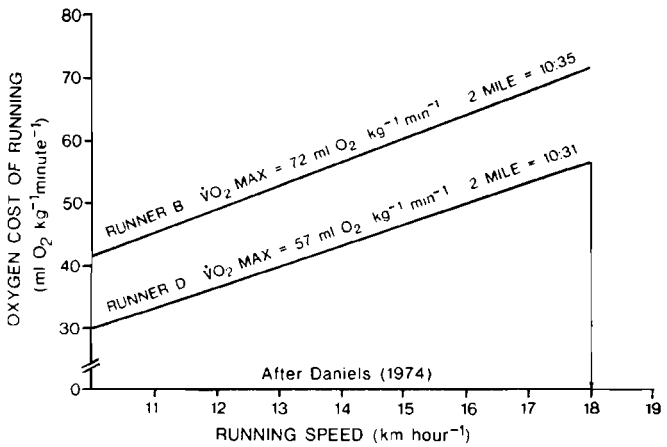

Figure 9—Relationship of oxygen cost and running speed for two athletes with different $\dot{V}O_{2max}$ values and different running economy but with similar running performances and peak treadmill running speeds, from Daniels (19).

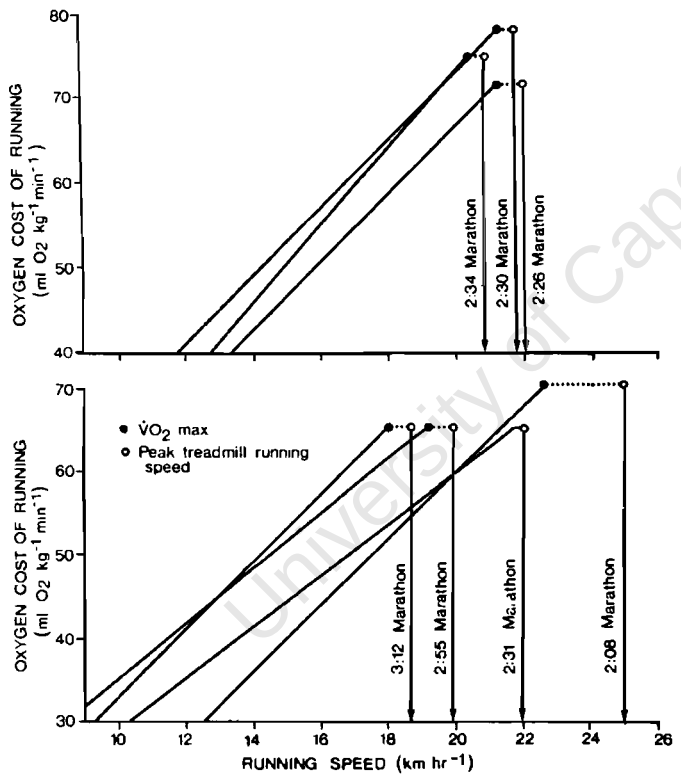

Figure 10—*Top:* Relationship of oxygen cost and running speed for three runners with similar best 42,2 km standard marathon running times but with different $\dot{V}O_{2max}$ values. Note that the regression line for oxygen consumption and running speed is based on steady-state exercise at speeds up to 21 km·hr^{-1} (54), whereas the peak treadmill running speed was measured during a progressive incremental exercise test (54). The apparent plateau in oxygen consumption at peak running speeds shown in this figure is an artefact of depicting data collected under two different experimental conditions on one graph. *Bottom:* Relationship of oxygen cost and running speed for four runners with similar $\dot{V}O_{2max}$ values but with different best 42,2 km marathon times. Note that peak treadmill running speed, not $\dot{V}O_{2max}$ or running economy, best predicts 42,2 km marathon time in these athletes.

speed of 17,7 km·hr^{-1}, running economy predicts running performance as the best runners in this group are also the most economical. It is clear from Figure 10, however, that neither running economy nor $\dot{V}O_{2max}$ is the principal factor predicting athletic performance. Our studies from which these data come confirm this and show that peak treadmill running velocity ($r = -0,90$) and the running velocity at the lactate turnpoint ($r = -0,88$) are the best predictors of running performance, whereas running economy ($r = 0,20$) and $\dot{V}O_{2max}$ ($r = -0,76$) are less good predictors (Noakes et al., unpublished data).

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Training can influence both running economy and the maximum achieved workload; thus, it may have a variable effect on $\dot{V}O_{2max}$. If the effect on running economy is greater than the effect on peak achieved workload, then $\dot{V}O_{2max}$ can actually *fall* with training. Such an effect has been most clearly shown in training studies of rats undertaken in our laboratory (Lambert et al., unpublished data). These studies show that initially $\dot{V}O_{2max}$ fell slightly with training whereas peak achieved workload and running economy improved markedly (Figure 11). Usually, however, the increase in peak achieved workload exceeds the increase in running economy; thus, $\dot{V}O_{2max}$ rises with training.

Nevertheless, these studies show that it is not possible to interpret changes in $\dot{V}O_{2max}$ with training and detraining if the changes in running economy and peak achieved workload are not also reported. Unfortunately, few researchers report all these variables in their studies.

In summary, it is suggested that the primary variable predicting athletic potential, at least in running, is the maximum speed or workload that the athlete can achieve during the maximum test. The actual value for the oxygen consumption measured at that peak workload will be dependent on each athlete's running economy. What determines the maximum speed or workload achieved during the maximal test is presently unclear but may relate either to the skeletal muscle or to respiratory factors detailed earlier. In our own preliminary findings we have found that the fastest 10-km runners have the most powerful muscles when measured on the isokinetic cycle ergometer (Stevenson et al., unpublished observations). Jones and McCartney (37) have also found a relationship between $\dot{V}O_{2max}$ and total work output during maximal isokinetic exercise of 30 s duration. Together these findings suggest that skeletal muscle contractility differs between fast and slow runners and between runners with high and low $\dot{V}O_{2max}$ values.

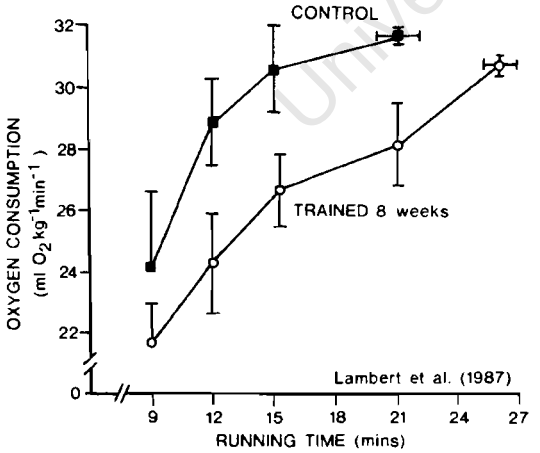

Figure 11—$\dot{V}O_{2max}$, oxygen cost of running and run time to exhaustion during a progressive incremental exercise test in control rats and in rat trained for 8 wk. Note that running economy and run time to exhaustion, but not $\dot{V}O_{2max}$, are altered by training—unpublished data of Lambert et al.

OTHER PREDICTORS OF ATHLETIC POTENTIAL

The case has been made that the peak achieved workload is a better predictor of running performance than is either the $\dot{V}O_{2max}$ or the running economy. It is clear, however, that both the lactate turnpoint and the respiratory ventilation threshold ("anaerobic threshold") are additional variables that accurately predict athletic performance, especially in running races of 10–42 km (38, 59). However, what is less apparent is why these variables should predict performance at race distances from 5–42 km. What are the physiological cues that athletes monitor during races of those distances, and which are related to their blood lactate levels?

A likely explanation has been provided by Reybrouck

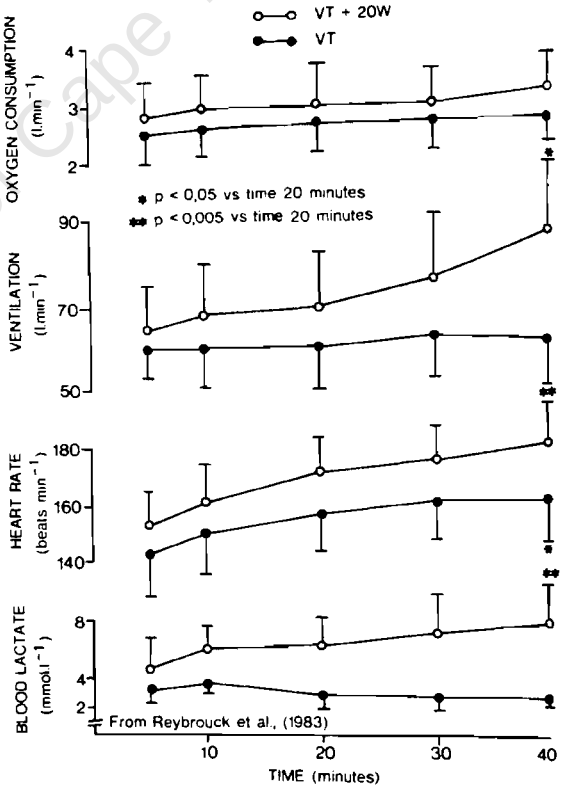

Figure 12—Changes in oxygen consumption, in ventilation, in heart rate, and in blood lactate levels during 40 min of exercise at the ventilation threshold for prolonged work (VT) and at a higher workload (VT + 20W), from data of Reybrouck et al. (51). Note the terminal increase in ventilation, in heart rate, and in blood lactate levels at the higher workload.

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et al. (51), who have identified two ventilation turnpoints for exercise. The first corresponds with the respiratory ventilation threshold ("anaerobic threshold") and the lactate turnpoint and is identified during progressive exercise to exhaustion; the second is identified as the ventilation rate, oxygen uptake, or workload that can be maintained for 20–40 min without there being a progressive increase in ventilation. Prolonged exercise undertaken at workloads beyond that threshold causes a progressive increase in ventilation, heart rate, oxygen consumption, and blood lactate levels (Figure 12).

Clearly, the second ventilation threshold (ventilation threshold for prolonged exercise) identifies a non-steady-state condition corresponding to blood lactate levels of approximately 4 $mmol \cdot l^{-1}$, a finding that might also explain the predictive value of the 4 $mmol \cdot l^{-1}$ blood lactate level proposed by Heck et al. (30). It is clear that prolonged exercise at intensities above the second ventilation threshold may ultimately be limited by progressive dyspnea. Possibly the predictive value of blood lactate levels during exercise can be explained on the basis of related changes in ventilation.

CONCLUSIONS

The belief that oxygen delivery alone limits maximal exercise performance has straightjacketed exercise physiology for the past 30 yr. Thus, performance, particularly during maximal but also during submaximal exercise, has been explained exclusively in terms of oxygen transport and oxygen and fuel utilization, and other factors determining muscle contractile function have largely been ignored. An important detrimental effect has been that the teaching of muscle contractile function has been largely ignored in texts of exercise physiology, which have concentrated exclusively on cardiovascular and respiratory limits to exercise performance. However, it is clear that, in the future, greater attention will need to be paid to other factors determining muscle contractility, in particular to intracellular calcium transport and myofibrillar ATPase activity.

Future exercise physiologists need to consider the following: 1) that they research more critically those factors which explain why muscle contractility "fails" at high exercise intensities, 2) that they examine the possibility that differences in muscle contractility might explain differences in athletic potential (15, 30, 37, 54), and 3) that they do not ignore the possibility that an important component of training, detraining, and other interventions may be directly to alter muscle contractility.

Brett Adams, Gerrit Kempeneers, Vicki and Mike Lambert, Kathryn Myburgh, Angus Scrimgeour, Kevin Stevenson, and Linday Weight are thanked for collaborative work on which aspects of this review are based. The constructive comments and helpful suggestions of two anonymous reviewers are most gratefully acknowledged.

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1996 J. B. WOLFFE MEMORIAL LECTURE

Challenging beliefs: *ex Africa semper aliquid novi*

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ABSTRACT

NOAKES, T. D. Challenging beliefs: *ex Africa semper aliquid novi. Med. Sci Sports Exerc.*, Vol. 29, No. 5, pp. 571–590, 1997. The basis of the scientific method is the development of intellectual models, the predictions of which are then subjected to scientific evaluation. The more robust test of any such model is one that aims to refute or falsify its predictions. Successful refutation forces revision of the model; the revised model persists as the "truth" until its predictions are, in turn, refuted. Thus, any scientific model should persist only as long as it resists refutation. An unusual feature of the exercise sciences is that certain core beliefs are based on an historical physiological model that, it will be argued, has somehow escaped modern, disinterested intellectual scrutiny. This particular model holds that the cardiovascular system has a limited capacity to supply oxygen to the active muscles, especially during maximal exercise. As a result, skeletal muscle oxygen demand outstrips supply causing the development of skeletal muscle hypoxia or even anaerobiosis during vigorous exercise. This hypoxia stimulates the onset of lactate production at the "anaerobic," "lactate," or ventilation thresholds and initiates biochemical processes that terminate maximal exercise. The model further predicts that the important effect of training is to increase oxygen delivery to and oxygen utilization by the active muscles during exercise. Thus, adaptations that reduce skeletal muscle anaerobiosis during exercise explain all the physiological, biochemical, and functional changes that develop with training. The historical basis for this model is the original research of Nobel Laureate A. V. Hill which was interpreted as evidence that oxygen consumption "plateaus" during progressive exercise to exhaustion, indicating the development of skeletal muscle anaerobiosis. This review confirms that Hill's research failed to establish the existence of the "plateau phenomenon" during exercise and argues that this core component of the historical model remains unproven. Furthermore, definitive evidence that skeletal muscle anaerobiosis develops during submaximal exercise at the anaerobic threshold initiating lactate production by muscle and its accumulation in blood is not currently available. The finding that exercise performance can improve and metabolism alter before there are measurable skeletal muscle mitochondrial adaptations could indicate that variables unrelated to oxygen use by muscle might explain some, if not all, training-induced changes. To accommodate these uncertainties, an alternate physiological model is proposed in which skeletal muscle contractile activity is regulated by a series of central, predominantly neural, and peripheral, predominantly chemical, regulators that act to prevent the development of organ damage or even death during exercise in both health and disease and under demanding environmental conditions. During maximal exercise, the peripheral regulation of skeletal muscle function and hence of oxygen use by skeletal muscle, perhaps by variables related to blood flow, would prevent the development of muscle rigor, especially in persons with an impaired capacity to produce ATP by mitochondrial or glycolytic pathways. Regulation of skeletal muscle contractile function by central mechanisms would prevent the development of hypotension and myocardial ischemia during exercise in persons with heart failure, of hyperthermia during exercise in the heat, and of cerebral hypoxia during exercise at extreme altitude. The challenge for future generations of exercise physiologists is to identify how the body anticipates the possibility of organ damage and evokes the appropriate control mechanism(s) at the appropriate instant.

$\dot{V}O_{2max}$, ANAEROBIOSIS, ANAEROBIC THRESHOLD, LACTATE, MITOCHONDRIA, CARBOHYDRATE, SCIENTIFIC METHODS, POPPER

The invitation to present the J. B. Wolffe Memorial Lecture is one of the greatest honors to which an exercise scientist can aspire. I am very mindful of the unique nature and real significance of this lecture. I am also acutely aware that among those who have presented this lecture are the intellectual giants of our discipline—the gods who have inspired me and many others to greater effort. Not once in my most extravagant dreams did I ever expect to share this moment with such illustrious names, and I am humbled by that association.

But with this great honor comes an important responsibility: to fashion a message that will be relevant to the diverse interests of all members of the College. How can one possibly say anything that will be an inspiration to such a broad community of scientists?

My colleague, Dr. Randy Eichner, has called me a "gentle iconoclast." The less-guarded assessment of a fellow scientist from the Antipodes, is that "loose cannon" might be a more appropriate epitaph. In keeping with those labels, I wish to review some contentious beliefs in exercise physiology to illustrate my understanding of the nature of scientific inquiry. Although the focus will be on exercise physiology, I hope there will be

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a broader message for all exercise scientists, regardless of their specialization.

WHY ME?

When invited to deliver this lecture, my immediate response was to wonder why I had been so honored. My conclusion is that my selection resulted from the pivotal influences of (i) having been born and trained in Africa; (ii) the impact of North America on my life and its scientists on my career; (iii) the nature of my training in medicine; and (iv) perhaps somewhat surprisingly, by my lack of formal training in the exercise sciences, especially in biochemistry and research methodology.

THE INFLUENCE OF AFRICA

Two facts about the continent of my birth, Africa, are not widely appreciated. The first is that one of the oldest known medical texts, the Papyrus Ebers dated 1550 BC (40, p. 21), comes from Egypt. Indeed, the first correct description of the pulmonary circulation may have been made by the Egyptian physician, Ibn Al-Nafis (55, p. 264), four centuries before William Harvey provided what is usually accepted as the definitive initial description of the systemic and pulmonary circulations.

The second fact is that the ancestral humanoids probably evolved on the plains of South and East Africa and not in the far East as originally supposed.

The initial discovery underpinning the African origin of Man was made by Professor Raymond Dart (26,27), formerly Dean of the Medical School of the University of the Witwatersrand in Johannesburg. The lesson of his discovery is twofold. First, Dart drew his conviction from a single observation that the foramen magnum of the skull unearthed in Taung, Botswana, and later named by him, Australopithecus Africanus (Southern Ape), was situated directly over the vertebral column. Dart concluded that this could only occur if Australopithecus walked upright. Second, Dart's postulate that Australopithecus was an early hominid was initially ridiculed, perhaps because of twin prejudices that little of value comes from Africa and that humans must have evolved in some more exotic location, probably in the East, perhaps in Java. However, Dart persisted in his certitude, and additional findings in both South and East Africa confirmed his faith in what has been acknowledged as one of the 20 most significant discoveries of the 20th century. Professor Dart epitomized the scientist's need to follow his or her intuition even if based on a single, but conclusive, observation. Dart was also one of the first African scientists to show that our continent does perhaps have something to offer the international scientific community.

Perhaps either of these could justify Pliny's statement to the effect that there is always something new from Africa. But for the purpose of this paper, the title expresses the pride that I and my fellow scientists in the developing world have for our respective nations and their scientific and other achievements.

Another unusual benefit of living in South Africa for the past four decades has been the opportunity to participate in an extraordinary social and political change. My fortune was to have been prepared, at least in part, by a short period of study in the United States at the time of that nation's own greatest recent social upheaval.

THE EARLY AND CONTINUING INFLUENCE OF THE UNITED STATES OF AMERICA

My first direct contact with the United States occurred as a high school exchange student studying at Huntington Park High School in Los Angeles for the 1967/68 academic year. For one who had studied at a racially segregated school fashioned on the privileged British public school model, the abrupt exposure to the more open and egalitarian society that I encountered in Los Angeles had a profound and lasting effect. It introduced me to the idea that two nations could operate at polar ends of the social structure. Perhaps that experience made me wonder what exactly is the "truth."

Later described as the year which "shaped a generation" and which "like a knife blade, ... severed past from future" (75), 1968 taught me about the rapidity with which change can occur—a feature that is perhaps less surprising to citizens of the United States than to a young South African, at least in the 1960's. It was also during that period that the event occurred that would have the single greatest influence on my future career; an event to which the United States made a crucial contribution.

THE INFLUENCE OF THE WORLD'S FIRST SUCCESSFUL HUMAN HEART TRANSPLANT

On Sunday, December 3, 1967, the world's first successful human heart transplant was performed at what would become my alma mater, Groote Schuur Hospital, in Cape Town by a South African team led by Professor Christiaan Barnard (5). I shared the wonderment of my host nation that such an historic achievement had occurred outside the United States. In fact, this event, which stimulated my decision to follow a medical career, was possible only because of the brilliant tutelage that Barnard received at the University of Minneapolis under cardiac surgeon and scientist, Professor Owen Wangenstein (7). Wangenstein arranged that when he returned to South Africa after completing his training, Barnard was accompanied by a special gift from President Lyndon Johnson and the United States government—the first heart-lung machine ever brought to the African continent (22). Without the generosity of that gift from the United

States, perhaps I would not have followed my career in the exercise sciences.

Two features were crucial for Barnard's success. First, he required inordinate courage for he knew that two consecutive failed cardiac transplantations would terminate his surgical career. In fact, the early results of Barnard's team were the best of any group then performing that operation (6).

Barnard's courage is a feature of his Afrikaner (Dutch) heritage and was strengthened by a capacity to think differently, an attitude epitomized by his statement that: "Most of us think along straight lines, like a bus or a train or a tram. If the destination isn't up on the board, few of us would know where we are going—and that applies even to scientific researchers who should know better. We tend to let tradition lead us by the nose. It takes an effort of will to break out of the mold" (22, p. 65).

So my choice of career was strongly influenced, albeit indirectly, by the rich and outward-looking academic culture that is perhaps the finest of the many astonishing achievements of the United Stated of America and one of its great gifts to the international scientific community. That intellectual inspiration has only increased with time, not least through my more than twenty-year membership of the American College of Sports Medicine and through contact with the exceptional scientists who ensure the continued excellence of our discipline.

THE INFLUENCE OF MY MEDICAL TRAINING

As a result of the influence of Professor Barnard's achievement, I entered medical school at the University of Cape Town in early 1969. During my medical training I acquired other insights that I now consider valuable. The first is the need to understand the whole body. In medicine this insight is imperative because disease, like health, invades all the body's organs. Similarly, no medical or biological problem exists in an isolated section of the body. There are advantages, even for exercise scientists, to appreciate the broader picture and to avoid intemperate specialization in a small region or tissue of the body.

The second lesson that one immediately learns when first exposed to patients is one's high level of personal stupidity. Indeed, there is a collective level of medical ignorance, so brilliantly described by Dr. Lewis Thomas (108, p. 10): "The greatest single achievement of science in this most scientifically productive of centuries is the discovery that we are profoundly ignorant. . . I wish there were some formal courses in medical school on medical ignorance; textbooks as well, although they would have to be very heavy volumes. We have a long way to go." Indeed, the beauty of the textbooks of ignorance would be their accuracy. I am reminded of these quotations whenever a scientist expresses the ignorance of absolute certainty. Regardless of any appearance of individual brilliance, we are each profoundly ignorant. And never more so than when we are absolutely certain of our conviction.

A third lesson is the crucial importance of challenging the truth. The single characteristic that distinguishes medicine from other "alternative" practices is the controlled clinical trial in which the merit of a particular medical intervention is compared either with doing nothing or with the established practice(s). The results of such trials cause medical "truths" to be recycled very rapidly. Indeed, medical "truths" change with the weekly appearance of the *New England Journal of Medicine* and many other influential medical publications. Thus, the emphasis of medical research is specifically to disprove and thereby to improve current practice. It is this ethos which distinguishes medicine from those professions that are based on fixed beliefs that are hallowed, changeless, and beyond question. My Professor of Medical Biochemistry, Wieland Gevers, encouraged the heresy that the active skeletal muscles may not become "anaerobic" during exercise and that separate biochemical processes explain the production of lactate and protons by the active muscles during exercise (38).

This distinctive characteristic of medicine to challenge the truth (88) explains the intellectual paradox captured in the quotation attributed to a former Dean of Harvard, Dr. Sydney Burwell by G. W. Pickering (92), himself formerly Professor of Medicine at the University of London: "My students are dismayed when I say to them, 'Half of what you are taught as medical students will in 10 years have been shown to be wrong. And the trouble is, none of your teachers know which half.'"

WHAT MY MEDICAL TRAINING FAILED TO TEACH ME

Like most medical doctors who have experienced a traditional clinical training, I have very real gaps in my understanding of the tools of science, including statistics and research methodology. My undergraduate training also occurred before the modern explosion of knowledge in both biochemistry and the exercise sciences. As a result, much of my knowledge is self acquired; my tutors have been the writers of what I consider to be some of the classic texts in my field of interest (3,17,23,80,98).

Learning in this way has important disadvantages, but one unique advantage is the avoidance of indoctrination, which is the tendency towards a stubborn, if subconscious, acceptance of a specific scientific mindset or prejudice that we may acquire from our venerated tutors whom we may assume to be intellectually infallible (62). For a crucial outcome of our scientific training is that it conditions us to accept only a limited sample of all the possible truths.

Ignorance can be a formidable attribute if it provides the freedom to consider any intellectual possibility. For it

is such ignorance that can encourage the development of novel scientific insights.

WHAT SCIENCE HAS TAUGHT ME

The concept of refutability and the burden of disproof. In his influential text, Viennese philosopher Sir Karl Popper (93), posed the fundamental question: What identifies empirical science and therefore distinguishes it from pseudoscience? He concluded that: "A statement (a theory, a conjecture) has the status of belonging to the empirical sciences if and only if it is falsifiable" (93). According to this criterion, a statement or theory is falsifiable, that is, able to be refuted, if and only if there exists at least one potential falsifier—at least one basic statement that conflicts with it logically. He continues that the falsifier does not itself have to be known to be true, only that it logically refutes the conjecture.

In Popper's view, an important aim of science is therefore to generate theories that are able to be refuted (falsified). Successful refutation (falsification) of successive conjectures leads to new and occasionally revolutionary theories, each of which is likely to be somewhat closer to the truth than its predecessors. Victor Katch (59) was one of the first to bring this to the attention of modern exercise scientists.

Popper also concludes that we will never know whether a specific conjecture is the final truth because our scientific methods and our logic are too imprecise ever to be certain that we have subjected a particular theory to every possible test of falsification. Thus, a theory that has yet to be refuted is the nearest we ever approach the truth. In this analysis, even Einstein's theory of relativity is simply a conjecture which has, for the most part, escaped refutation (116). Einstein understood this for he wrote: "No fairer destiny could be allowed to any physical theory than that it should itself point out the way to introducing a more comprehensive theory in which it lives on as a limiting case" (35, p. 131).

These are lofty goals, but they do not always reflect reality. For the surprising nature of much scientific endeavor is a profound resistance to those new ideas that threaten to refute favored dogmas.

The development of intellectual mind-sets (paradigms). A characteristic of the scientific mind is the development of intellectual mind-sets or frameworks within which we interpret all new information (62). Popper described this subconscious process accordingly: "Thinking people tend to develop some framework into which they try to fit whatever new idea they may come across; as a rule, they even translate any new idea which they meet into a language appropriate to their own framework. One of the most characteristic tasks of philosophy is to attack, if necessary, the framework itself" (93).

The value of these intellectual frameworks is that, when accepted by the entire community, they facilitate communication. The basis for this common understanding does not need to be reviewed endlessly as all the experts in that field accepts the truth of the model and its predictions. Frameworks or paradigms represent those scientific areas in which an intellectual truce has been declared, the intellectual battles have been fought, the arguments have been exhausted, and a common consensus has been achieved. There is a common acceptance that no further advantage can be gained by arguing the intellectual basis of the paradigm. Rather, the accepted framework makes predictions which scientists are then able to evaluate. Kuhn (62) refers to this as "normal" science. As elegantly described in the analogy of Friedman (37), the danger of such frameworks is that, like clothes, these ideas become comfortable and are not easily discarded. "Accepting a new paradigm is like acquiring a new wardrobe. Initially, the garments fit well, look stylish, and are suitable for almost all occasions. However, with the passage of time, the clothes become too loose or too tight, frayed and tattered, and the wearer begins to feel unsuitably dressed for certain events. At this point, he or she can either alter the outfits or purchase a new wardrobe. But the older clothes are not so easily cast aside. They are more comfortable in some ways, they served long and well, they are like old friends; a certain attachment has set in. Indeed the wearer may decide to keep the old wardrobe and restrict his or her activities accordingly, passing up occasions at which the clothes seem out of place. The activities that are dropped become defined as unimportant and eventually no longer belong to the wearer's 'real' world. Choosing a new wardrobe, on the other hand, is comparable to what Kuhn terms a 'paradigm revolution': the basic framework that defines activity is altered, and 'normal' science is replaced with a new range of possibilities. We may call this a 'new reality' " (37).

Paradigms and model-dependent reality. The eminent mathematician Stephen Hawking has written a remarkably successful popular book on astrophysics (42). His book describes models from which we can attempt to understand how the universe is (currently) believed to work. The models make predictions that can be tested, but these are not guaranteed to be either true or real. As Hawking explains: "We cannot distinguish what is real about the universe without a theory . . . (But) . . . it makes no sense to ask if a theory corresponds to reality, because we do not know what reality is independent of a theory. . . . How can we know what is real, independent of a theory or model with which to interpret it?" (43, p. 38).

Exercise scientists spend their academic lives developing models of how the body works. We need to remember that these models do not necessarily reflect reality or absolute truth.

The nature of truth in scientific endeavor. Consideration of these views allows one to propose that scientific truth is subject to change which often occurs with rude suddenness; that truth is model-dependent; and that truth reveals itself through refutation of the less-true.

If truth is constantly in flux, it follows that one measure of the vigor of any scientific discipline is the frequency with which its major hypotheses are refuted and reformulated. On this basis, a science like astrophysics might be considered vigorous as the ideas and theories in the discipline are always in flux. So one might ask, how do my particular areas of interests, exercise physiology and sports medicine, measure up?

This analysis begins by considering two hypotheses, the refutations of which have been readily accepted. Then follows an analysis of five topics which, in my opinion, provide evidence for substantial resistance to novel interpretations, suggesting that the concept of refutability is not always eagerly accepted in all areas of our discipline.

ACCEPTED REFUTATIONS IN THE EXERCISE SCIENCES

My introduction to more serious science started with an attempt to refute the statement which claimed that: "A search of the literature has failed to document a single death due to coronary atherosclerosis among marathoners of any age. Marathoners were defined as those completing 42.2 km in under 4 hours and only autopsied cases were considered" (8). This statement formed the basis for a conjecture which soon became known as the Bassler hypothesis: "As no cases of fatal atherosclerosis have been documented in marathon finishers of any age, it follows that such activity confers virtual immunity from fatal heart attacks" (102). To this was added the rider: ". . . it is biologically impossible for atherosclerosis to progress in anyone capable of even walking the 42-km distance! Indeed reversal of the disease is seen" (10). Insurance against heart attack could also be achieved with a relatively small investment: "For the nonsmoker who trains at distances over 6 miles for a total of 100 miles, protection starts here and continues as long as he continues running" (9). The dramatic growth of marathon running at that time helped to popularize Bassler's thesis.

This conjecture has the characteristic of a scientific theory as it is open to refutation, which was provided by a single report detailing the deaths of marathon runners from coronary atherosclerosis (87). This refutation was readily accepted (95), perhaps because it does not impact on the more important hypothesis, also the subject of a previous Wolffe lecture and for which there is no contradictory evidence: that persons who are vigorously active may live longer and suffer less from heart attacks, hypertension, diabetes mellitus, and certain cancers than their less active peers (89).

Seldom is a single case report sufficient to refute an hypothesis; more commonly, a more detailed experiment is required. The study of Coyle et al. (24) provides a fine example of work that resolved a controversy that had raged for at least 50 years and that had important practical implications for athletes competing in endurance events. Those authors evaluated the popular conjecture that held that only water should be ingested during exercise. This hypothesis stems from the intellectual model that holds that carbohydrate ingestion during exercise delays the rate of gastric emptying, slowing the rate at which fluid is delivered to the small intestine, thereby promoting the development of dehydration and the probability that heat injury will develop especially during prolonged exercise (84,85). The hypothesis drew strength from a study, published in the *New England Journal of Medicine* in 1981 (36), which concluded that: ". . . correction of hypoglycemia by glucose ingestion (during prolonged exercise) does not consistently delay exhaustion or alter the subjective sensation of exertion during the exercise. These findings thus do not support a role for glucose ingestion in improving performance during prolonged exercise, and they may have relevance to endurance sports such as marathon running."

What is particularly remarkable is that these conjectures were universally accepted despite the presence of a number of refutations, published half a century earlier, that clearly showed that carbohydrate ingestion either reversed or delayed the onset of fatigue during prolonged exercise, including marathon running (21,33,66). Indeed, on the basis of the evidence available in 1936, Grace Eggleton (34, p. 153) had written that: "When they (long distance runners) have run to exhaustion, the level of blood sugar is found to be abnormally low . . . If the eating of sugar candy during a race was encouraged . . . it seems possible that new records might be achieved in long-distance running." As Popper has warned, it is usually unwise to accept a conjecture for which there is a single logical refutation already present in the literature. Yet, in this example, besides the three published refutations, there was a substantial volume of anecdotal evidence favoring the ergogenic benefits of carbohydrate ingested during prolonged exercise (83,86).

Coyle et al. (24) confirmed the validity of these historic refutations by showing that, when they ingested a concentrated carbohydrate beverage, trained endurance cyclists who had not eaten for 12 h, were able to exercise for up to 33% longer than when they ingested a sweetened placebo.

The above example should teach us two important lessons. One is that any hypothesis can be immunized from all attempts at refutation once it becomes the established mind-set supported by influential scientists. As Miller (73, p. 10) has exhorted: "It is the perpetuation of errors that interferes with our understanding; and it is this, rather than their perpetration, that we must exert

ourselves determinedly to avert." Influential scientists can harm their discipline if they lose the desire to challenge the dogmas they have created.

The second important lesson of this example was the rapidity with which its results were accepted by the scientific community; how swiftly its conclusions were integrated into a new intellectual model, and how decisively this new information altered the eating and drinking habits of athletes competing in endurance events. Usually novel ideas that refute the existing mind-set are accepted only by the next generation of scientists.

Another refutation that has been less readily accepted deals with the popular prejudice that people collapse during or after prolonged exercise, especially marathon and ultramarathon running, because they develop dehydration-induced hyperthermia (85). This theory can be questioned on two grounds. The first is the finding that the vast majority of athletes who collapse during or after exercise, or with the experimental condition termed "heat strain" (100), do not have abnormally elevated rectal temperatures (53,96,97,100) and are therefore not suffering from hyperthermia. If the theory linking hyperthermia to dehydration (118) is correct, then the athletes with the condition are probably not excessively dehydrated. Similarly, collapse from "heat strain" is not prevented by adequate fluid ingestion (100), indicating that dehydration is not an etiological factor for collapse from this condition. But adequate fluid ingestion during exercise especially in the heat does confer significant physiological benefits and does increase substantially the duration of exercise that can be sustained before the onset of collapse from "heat strain" (100).

More to the point, the finding that 85% of such collapses in competitive athletes occur after the athlete has already completed such distance races (53), suggests that severe dehydration is not the primary determinant of collapse. For if severe dehydration caused collapse by reducing the circulating blood volume and hence the cardiac output, one would expect dehydration-induced collapse to occur during exercise when the cardiovascular system is under the greatest stress. Instead, the majority of such collapses occur at the end of exercise when the cardiovascular system is reverting to the resting state and the athlete may be experiencing postural hypotension (54).

Attempts to promote this line of argument (85) continue to be ignored because of the entrenched mind-set that dehydration alone explains the majority of the medical problems that develop during exercise. The historical origin of this prejudice has been described (85).

Why are novel ideas accepted with reluctance by the scientific community? Popper (93, p. 14) has described why scientists find it so difficult to discard their intellectual wardrobes: "Most of us . . . hold a great number of theories consciously .. and we may be prepared both to defend these by argument and to give them up when good arguments are brought against them. *But we also hold theories that we take for granted more or less unconsciously and therefore uncritically; and these uncritically held theories often contain the strongest reason for continuing to hold those other theories consciously* (author's emphasis). . . . . it may become necessary to attack beliefs which, whether or not they are consciously held, are taken so much for granted that any criticism of them is felt to be perverse or insincere. Whenever the framework itself is attacked, its defenders will as a rule interpret, and attempt to refute, the attack within their own adopted framework."

Hawking has described the same phenomenon (43, p. 36): "The theory always came first, put forward from the desire to have an elegant and consistent mathematical model. The theory then makes predictions, which can be tested by observation. If the observations agree with the predictions, that doesn't prove the theory; but the theory survives to make further predictions, which again are tested against observation. If the observations don't agree with the predictions, one abandons the theory. Or rather, that is what is supposed to happen. In practice, people are very reluctant to give up a theory in which they have invested a lot of time and effort. They usually start by questioning the accuracy of the observations. If that fails, they try to modify the theory in an *ad hoc* manner. Eventually the theory becomes a creaking and ugly edifice. Then someone suggests a new theory in which all the awkward observations are explained in an elegant and natural manner."

Hawking also identifies a popular method that is used to delay the acceptance of a new conjecture. In this technique labeled "refutation by denigration," the scientific credibility of the person who questions the accepted model is brought into doubt and his or her professional standing is subtly undermined. It is the classic technique of shooting the messenger so that the message may be conveniently ignored. This method is unfortunately still quite popular in the exercise sciences. It has no part in mature science and must be exposed whenever and wherever it reveals its ugly presence.

It would seem that even the intellectually brilliant are not immune from this reluctance to accept a new intellectual model. Both Newton and Einstein, two of the most revolutionary scientists, could not accept predictions of their own theories that were in conflict with a religious dogma. Newton refused to accept that the absolute position in a space of a large object could not be defined as this conflicted with his belief in an absolute God. Similarly, Einstein would not believe that the position of the very small was also indeterminate (the Heissenberg Uncertainty Principle) because it also conflicted with his religious belief. "God," Einstein wrote, "does not play dice" (43, p. 91). His prediction of the existence of astronomical black holes lead Hawking to

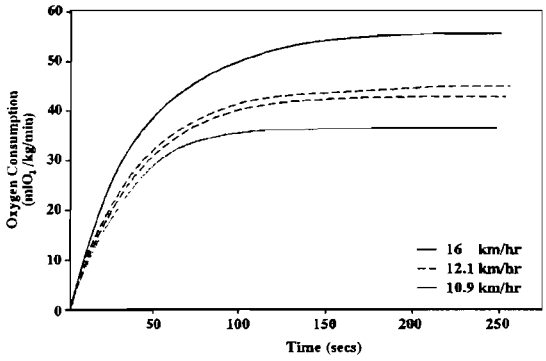

Figure 1—Oxygen consumption of A. V. Hill when he ran at three different speeds for up to 4 min. Data redrawn from Hill and Lupton (49) as previously published in reference 82. Noakes, T. D. Implications of exercise testing for prediction of athletic performance: a contemporary perspective. *Med. Sci. Sports Exerc.* 20:319–330, 1988.

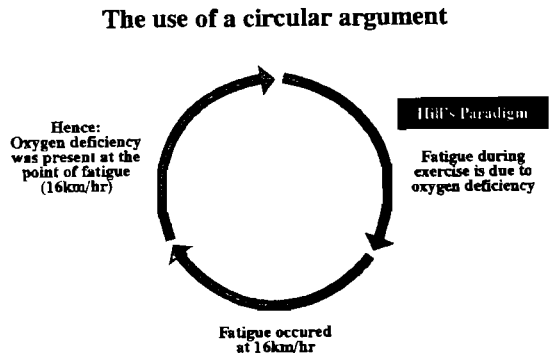

Figure 2—Hill's conclusion that his oxygen consumption was less than his requirement when running at 16 km·h^{-1} (Fig. 1), was based on a circular argument. His subconscious assumption was that fatigue during exercise is owing to oxygen deficiency in the active muscles.

suggest that: "God not only plays dice but also sometimes throws them where they cannot be seen" (43, p. 103).

I have encountered five intellectual frameworks in the exercise sciences that, in my opinion, have to a lesser or greater extent, become "ugly and creaking edifices." A feature of the majority is that they share a common origin in the hypothesis that the active skeletal muscles contract anaerobically during high intensity exercise. What are these conjectures and what evidence or logic might seem to refute them?

SOME UGLY AND CREAKING EDIFICES

1. The maximum oxygen consumption of Hill ($\dot{V}O_{2max\text{-}hill}$). The work of Nobel Laureate Archibald Vivian Hill et al. (47–51) forms the basis for the popular conjecture that an oxygen limitation develops during maximal exercise causing skeletal muscle hypoxia to terminate exercise. The critical flaw in logic perpetuated in those studies has been described in two previous tutorial lectures to our College and in one publication in this journal (82). These refutations of Hill's conjecture and its potential implications for some crucial areas of the exercise sciences have, with a few notable exceptions (2,77,78,99), been essentially ignored. Perhaps this fourth attempt to challenge an entrenched mindset will be more successful!

In their experimental series, Hill et al. measured oxygen consumption ($\dot{V}O_2$) every 30 s in subjects who ran for 3 min at different speeds on a circular grass track 85 m in circumference. Their relevant findings are reproduced (again) in Figure 1. The authors' interpretation of their data was the following (49):

"When muscular exercise is taken in man at a constant speed, the lactic content of his active muscles increases gradually from its resting minimum at the start. The rise in lactic acid content increases the rate of oxidation, so that finally if the oxygen supply is adequate, a 'steady state' is reached in which the rate of lactic acid production is balanced by the rate of its oxidative removal, and its concentration remains constant in the muscle as long as exercise at that speed is maintained. The lower three curves represent a genuine steady state and the uppermost curve only an apparent steady state in which the oxygen intake is at its maximum and the oxygen debt is rapidly increasing."

Hill and Lupton concluded that the constant $\dot{V}O_2$ they measured at the fastest running speed (16 km·h^{-1} in Fig. 1) represented an apparent, not a true, steady state. The basis for this conclusion was a circular argument based on Hill's subconscious model explaining fatigue during exercise (Fig. 2). For Hill began with the subliminal premise that fatigue during exercise is caused by an oxygen deficiency; he naturally interpreted his findings within that conceptual framework.

From the subjective feelings of the fatigue that he experienced when he ran at 16 km·h^{-1}, Hill drew the equally subjective conclusion that he must have developed an oxygen deficiency. As a result he concluded that his real $\dot{V}O_2$ must have been higher than that which was objectively measured at 16 km·h^{-1}. Thus, Hill et al. (50) speculated: "Considering the case of running... there is clearly some critical speed for each individual... above which, the maximum oxygen intake is inadequate, lactic acid accumulating, a continuously increasing oxygen debt being incurred, fatigue and exhaustion setting in." Hill (47) further concluded that: "The oxygen intake may attain its maximum and remain constant merely because it cannot go any higher owing to the limitations of the circulatory and respiratory systems."

Not only did Hill et al. (50) fail to measure concurrently either the oxygen debt or muscle or blood lactate levels during these or subsequent studies, they also failed to subject their hypothesis to the accepted process of refutation. For the next logical study would have been to

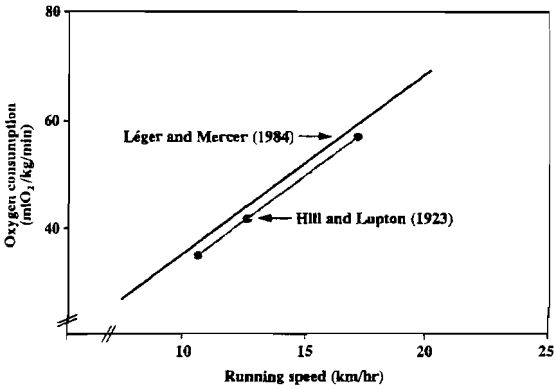

Figure 3—There is a linear relationship between running speed and the average $\dot{V}O_2$ measured at the different running speeds shown in Figure 2. The relationship is similar to that reported in the literature. Data redrawn from Hill and Lupton (49) as previously published in reference 82. Noakes, T. D. Implications of exercise testing for prediction of athletic performance: a contemporary perspective. *Med. Sci. Sports Exerc.* 20:319–330, 1988.

measure Hill's $\dot{V}O_2$ when he ran at a speed faster than 16 km·h^{-1}. Their hypothesis would have been supported if the $\dot{V}O_2$ at that higher speed was either the same or lower than that measured at 16 km·h^{-1}.

However, as that experiment was not performed, Hill et al. could not conclude that Hill's $\dot{V}O_2$ had "plateaued" and was indeed maximal at 16 km·h^{-1}. Thus, their major conclusion that $\dot{V}O_2$ reaches a plateau during exercise of progressively increasing intensity was not proven because this test of refutation was not conducted. Fortunately, it is possible to submit their conclusion to retrospective refutation.

The data shown in Figure 3 confirm that Hill did not reach "some critical speed . . . above which the maximum oxygen intake is inadequate." For the data clearly show a linear relationship between Hill's mean $\dot{V}O_2$ at three different speeds. Hence, there is no evidence in these data for the plateau phenomenon, indicating that any postulated $\dot{V}O_{2max\cdot Hill}$ had not occurred. The implications of this refutation of Hill's conjecture are two-fold. First, it raises the question of whether the plateau phenomenon indicating $\dot{V}O_{2max}$ really exists (82). Second, by logical extension, it questions the hallowed notion than anaerobiosis develops during exercise and that it is this anaerobiosis that induces specific physiological and biochemical changes that terminate high intensity exercise.

Hill and Lupton (49) were silent on the mechanisms causing fatigue during exercise at or above their postulated $\dot{V}O_{2max\cdot Hill}$. They proposed only that "lactic acid" was involved but evaded the issue of how elevated "lactic acid" concentrations either in muscle or blood cause fatigue (49).

If Hill and Lupton's work offers no basis for the hypothesis that $\dot{V}O_2$ plateaus during maximal exercise, what other evidence is there to sustain this particular conjecture?

After Hill and Lupton's work, the next classical study usually considered as additional definitive proof of the plateau phenomenon is that of Mitchell et al. (74). However, that study was not designed to test the $\dot{V}O_{2max\cdot Hill}$ hypothesis for it began by echoing Hill's assumption that, during progressive exercise, there is a workload at which "maximal oxygen intake per unit of time is reached; beyond this point the workload can usually be increased still further but, ordinarily, oxygen intake levels off or declines" (74, p. 538). Rather, the aim of that study "was not, however, merely to re-examine previously established characteristics of maximal oxygen intake but, rather, to inquire into its physiological meaning" (74, p. 543). Hence, they determined the cardiorespiratory changes, in particular in cardiac output and in arterial and venous oxygen tensions including the arteriovenous (AV)oxygen difference, that occurred during steady state exercise of short duration at near maximal exercise intensities. During those experiments, $\dot{V}O_2$ was calculated from expired gas samples collected during the last minute of consecutive, but interrupted, exercise bouts that lasted 2.5 min.

Their principal finding was that increases in both cardiac output and in the AV oxygen difference contributed to the maximal oxygen consumption, with the rise in cardiac output being the more important. They concluded that "the maximal oxygen intake is a measure of cardiac capacity and the ability to increase the AV oxygen difference, not of the ability of the vascular bed to accommodate left ventricular output" (74, p. 545). As an aside, they also reported that 72% of subjects showed a "plateau phenomenon" defined as an increase in $\dot{V}O_2$ of less than 54 ml at the highest exercise workload. But that finding had no bearing on their conclusion. Based on Hill's conclusions, the authors had already assumed that there is a $\dot{V}O_{2\ max.Hill}$ which is determined by limitations in the cardiovascular system.

But does that study also provide any definitive information about the "plateau phenomenon"? The only physiological model, which allows conclusions to be drawn from the testing protocol used by Mitchell et al. (74) in which the interrupted exercise bouts last less than 3 min, is one in which $\dot{V}O_2$ rises very rapidly at the onset of exercise, reaching its maximum within 90 s of the onset of exercise. If that model is incorrect, then conclusions about the "plateau phenomenon" cannot be drawn from that testing protocol. For example, an apparent "plateau phenomenon" would occur with the testing protocol of Mitchell et al. (74) if the initial rate of increase in $\dot{V}O_2$ were the same for all the high work rates that they studied. Proof that their interrupted testing protocol identifies a real plateau in $\dot{V}O_2$ would require that additional samples be taken at later time points to ensure that there

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had been no further increase in $\dot{V}O_2$ after the first 2.5 min of exercise.

Subsequent searches have found the "plateau phenomenon" to be elusive (2,25,82). An early attempt to identify this phenomenon in adult men concluded that: "The plateau is theoretically exact, in practice it is much less so" (25). The most recent review published in September 1995 (56) concluded that: "there is no general agreement on the use of specific criteria for establishing that $\dot{V}O_{2max}$ has, in fact, been achieved."

Only one study has attempted directly to determine whether oxygen consumption during progressive, ramp exercise reaches a maximum "beyond which no effort can drive it" (47). Myers et al. (78) summed $\dot{V}O_2$ over one or more breaths during both steady-state and progressive (ramp) exercise. Using a rolling average, they continuously calculated the rate and direction of change in $\dot{V}O_2$ throughout exercise. They showed that there is considerable variability in $\dot{V}O_2$ measured breath-to-breath or averaged over short intervals and that this variability is a result of changes, predominantly in tidal volume. The result is that instantaneous $\dot{V}O_2$ does not rise as an exactly linear function of a progressively increasing (ramp) work rate but in a rather more irregular pattern. This variability is reduced when longer sampling times are used so that $\dot{V}O_2$ rises as a linear function of work rate when sampling times of 60 s or more are used.

Myers et al. (78) concluded that the rate of change in $\dot{V}O_2$ during ramp exercise is erratic and frequently transiently negative indicating a "plateau phenomenon" even during submaximal exercise. They proposed that: "... considerable variability exists in the slope of the change in VO_2 with a consistent change in external work ... suggesting that a plateau (defined as the slope of a VO_2 sample at peak exercise that does not differ significantly from a slope of zero) in VO_2 is not a reliable physiological marker for maximal effort" (78).

This finding has implications for the duration of the sampling period used to establish whether the plateau phenomenon exists; the shorter the sampling period, the less likely it is that a definitive plateau phenomenon will be identified. One might suggest that a phenomenon that can be identified only with some difficulty and under certain specific experimental conditions is unlikely to be a fundamental biological truth.

In summary, Hill's original interpretation of his own data is in error. This error has been perpetuated for 70 years with the result that Hill's theory of the plateau phenomenon, although unproven, persists as a fiercely protected paradigm in the exercise sciences. It is important that we appreciate the uncertain status of the plateau phenomenon so that we are not unwitting agents of its continued perpetuation.

2. Progressive muscle hypoxia limits maximal exercise performance. The second creaking and ugly edifice follows directly from the first. It holds that hypoxia develops in the active muscles during exercise and that this hypoxia causes fatigue and therefore limits maximal exercise performance under all conditions. This model holds that the hypoxia results from an inability of the heart to increase its cardiac output sufficiently to match the maximum demands of the active skeletal muscles (98).

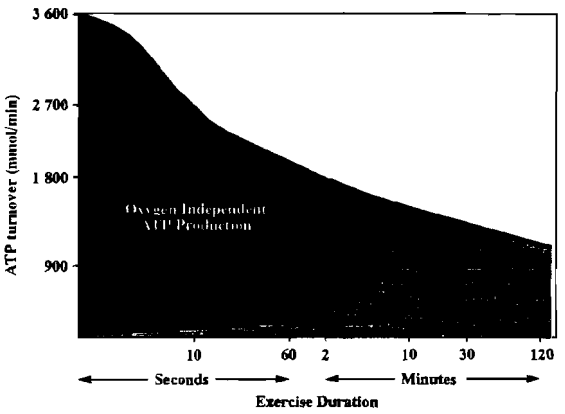

Figure 4—The maximum rate of sustainable ATP turnover falls sharply with the increasing duration of activity. ATP production during high intensity exercise of short duration (<30 s) is provided by oxygen-independent pathways.

The first issue of concern with the theory of muscle hypoxia is that there is no logical reason why exercise should terminate shortly after the development of the plateau phenomenon as is usually described. This ignores the known capacity of skeletal muscle to generate energy by oxygen-independent metabolism.

Figure 4 is a usual textbook figure showing the rates of ATP production that can be sustained for varying durations of exercise. The diagram indicates the large capacity for oxygen-independent ATP production that can be activated during high intensity exercise of short duration (less than 10–30 s). But if the plateau phenomenon is correct, it requires that progressive ramp exercise, which starts at a low work rate, does not activate fully the oxygen-independent metabolic pathways. For the plateau phenomenon predicts that exercise terminates immediately or shortly after the maximum skeletal muscle oxidative capacity has been reached and without full activation of the oxygen-independent metabolic pathways.

Figure 5 presents the argument more directly. It shows that adding the maximum ATP-generating capacity of only the oxygen-independent glycolytic pathway (~ 500 mmole·min^{-1}) (105) to the maximum skeletal muscle oxidative capacity, measured as the $VO_{2\ max.Hill}$, should allow the athlete to continue exercising to a work rate equivalent to an additional $\dot{V}O_2$ of 1.7 L·min^{-1} after the development of the plateau phenomenon. No proponent of the plateau phenomenon has yet described this phenomenon.

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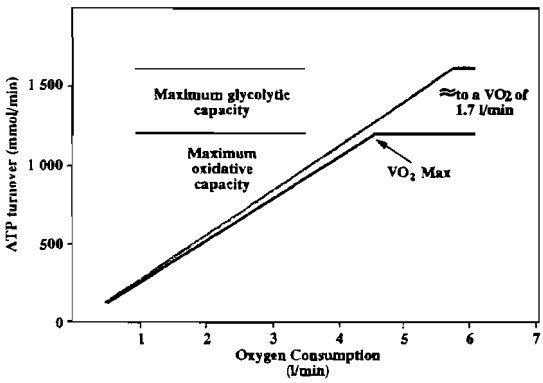

Figure 5—The additional energy provided by the maximum rate of oxygen-independent glycolytic ATP production should allow exercise to continue to a work rate 1.7 L·min^{-1} above that at the theoretical "plateau phenomenon" which, it is assumed, corresponds to the maximum achieveable skeletal muscle oxidative capacity.

Accordingly, one might hypothesize that progressive exercise to exhaustion in which exercise starts at submaximal work rates must terminate before the maximum rates of oxygen-independent ATP production are reached. If this is correct, it suggests that contraction of the exercising muscles ceases before their maximum metabolic capacity— in particular their maximum capacity for oxygen-independent ATP production—is used. Specific findings in both healthy and diseased subjects support this interpretation.

First, the novel study of Spriet et al. (104) was designed specifically to determine whether skeletal muscle forced to exercise under ischemic and ultimately anaerobic conditions would continue to contract until ATP depletion and rigor developed. To test this theory, the quadriceps muscle group of human subjects was rendered ischemic by the application of a pressure tourniquet to the upper thigh and forced to contract repetitively by electrical stimulation.

The key findings were (i) that skeletal muscle ATP concentrations fell to 57% of the resting values and (ii) that skeletal muscle contractile function fell progressively. More importantly, rates of muscle ATP production fell coincident with falling rates of muscle ATP use. Thus, the likely conclusion is that under ischaemic conditions and, by extension, presumably also under hypoxic conditions, skeletal muscle contractile function and hence rates of muscle ATP use are regulated to prevent any large variance in the protected variable skeletal muscle ATP concentrations. If correct, this model represents a substantial change from the traditional model of Hill (47) which postulates that energy demand outstrips supply during high intensity exercise. The new model proposes that energy demand is regulated by the rate of energy supply specifically so that demand can never outstrip supply.

In diseases of skeletal muscle metabolism including muscle phosphorylase deficiency and the mitochondrial myopathies in which capacity to produce ATP by either oxidative or glycolytic pathways is reduced, exercise does not cause an abnormally large reduction in skeletal muscle ATP concentrations (67). This provides further evidence for the hypothesis that skeletal muscle contractile function and its rate of ATP use is regulated by the rate of muscle ATP supply so that muscle ATP concentrations are protected.

Perhaps the most striking example of this phenomenon occurs during exercise at extreme altitude, for example, at or near the summit of Mount Everest (8848 m). Maximum oxygen consumption falls with the reduction in barometric pressure so that at altitudes in excess of 8000 m the $\dot{V}O_{2max}$ is elicited even by the most gentle exercise. Indeed, even in climbers using supplemental oxygen, maximum effort near the summit of Mount Everest consists of prolonged periods of rest interspersed with very brief bouts of exercise. The experience is perhaps best described by the first man to reach the summit of Mount Everest without the use of supplemental oxygen, Reinhold Meisner (107): "We can no longer keep on our feet to rest. . . . Every 10–15 steps we collapse into the snow to rest, then crawl on again."

On first principles, one would predict that Meissner's symptoms were caused by a severe metabolic acidosis resulting from profound muscle hypoxia causing very high circulating blood lactate concentrations. This postulate was tested by Howard Green et al. (39) in the landmark Operation Everest II study which was made possible largely through the tenacity of Dr. John Sutton.

They showed that peak blood lactate concentrations during maximal exercise ***fell*** rather than increased as a function of increasing altitude (39). This observation, now known as the "lactate paradox," is not novel. David Dill (32, p.173) first described the phenomenon in 1938 and proposed that: "The inability to accumulate much lactic acid in great heights or to disturb the internal economy of the organism so profoundly as at sea level may be looked upon as useful safeguards against overexertion. It is as though the body, realizing the delicacy of its situation with regard to oxygen supply, sets up an automatic control over anaerobic work which renders impossible the severe acid-base disturbances which can be voluntarily induced at sea level." Notice Dill's profoundly novel suggestion that an automatic internal control may act as a safeguard to regulate skeletal muscle contraction. A recent study has confirmed that his explanation for the lactate paradox is correct.

Kayser et al. (60) exposed the same group of subjects to exercise at 122 and 5 050 m above sea level. During exercise, integrated electromyographic (IEMG) activity of the vastus lateralis muscle was measured. IEMG activity increased progressively during exercise at sea level but not at altitude. Furthermore, IEMG activity was sub-

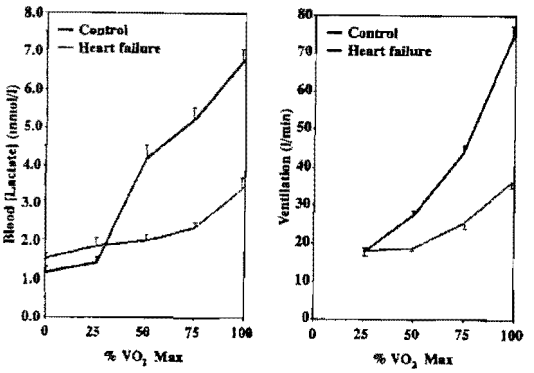

Figure 6—Blood lactate concentrations (*left panel*) and ventilation rates (*right panel*) during progressive exercise to exhaustion in patients with heart failure and in controls. Values are substantially lower in heart failure patients at all exercise intensities in excess of 25% $\dot{V}O_{2max}$. Data of reference 31. Derman, K. L. Exercise tolerance and skeletal muscle structure and function in patients with severe chronic heart failure. MSc thesis. University of Cape Town, 1995.

stantially higher at exhaustion at sea level than at altitude. But IEMG activity increased in subjects exercising at altitude when they inhaled 100% oxygen and were able to exercise to higher work rates.

The interpretation of these findings is that skeletal muscle recruitment is reduced during exercise at altitude. Hence the authors concluded that: "These results suggest that during chronic hypobaric hypoxia, the central nervous system may play a primary role in limiting exhaustive exercise and maximum accumulation of lactate in blood" (60).

The "lactate paradox" is also observed in patients with certain chronic medical conditions including chronic renal (61) and cardiac disease (31). The logical assumption is that patients with renal failure are unable to exercise because of an anemia that reduces oxygen transport capacity to the active muscles during exercise; in heart failure, there is a reduced capacity to increase blood flow to the active skeletal muscles during exercise. As a result, the muscles of both groups of patients should develop a premature hypoxia during exercise, leading to the production of high and limiting concentrations of lactate in muscle and blood. But this does not occur.

For example, a recent study (31) of the physiological responses to maximal exercise in patients with heart failure showed that blood lactate concentrations and rates of pulmonary ventilation were substantially lower in patients than in age-matched controls at any $\%\dot{V}O_{2max}$ (Fig. 6). Furthermore, patients showed severe morphological abnormalities in skeletal muscle. The probable conclusion is that the impaired exercise tolerance of these patients results either from a reduced capacity to recruit skeletal muscle during exercise or from impaired skeletal muscle contractile function.

TABLE 1. Changes in exercise tolerance and $VO_{2\ max}$ after cardiac transplantation.

	Controls	Heart Failure Patients	Following Cardiac Transplantation
Peak workload (W)	190 ± 30	65 ± 20	80 ± 20
$VO_{2\ max}$ (mL·kg^{-1}·min)	30 ± 3	12 ± 2	17 ± 2
Peak lactate (mmol·l)	6.9 ± 0.7	3.4 ± 0.4	4.0 ± 0.4
Skeletal muscle histology score (units)	2 ± 1	12 ± 3	11 ± 2

Unpublished data of E. W. Derman, University of Cape Town.

Indeed, the peripheral nature of the lactate paradox can be shown in persons with heart failure who have undergone cardiac transplantation. Derman (31) has also compared the exercise capacity of patients before and after cardiac transplantation with that of controls. She showed that there were small but insignificant increases in peak workload and $\dot{V}O_{2max}$ 2 months after cardiac transplantation, but peak venous blood lactate concentrations remained low and abnormal skeletal muscle histology scores were not improved (Table 1). All values were significantly different from those measured in controls. Subsequent studies suggest that, in the absence of exercise training, skeletal muscle histological abnormalities persist for at least 12 months after cardiac transplantation.

Another study (72) confirms that peak $\dot{V}O_2$ remained very low (~16 mL·kg^{-1}·min^{-1}) and did not increase during the first 12 months after cardiac transplantation, confirming that replacing the heart does not normalize the impaired exercise tolerance and low peak $\dot{V}O_2$ values of patients with chronic heart failure.

In summary, these studies indicate that progressive skeletal muscle anaerobiosis is an unlikely mechanism limiting or impairing exercise performance in a variety of experimental and clinical settings. Rather, these findings invite the hypothesis that skeletal muscle contractile function is regulated during exercise in both health and disease by a hierarchy of central and peripheral mechanisms, the goal of which is likely to prevent organ damage, including death. The evidence for this grand hypothesis is the following:

Skeletal muscle function during exercise appears to be regulated by different mechanisms (i) to prevent the development of muscle ATP depletion causing irreversible skeletal muscle rigor during high intensity exercise (67,104); (ii) to prevent cerebral hypoxia during exercise at altitude (32,39,60); (iii) to prevent a catastrophic fall in blood pressure (98) that would reduce perfusion of the diseased coronary arteries in chronic heart failure; (iv) to prevent catastrophic hyperthermia (heatstroke) during prolonged exercise in the heat (81); and (v) to prevent glucopenic brain damage during prolonged exercise when hypoglycemia results from liver glycogen depletion (13).

Perhaps the tantalizing challenge for exercise scientists is to define the control mechanisms that provide these

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safeguards. Central control mechanisms may include brain receptors for hypoxia to limit exercise at altitude, for blood glucose concentrations to limit exercise during hypoglycemia, and for temperature to prevent heatstroke. Peripherally-based receptors would need to link metabolic and cardiovascular signals. The intriguing finding that blood flow may regulate skeletal muscle contractile function independent of oxygen delivery (106) raises the possibility that a peripherally-located flow signal may also regulate skeletal muscle contractile function. Indeed, the possible role of the vascular endothelium needs to be considered.

A credible hypothesis can be advanced to explain why skeletal muscle contractile function should be controlled by its blood flow. Rowell (98) has concluded that overall cardiovascular function is regulated during imposed stresses including exercise to maintain the arterial blood pressure. A major determinant of this control is regulation of blood flow to, and blood volume distribution in, the different arterial and venous beds. During exercise, skeletal muscle contractile activity is the major determinant of the overall blood flow and blood volume distribution with the result that the greater percentage of the cardiac output is directed to the active skeletal muscles.

Thus, it makes sense that the variable, skeletal muscle contractile activity, which can most effect whole body blood flow distribution during exercise and therefore the maintenance of an adequate blood pressure, should itself be regulated by the blood flow it receives. If blood flow does regulate skeletal muscle contractile function, then the maximum cardiac output would indeed limit peak exercise performance as traditionally argued (3,74,98). However, this limitation would not be determined by a limiting rate of oxygen delivery to the working muscles, but rather by a limiting cardiac output that is unable to counter the blood pressure lowering effects of any additional fall in total peripheral resistance that would occur if further skeletal muscle recruitment were to induce additional vasodilation in an attempt to increase skeletal muscle blood flow further.

In summary, the testable hypothesis is proposed that exercise under different conditions is limited in both health and disease by a regulated process of skeletal muscle "mechanical arrest." During high intensity exercise, this control would prevent the development of irreversible damage (rigor) in the active skeletal muscles. This control could be provided by blood flow regulation of skeletal muscle contractile function and could result from the accumulation of metabolites which reduce skeletal muscle contractile activity and hence the blood flow requirement. On theoretical grounds, control of overall skeletal muscle contractile function by blood flow is an attractive hypothesis as it provides the link for the simultaneous regulation of overall cardiovascular function with skeletal muscle metabolism and contractile activity.

Perhaps the challenge for exercise scientists is better to understand the effectors that might regulate this elegant, albeit still hypothetical, model.

3. Anaerobiosis explains the onset of lactate production by skeletal muscle at the "anaerobic threshold." The third creaking and ugly edifice holds that oxygen delivery to the active muscles becomes inadequate, not at the $\dot{V}O_{2max\cdot Hill}$, but at a lower work rate. This hypothesis stems from another central component of Hill and Lupton's belief that "lactic acid" accumulates in muscles that contract anaerobically, thereby developing an "oxygen debt." The modern confirmation that blood and muscle lactate concentrations increase during submaximal exercise has fortified this belief that anaerobiosis develops in muscle before the plateau in $\dot{V}O_2$ at a submaximal exercise intensity since identified as the "anaerobic threshold" (109–111,114). Extension of this hypothesis holds that the resulting metabolic acidosis which develops at, and accelerates above, the anaerobic threshold leads to bicarbonate buffering of the excess hydrogen ions released in this process causing an increased CO_2 production. This, in turn, stimulates ventilation leading to simultaneous "anaerobic" and "ventilation" thresholds (eqs. 1 and 2).

$$\text{Glucose} \rightarrow 2 \text{ lactate} + 2H^+ \quad [1]$$

$$H^+ + HCO_3^- \rightarrow H_2O + CO_2 \quad [2]$$

There are four potential sources of refutation of this specific model.

First, the terminology is inexact. Anaerobic means in the absence of oxygen. But as every manufacturer of expensive equipment for the measurement of $\dot{V}O_2$ during exercise will be quick to assert, whole body $\dot{V}O_2$ is not zero during submaximal exercise. Hence, the muscles are not contracting anaerobically during submaximal exercise. An important discipline of science is to use words according to their exact meanings. When applied to submaximal exercise, the use of the term "anaerobic" is clearly incorrect. Perhaps the intended meaning is that the active muscles becomes hypoxic during exercise in which case the more correct term should be the "hypoxic threshold." If so, the existence of an hypoxic threshold should be identifiable during progressive exercise.

If such a threshold exists, then at some submaximal work rate below the $\dot{V}O_{2max\cdot Hill}$, $\dot{V}O_2$ must begin to lag behind demand, rendering the active muscles increasingly hypoxic. At that point, $\dot{V}O_2$ will no longer increase linearly with increasing work rate. Thus, the hypoxic threshold should be identifiable as a submaximal work rate well below the $\dot{V}O_{2max\cdot Hill}$ at which $\dot{V}O_2$ no longer increases as a linear function of increasing work rate (Fig. 7).

But this too does not occur. For if the average sampling time is sufficiently long (30–60 s), so that the breath-to-breath variation in $\dot{V}O_2$ (77) is smoothed, $\dot{V}O_2$ rises as a

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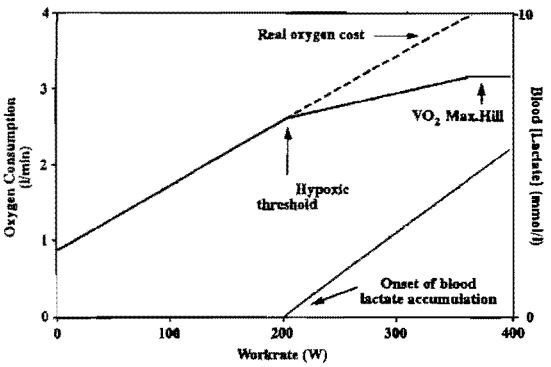

Figure 7—The hypoxic or anaerobic threshold should be identifiable as the submaximal work rate above which (i) the rise in $\dot{V}O_2$ with increasing work rate deviates from linearity and (ii) lactate first appears in the blood. Neither phenomenon occurs.

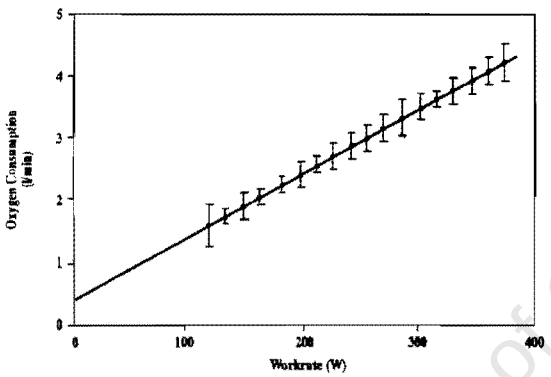

Figure 8—Whole body $\dot{V}O_2$ rises as a linear function of increasing work rate without evidence for an hypoxic threshold at submaximal work rates or, in this series of a "plateau phenomenon." Data from reference 30. Dennis, S. C., T. D. Noakes, and A. N. Bosch. Ventilation and blood lactate increase exponentially during incremental exercise. *J. Sports Sci.* 10:437–449, 1992.

linear function of increasing work rate even to exhaustion with no evidence of a plateau at the hypoxic threshold (30) (Fig. 8). Thus, the absence of this theoretical hypoxic threshold during the submaximal component of the maximal exercise test is the second potential refutation of this creaking and ugly hypothesis.

The third potential refutation of this hypothesis has been provided by new studies of lactate kinetics during submaximal exercise. The question addressed by these studies is: "What stimulates muscles to increase their production of lactate, thereby causing blood and muscle lactate concentrations to rise during exercise?"

The popular explanation for the increase in the blood lactate concentrations during exercise is probably not greatly different from that described in the classic textbook (4): "The production of lactic acid, which culminates in a muscular contraction, is a non-oxidative process and can take place in the absence of oxygen: its subsequent removal is an oxidative process and demands an adequate supply of oxygen. Fletcher and Hopkins consider that the appearance of lactic acid precedes, and is intimately bound up with, the mechanical shortening of the muscle whereas its oxidation is effected after the contraction is over, and brings about the return of the muscle to its former resting condition."

Their explanation includes two ideas: first, that "lactic acid" is produced exclusively by non-oxidative or anaerobic processes, and second, that lactic acid is the messenger that induces the muscle to contract. The latter postulate is now known to be incorrect; calcium, not lactic acid, is the chemical that initiates muscle contraction. Furthermore, if blood lactate concentrations rise only as the result of hypoxic conditions in muscle, then this model predicts that blood lactate concentrations should be zero at all exercise intensities below the "hypoxic" threshold.

The first major advance in the understanding of factors determining the rise in blood lactate concentrations during exercise was provided by George Brooks et al. (14–17). Their work has established that the blood lactate concentration is the result of two processes, the production of lactate (appearance, Ra) and its removal (disappearance, Rd) and that these processes can be studied with the use of radiolabeled tracers. This technique is still not widely used, and this may perhaps explain why these fundamental concepts have yet to receive more universal acceptance.

Using this technique, Dr. Holden MacRae, currently of Pepperdine University in Malibu, together with Professor Steven Dennis and Dr. Andrew Bosch in our laboratory, completed a series of experiments determining the effects of endurance training on lactate metabolism measured with C^{14} lactate tracers (68–70). Figure 9 shows changes in blood lactate concentrations, $\dot{V}O_2$, lactate Ra and Rd, and carbohydrate oxidation during exercise at different work rates. It shows that even at low work rates of 60 W equivalent in these subjects to about 30% $\dot{V}O_{2max}$, there was an appreciable lactate Ra. Clearly lactate production at low work rates cannot be a result of skeletal muscle hypoxia. As rates of lactate disappearance (Rd) matched lactate Ra, blood lactate concentrations remained constant at those low work rates, but were not zero.

Both lactate Ra and Rd rose as curvilinear functions of increasing work rate. But at higher work rates, lactate Ra exceeded lactate Rd so that the blood lactate concentration began to rise. At those work rates, $\dot{V}O_2$ continued to rise as a linear function of work rate without any evidence for an "hypoxic threshold" coincident with this increasing rate of lactate production and rising blood lactate concentrations.

The figure also shows that the curvilinear rises in lactate Ra and Rd and in the blood lactate concentrations are matched by a curvilinear increase in the rate of

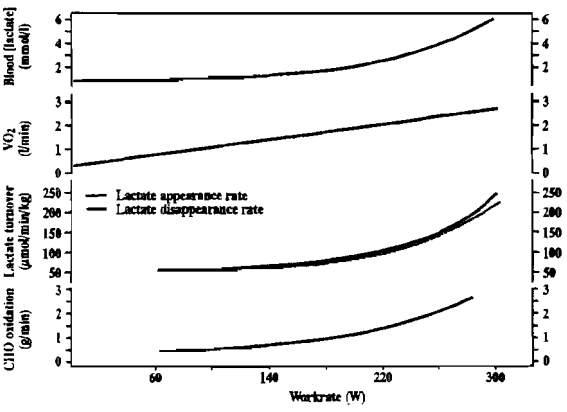

Figure 9—Changes in blood lactate concentrations, $\dot{V}O_2$, lactate Ra, lactate Rd, and rates of carbohydrate oxidation with increasing work rate during progressive exercise to exhaustion. Note that blood lactate concentrations, lactate Ra, lactate Rd, and rates of carbohydrate oxidation all increase as curvilinear functions of increasing work rate and that lactate Ra, lactate Rd, and blood lactate concentrations are not zero at low exercise intensities. $\dot{V}O_2$ also increases linearly with increasing work rate without evidence for an "bypoxic threshold."

carbohydrate oxidation measured under steady state conditions at the different work rates.

Hence these studies confirm (i) that blood lactate concentrations are not zero at rest; (ii) that there is a measurable lactate Ra at rest and at low exercise intensities; (iii) that lactate Ra and Rd both rise with increasing work rate until a submaximal $\dot{V}O_2$ is reached, at which Ra exceeds Rd causing blood lactate concentrations to rise; (iv) that the work rate at which lactate Ra exceeds Rd corresponds to a $\dot{V}O_2$ that is rising as a linear function of increasing work rate without evidence for an "hypoxic threshold;" and (v) that lactate Ra, Rd, blood lactate concentrations, and rates of carbohydrate oxidation and of ventilation (30) all increase as curvilinear functions of work rate suggesting perhaps that a common metabolic sequence links these phenomena.

Indeed the fourth source of refutation of the traditional model is a more reasoned explanation for the metabolic sequence that might explain these curvilinear relationships. It is based on the more modern understanding of how protons are generated with increasing rates of carbohydrate oxidation during exercise. Central to this theory is the contention that proton production during exercise is a continuous and not a threshold phenomenon.

Equations 1 and 2 show the original interpretation of how anaerobiosis induces the conversion of glucose to lactic acid with the production of two protons that are buffered in the blood by bicarbonate ions with the release of CO_2, which then stimulates ventilation at the hypothetical ventilation threshold. This interesting hypothesis is threatened by its inaccuracies.

For the critical point ignored in equation 1 is that the conversion of glucose to lactate generates ATP. When the ionic charges associated with this conversion are added to the original equation, it is clear that there is no net proton production when glucose is converted to lactate (29,38,71) (eq. 3). Hence the question arises: From where might the protons arise during accelerated glycolysis?

$$\text{Glucose} + 2\text{Mg ADP}^- + 2\text{Pi}^{2-} \rightarrow 2\,\text{lactate}^- + 2\,\text{MgATP}^{2-} \quad [3]$$

One argument (29,38) holds that protons accumulate during high intensity exercise because such exercise must be fueled almost exclusively by carbohydrate metabolism. The conversion of glucose or glycogen to lactate or pyruvate generates ATP; the protons required for that ATP synthesis are generated by the steps of the glycolytic pathway. Subsequent hydrolysis of glycolytically-produced ATP releases protons that are not needed for the resynthesis of ATP by that pathway (eq. 4). This contrasts with the resynthesis of ATP via either oxidative phosphorylation or net creatine phosphate breakdown. In those pathways the H^+ ions arising from ATP hydrolysis are re-consumed in ATP resynthesis:

$$\begin{array}{lcl} & \text{MgATP}^{2-} \rightarrow \text{MgADP}^- + \text{P}_i^{2-} \rightarrow & \text{H}^+ \\ \text{pyruvate}^- & | \qquad\qquad | \qquad | & \text{glucose} \\ \text{or} & \text{---------------------} & \text{or} \\ \text{lactate}^- & & \text{glycogen} \end{array} \quad [4]$$

At first, the protons generated by high rates of glycolytic ATP breakdown are (i) taken into the mitochondria with pyruvate, (ii) used in the reduction of pyruvate to lactate via the cytosolic pyruvate$^-$ + NADH + $H^+ \leftarrow\rightarrow$ lactate + NAD^+ equilibrium, and (iii) buffered by intracellular histidine residues and by inorganic phosphate. However, unbuffered intracellular protons leave the cell via the sarcolemmal Na^+/H^+ exchangers and the H^+ + lactate$^-$ symport. As a result, this model predicts (i) that muscles "dump" lactate to remove H^+ into the bloodstream whenever carbohydrate utilization is increased to provide energy for exercise of very high intensity and (ii) that the respiratory compensations for "lactic acidosis" are not "threshold" responses to muscle hypoxia as has been proposed (109–111,113).

Indirect evidence for this postulate has been provided by MacRae et al. (70) who studied the effects of training on blood lactate concentrations, lactate Ra and Rd, and the ventilatory responses to exercise in previously untrained cyclists.

Figure 10 (*left panel*) shows that this training program greatly reduced the blood lactate concentrations at any submaximal work rate. However, the effect of training on the ventilatory response to exercise was relatively modest. Thus, training dissociated the relationship between changes in blood lactate concentrations and in ventilation predicted by the anaerobic threshold hypothesis. A number of other interventions have also dissociated these two variables (41,45,57,118). Perhaps the most telling such

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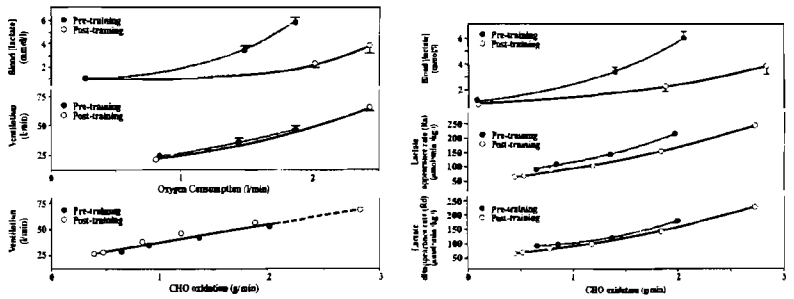

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Figure 10—Effects of training on blood lactate concentrations and rates of ventilation with increasing $\dot{V}O_2$, as well as the relationship between the rates of ventilation and carbohydrate oxidation (*left panel*). Note that the linear relationship between the rates of ventilation and of carbohydrate oxidation is unaltered by training. *Right panel* shows the effects of exercise training on blood lactate concentrations and on lactate Ra and lactate Rd at increasing rates of carbohydrate oxidation. Data from reference 70. MacRae, H. S-H., T. D. Noakes, and S. C. Dennis. Role of decreased carbohydrate oxidation on slower rises in ventilation with increasing exercise intensity after training. *Eur. J. Appl. Physiol.* 71:523–529, 1995.

finding is that patients with McArdle's syndrome who lack the enzyme, glycogen phosphorylase, and whose skeletal muscles are therefore unable to produce lactate during exercise nevertheless show a "ventilation threshold" (41), perhaps resulting from some residual capacity to generate glycolytic ATP. Interestingly, a linear relationship between ventilation and the rate of carbohydrate oxidation was unchanged after training (Fig. 10, *left panel*). Figure 10 (*right panel*) shows that training reduces the blood lactate concentration at any rate of carbohydrate oxidation because lactate Ra is reduced whereas lactate Rd is unchanged (68).

The finding that the rates of ventilation and of carbohydrate oxidation are linearly related both before and after training can be explained by a physiological model in which the progressive curvilinear increase in carbohydrate oxidation during ramp exercise causes a progressive increase in the rate of H^+ production according to equation 4. In turn, this continual increase in proton production causes the exponential increase in ventilation with increasing work rate, a relationship that was unaffected by exercise training.

In summary, there are four crucial sources of refutation for the anaerobic threshold hypothesis. In particular, the terminology is incorrect; there is no identifiable "hypoxic threshold" during progressive exercise; studies of lactate kinetics show that blood lactate concentrations rise during exercise when lactate Ra exceeds lactate Rd; and, finally, the conversion of glucose or glycogen to lactate does not produce H^+. Rather, utilization of glycolytically-produced ATP releases the H^+ which are reconsumed only if the ATP is regenerated via the oxidative mitochondrial pathways. Hence H^+ production by muscle is not a threshold phenomenon but increases progressively with increasing rates of carbohydrate and glycolytic ATP use. Thus, all the phenomena traditionally described on the basis of an "anaerobic threshold," might be better explained by the progressively increasing rate of carbohydrate oxidation that occurs during ramp exercise of increasing intensity.

Therefore, one might argue that the lactate "anaerobic" threshold is a theoretical concept for which, like the Bassler hypothesis and the $\dot{V}O_{2max\text{-}Hill}$, there is currently no firm experimental support. Furthermore, no logical argument can be presented to support this specific conjecture. Rather, an alternate hypothesis is compatible with all the present observations.

4. Mitochondrial adaptations and exercise performance. If oxygen delivery to muscle determines exercise performance, then it has been logical to assume that any training adaptations that improve exercise performance, must also enhance oxygen delivery to, and utilization by, the active muscles during exercise. The universal finding that the $\dot{V}O_{2max}$ increases with training (3,98), is compatible with this interpretation.

Furthermore, since the earliest study showing that chronic exercise produces mitochondrial adaptations in those skeletal muscles that are active during the training program (28,52), it has been assumed that these changes also explain the training-induced adaptations in skeletal muscle metabolism and performance. But such cross-sectional studies are unable to prove this assumption. To verify that skeletal muscle mitochondrial adaptations cause the training-induced changes in metabolism and performance, it is necessary to show that mitochondrial changes, metabolism, and performance all change in the same temporal sequence and to a similar degree during longitudinal training studies. But such longitudinal studies have shown that training-induced changes in exercise performance or metabolism can occur without or before there are measurable skeletal muscle mitochondrial adaptations.

For example, in one study (64) rats were trained for either 4, 8, or 12 wk and sequential changes in their run time to exhaustion during maximum and submaximum exercise, and in their skeletal muscle oxidative capacity

were measured. The unexpected finding was that run time to exhaustion increased before skeletal muscle oxidative capacity altered.

Similarly, a study in humans showed that the addition of six to eight sessions of very high intensity training to their usual endurance-type training program substantially improved the performance of cyclists during a simulated 40-km time trial in the laboratory (112). That training *effect occurs without measu*rable changes in the activities of key skeletal muscle mitochondrial and glycolytic enzymes (113).

Similarly, training-induced changes in metabolism during exercise can occur before skeletal muscle mitochondrial enzyme activities increase. This has been shown most clearly by Phillips et al. (90,91). Their studies show that five consecutive daily training sessions, each of 2 h duration at 60% of $\dot{V}O_{2max}$, altered the metabolic response to exercise in previously untrained humans. These adaptations occurred before there were measurable changes in skeletal muscle mitochondrial enzyme activities. These metabolic adaptations were more marked after 30 d of training, by which time the first changes in the activities of the mitochondrial enzymes, SDH, MDH, and B-HAD, were measured.

Thus, the conclusion from these studies must be that factors other than increased skeletal muscle mitochondrial enzyme activities explain the early changes in exercise performance and metabolism that result from aerobic endurance training. The point is that skeletal muscle adapts in many ways to exercise training and the intellectual challenge is to determine (i) which of those changes explain the training-induced alterations in metabolism and performance and (ii) what are the real physiological and biochemical effects of the increased skeletal muscle mitochondrial enzyme activities. For example, studies showing that weight training can increase aerobic endurance performance and $\dot{V}O_{2max}$ suggest that skeletal muscle strength may be a factor influencing endurance capacity (82).

5. A high carbohydrate diet maximizes performance during training. The belief that a high carbohydrate diet is essential for the maintenance of optimal daily training loads stems from the original research that followed the introduction of the skeletal muscle biopsy technique in Sweden in the 1960's (1,11,46). This research established that the higher the carbohydrate content of the diet during the last few days before an exhausting exercise bout, the higher the initial muscle (and liver) glycogen content and the longer the duration of exercise that could be sustained until fatigue (Fig. 11). More modern studies confirm that a high carbohydrate diet can also increase performance during a set exercise task in which the speed of completion, rather than the duration of exercise, is the measure of performance (94). The logical assumption is that the ideal diet for a single exercise bout to exhaustion would also be optimum for

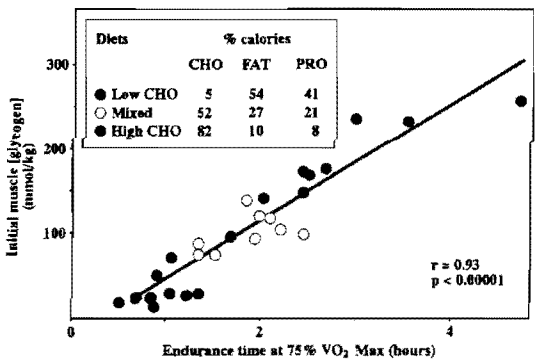

Figure 11—There is a linear relationship between the starting muscle glycogen content and the duration for which a subsequent bout of endurance exercise can be sustained. From data of reference 11. Bergstrom, J., L. Hermansen, E. Hultman, and B. Saltin. Diet, muscle glycogen, and physical performance. *Acta. Physiol. Scand.* 71:140–150, 1967.

repeated daily bouts of exercise, that is, for daily training. Thus, the consensus opinion is that a diet rich in carbohydrate (>70% of total energy intake) should be ingested by all endurance athletes during training (1,11,18,23,44, 79,83).

Three potential sources refute this consensus.

First, athletes do not eat such rich carbohydrate diets during training. In a review of the literature, Hawley et al. (44) show that the percentage of the energy intake provided by carbohydrate in the habitual diets of athletes has not changed materially over the past 50 years. This is despite the recent intrusion of sports nutritionists dedicated to the promotion of high carbohydrate diets for all endurance athletes. Thus, the diets of some marathon runners in the 1948 Olympics contained 44% carbohydrate (12); a more recent study found that carbohydrate contributed only 52% of the dietary energy intake of a group of marathoners (19). Figure 12 shows that these findings are representative of all the reported studies. This information is important because it conflicts so absolutely with what athletes are told. It is important that we should discover whether our scientific advice is incorrect.

The second source of refutation are interventional studies that have measured the effects of alterations in dietary carbohydrate content on performance during training. Two such studies (63,103) have shown that performance during training was not materially different in athletes eating diets with either high or low carbohydrate contents. Sherman and Wimer (101) have concluded that: "The hypothesis that insufficient dietary carbohydrate during training causes low muscle glycogen concentrations that, in turn, cause diminished training or performance capabilities and overreaching or staleness, is not strongly supported by the literature."

The third potential source of refutation are studies

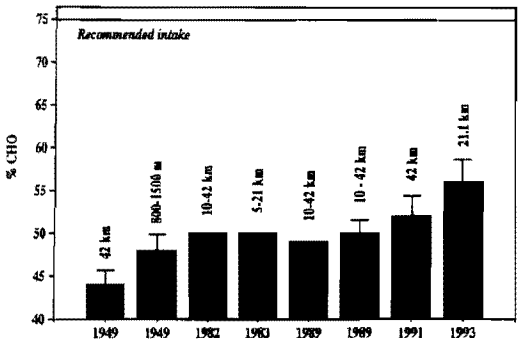

Figure 12—Actual vs recommended dietary carbohydrate intakes reported in studies of endurance athletes from 1949–1993. Note that the percentage contribution of carbohydrate to the daily dietary energy intake has not changed materially in the last half century and is substantially less than is currently recommended. Complete references to each individual study can be found in reference 44. Hawley, J. A., S. C. Dennis, F. H. Lindsay, and T. D. Noakes. Nutritional practices of athletes: are they sub-optimal? *J. Sports Sci.* 13:S75–S87, 1995.

showing that a period of adaptation to a low carbohydrate diet may improve subsequent performance during prolonged exercise. An early study in our laboratory showed that subjects who adapted to a low (7%) carbohydrate diet for 2 wk were able to exercise for longer during an exercise bout at 60% $\dot{V}O_{2max}$ that was preceded by bouts of high intensity exercise (65). Similarly, Muoio et al. (76) showed that endurance time at 70–85% $\dot{V}O_{2max}$ was increased in athletes who had pre-adapted to a high (40%) fat diet.

Pre-adaptation to a high fat diet may enhance performance by inducing specific adaptations in the skeletal muscle mitochondrial enzymes that increase the capacity to oxidize fat during exercise (20). This adaptation may explain why subjects who have adapted to a high fat diet continue exercising with muscle glycogen concentrations that are lower than those causing exhaustion in subjects who habitually ingest high carbohydrate diets (65).

Therefore, the conclusion must be that the ergogenic effects of a high carbohydrate diet are established only for acute ingestion during the last 3 or more days before a single bout of prolonged endurance exercise. There is a need to study the ergogenic effects of dietary manipulations other than a high carbohydrate diet, especially in activities that last more than 3–4 h and in which a greater capacity for fat oxidation might enhance performance, especially when muscle glycogen concentrations are low.

CONCLUSION

The English scientist of the last century, Thomas Huxley (58, p. 3), wrote that: "The known is finite, the unknown is infinite; intellectually we stand on an island in the middle of an illimitable ocean of inexplicability. Our business in every generation is to reclaim a little more land."

I come from the city of Cape Town, which is situated on a small peninsula surrounded by two great oceans at the very base of Africa. From that isolated peninsula so far away from the intellectual capitals of the world, I have fashioned a challenge for exercise scientists to reclaim some more land in our young discipline. I have indicated the debt that I owe to the United States and to this College and its members. I have tried to repay some of that debt by challenging especially the young members of our College to be true to the aims and methods of scientific endeavor as I understand them. The core challenge is always to question the very beliefs that we hold most dear.

The central conjecture that I have questioned originates from the statement by Hill et al. in the 1920's to the effect that: "The oxygen intake (during maximal exercise) may attain its maximum and remain constant merely because it cannot go any higher owing to the limitations of the circulatory and respiratory systems." This conjecture has exerted a profound influence on the teaching of exercise physiology for the past 70 years. It predicts a physiological model in which exercise, especially of high intensity, causes the oxygen demand of the active muscles to outstrip the available oxygen supply, requiring the muscles to contract in the face of a developing anaerobiosis. This physiological model also predicts: that anaerobic conditions in muscle terminate maximal exercise; that the onset of anaerobiosis occurs at the anaerobic or lactate threshold, causing blood lactate concentrations to rise during submaximal exercise; and that the principal effect of exercise training must be to induce skeletal muscle mitochondrial and capillary adaptations that increase the capacity of those muscles to use a limiting oxygen supply during exercise.

Yet the contradictory evidence is absolute. Hill's original conclusions were not supported by his own findings. Therefore, the original basis for this physiological model is without substance. If the basis for the model is in doubt, then it behooves us to question vigorously the further predictions of that original model.

The alternate model proposes that skeletal muscle contractile function is regulated by a hierarchy of controls specifically to prevent damage to any of a number of different organs. Severe anaerobiosis is one specific endpoint that must be thwarted so that irreversible rigor and necrosis in the active muscles is prevented. The challenge for exercise scientists is to understand how the body anticipates the potential for organ damage and how skeletal muscle contractile function is regulated specifically to preclude any such calamities.

No doubt many will be tempted to reject this new conjecture as the rantings of an irreverent and ill-educated foreigner. But that would be the most simple response because it does not require that one question

personal dogmas. Former United States President William Taft, who was himself raised in Cincinnati, the city hosting this year's J. B. Wolffe Memorial lecture, warned against this approach: "We cannot meet new questions nor build the future if we confine ourselves to the dogmas of the past."

This capacity to embrace new ideas and to challenge the dogmas of the past is perhaps the greatest treasure bequeathed to the world by the United States and Western culture. Columnist Jeff Wise (117) captured the importance of this influence: "If the West means anything at all, it is not a specific set of values, but a meta-value, an idea about ideas. It is about throwing open the gates to the richness of world culture and daring to embrace the best of what you find. The prospect can be intimidating; it promises wholesale cultural changes, possibly radical ones."

Perhaps the dare for our young exercise scientists is to be open to these ideas from Africa, regardless of the wholesale, perhaps intimidating intellectual challenges that they may pose. We will best serve our science if we continuously question all our beliefs, regardless of their origin or how hallowed they have become.

Besides those already acknowledged, persons too numerous to identify individually have influenced my career. To all who have participated in developing the sports sciences at the southern tip of Africa, including many international colleagues from the ACSM, there is a special debt of gratitude. My tutors at the Medical School of the University of Cape Town inspired a desire for excellence; my colleagues and our students in the Department of Physiology and the Sports Science Institute of South Africa provide the daily incentive to continue in that quest. The dedicated financial support of the University of Cape Town, the Medical Research Council of South Africa, the Liberty Life Insurance Company, the Founding Donors of the Sports Science Institute of South Africa, and a host of nutritional and pharmaceutical companies dedicated to the furtherance of scientific study have provided the material sustenance to sustain a dream. Most importantly, my wife, Marilyn Anne, and our children, Travis and Candice, have played pivotal roles by sharing life's joys and its tribulations with equanimity, love, friendship, and support.

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Editor's Note: In 1997, we published the 1996 J. B. Wolffe Memorial Lecture by T. D. Noakes entitled "Challenging Beliefs: *Ex Africa Semper Aliquid Novi*" (*Med. Sci. Sports Exerc.* 29:571–590, 1997) and by request a response to the challenge by Basset and Howley entitled "Maximal Oxygen Uptake: 'Classical' versus 'Contemporary' Viewpoints" (*Med. Sci. Sports Exerc.* 29:591–603, 1997). As expected, Noakes decided to rebut the response of Bassett and Howley, and the following presentation is his rebuttal.

As Editor-in-Chief, I encourage scientific debate, especially when our fundamental concepts are challenged and new concepts are proposed based upon sound principles of scientific inquiry. In my opinion, the arguments of Noakes should be heard, digested, and subsequently investigated as to their scientific fallibility. The aforementioned articles and the following presentation are the initial process in the evaluation of Noakes' concepts. As a follow-up to these presentations, I have recommended a debate to the 1999 ACSM Annual Meeting Program Committee, under the auspices of the Cardiorespiratory Interest Group, on the topic "Why Skeletal Muscles Cannot Become Anaerobic During Progressive Maximal Exercise Testing." If accepted by the Program Committee, the debate will be chaired by Bengt Saltin, M.D., and the discussants will be Pro—Timothy Noakes, M.D., and Con—Brian J. Whipp, Ph.D. This debate will be another part of the scientific inquiry necessary to address the challenge of Noakes. I encourage all our members and readers to become aware of the issues raised and in the future to accept or reject the concepts developed by Noakes based upon the weight of scientific evidence generated.

I am constantly reminding my students that to have one's fundamental concepts challenged requires us, as scientists, to respond with factual reasons as to why the challenge is incorrect and not respond that the challenge is incorrect because it does not fit what one's personal reference base expounds. In my opinion, the challenge by Noakes is one that we as members of the scientific community, which accepts the concept of maximum oxygen consumption ($\dot{V}O_{2max}$) and its measurement as a parameter of physiological function, must address and one that may lead us to accept a revised definition of $\dot{V}O_{2max}$.

Peter B. Raven, Ph.D., FACSM
Editor-in-Chief

Maximal oxygen uptake: "classical" versus "contemporary" viewpoints: a rebuttal

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ABSTRACT

NOAKES, T.D. Maximal oxygen uptake: "classical" versus "contemporary" viewpoints: a rebuttal. *Med. Sci. Sports Exerc.*, Vol. 30, No. 9, pp. 1381–1398, 1998. Bassett and Howley contend that the 1996 J. B. Wolffe lecture is erroneous because: 1) A. V. Hill did establish the existence of the "plateau phenomenon," 2) the maximum oxygen consumption ($\dot{V}O_{2max}$) is limited by the development of anaerobiosis in the active muscle, and 3) endurance performance is also determined by skeletal muscle anaerobiosis because the $\dot{V}O_{2max}$ is the best predictor of athletic ability. As a result, 4) cardiovascular and not skeletal muscle factors determine endurance performance. They further contend that Hill's "scientific hunches were correct," requiring "only relatively minor refinements" in the past 70 yr. But the evidence presented in this rebuttal shows that Hill neither sought nor believed in either the "plateau phenomenon" or the concept of the individual maximum oxygen consumption. These twin concepts were created by Taylor et al. (97) in 1955 and erroneously attributed to Hill. Rather Hill believed that there was a universal human $\dot{V}O_{2max}$ of 4 $L \cdot min^{-1}$. His error resulted from his incorrect belief that the real $\dot{V}O_2$, unmeasurable because it includes a large "anaerobic component," rose exponentially at running speeds greater than 13.2 $km \cdot h^{-1}$. But Hill and his colleagues were indeed the first to realize the danger that a plateau in cardiac output (CO) and hence in $\dot{V}O_2$ would pose for the heart itself. For unlike skeletal muscle, the pumping capacity of the heart is both dependent on, but also the determinant of, its own blood supply. Thus, if the CO reaches a peak causing the "plateau phenomenon," the immediate

cause of that peak will have been a plateau in myocardial oxygen delivery, causing a developing myocardial ischemia. The ischemia must worsen as exercise continues beyond the supposed $\dot{V}O_2$ "plateau." To accommodate this dilemma, Hill and his colleagues proposed a governor "either in the heart muscle or in the nervous system" necessary to prevent myocardial ischemia developing during maximal exercise. This governor would cause maximal exercise to terminate before the development of a plateau in either coronary flow, CO, or $\dot{V}O_2$, or the onset of skeletal muscle anaerobiosis. Accordingly, a new physiological model is proposed in which skeletal muscle recruitment is regulated by a central "governor" specifically to prevent the development of a progressive myocardial ischemia that would preceed the development of skeletal muscle anaerobiosis during maximum exercise. As a result cardiovascular function "limits" maximum exercise capacity, probably as a result of a limiting myocardial oxygen delivery. The model is compatible with all the published findings of cardiovascular function during exercise in hypobaric hypoxia, in which there is a greater likelihood that myocardial hypoxia will develop. **Key Words:** $\dot{V}O_{2max}$, ANAEROBIOSIS, ANAEROBIC THRESHOLD, OXYGEN DEBT, PLATEAU PHENOMENON, A. V. HILL, CARDIO-VASCULAR SYSTEM, SCIENTIFIC METHODS

In the written address delivered by his son at the opening of the Institute in Paris that would bear his name in perpetuity, Louis Pasteur implored his audience to "Worship the spirit of criticism" (73). If we are to advance the exercise sciences, then each J. B. Wolffe lecture should, at least in part, excite that spirit of criticism.

I am therefore most thankful to my North American colleagues, Drs. Bassett and Howley (4), for fashioning the contrary arguments to aspects of the 1996 J. B. Wolffe lecture and other of my writings. Such criticisms are an essential ingredient of the scientific process when they identify issues that require more careful analysis and explanation, thereby encouraging a more critical introspection. However, it is my view that Bassett and Howley's rebuttal was based upon an erroneous analysis of the published record, including my own, and contains critical errors of fact and interpretation. Also, the authors appeared to have missed two important subthemes of the J. B. Wolffe lecture.

The first is that data can only be interpreted in the framework of a specific model. In the words of Stephen Hawking (26): "How can we know what is real, independent of a theory or model with which to interpret it?" The truth is "true" only in the context of the specific model through which it is affirmed. Hence the real significance of any experimental study is the wisdom it reveals about the model used to interpret its findings. Throughout their review, Bassett and Howley (4) repeatedly use their model, which I term the cardiovascular/anaerobic model of exercise physiology and athletic performance, to interpret data which they then claim "proves" their model. But a model cannot be used to prove itself. This is precisely why information that refutes the predictions of a model is so valuable.

Second, a model should be considered correct only for as long as it explains all the observed phenomena. When there is information to refute a model, then the scientist's duty is to retire that old and dilapidated model not to fortify it against all criticism.

The central theme of the J. B. Wolffe lecture was an analysis of the cardiovascular/anaerobic model of exercise physiology and athletic performance, which enjoys the support of the majority of exercise physiologists. The lecture included an analysis of the original studies (28,30–32,35–38) that created the model and presented some experimental evidence that refutes three inferences from the model. These inferences are: 1) that progressive muscle hypoxia limits maximal exercise performance, 2) anaerobiosis explains the onset of lactate production by skeletal muscles at the "anaerobic threshold," and 3) that mitochondrial adaptations alone explain changes in performance with endurance training.

In their response, Bassett and Howley (4) argue that I have drawn erroneous conclusions from the studies of Hill and his colleagues and review other studies which, in their assessment, "prove" the cardiovascular/anaerobic model. These studies "prove" that the maximum oxygen consumption ($\dot{V}O_{2max}$) is indeed limited by the development of anaerobiosis in the active skeletal muscles. So, too, is endurance performance because the $\dot{V}O_{2max}$ is the best predictor of athletic ability. Finally, they wish to refute my earlier writings from other sources that speculate on those factors other than skeletal muscle oxygen delivery that may determine athletic performance; they did not recognize that the J. B. Wolffe lecture included an updated and substantially revised version of those speculations. More important to this debate was their failure to explain why no studies have yet refuted the cardiovascular/anaerobic model. As Einstein wrote of his own theories: "No amount of experimentation can ever prove me right; a single experiment may at any time prove me wrong" (17). Thus the authentic intellectual challenge for Bassett and Howley was to contest the refutations to the cardiovascular/anaerobic model that I presented, not to ignore these and instead to rehash conventional arguments that "prove" the traditional model and which are, in any case, available elsewhere. I present my rebuttal to Bassett and Howley's response to the Wolffe lecture structured according to the topics they have argued.

A. V. HILL'S CONCEPT OF THE $\dot{V}O_{2MAX}$

Did Hill and his colleagues establish the plateau phenomenon? I first became interested in the plateau phenomenon while writing the first edition of *Lore of Run-*

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ning (66). I was drawn to the topic by a statement in Costill's book (11): "Since the early work of Hill and Lupton (35), exercise physiologists have associated the limits of human endurance with the ability to consume larger volumes of oxygen during exhaustive exercise" (pp. 25–26). While this statement is factually correct, an analysis of the original publications of Hill et al. (35–38) revealed that none had studied the relationship between oxygen consumption and endurance performance. In fact, the oxygen consumption of seven athletes running at speeds up to about 17 $km \cdot h^{-1}$ was essentially all of relevance that was measured. From these rather meager data, a series of assumptions, subsequently described and analyzed in detail, generated a hypothesis linking oxygen consumption to endurance performance. The reality was somewhat less than the expectation generated by Costill's text.

During my analysis, I happened upon Hill's circular argument (Fig. 2 in 69) in which he used his personal feelings incorrectly to identify a supposed "plateau phenomenon" when he ran at 16 $km \cdot h^{-1}$ for 250 s (Fig. 2 in (68); Fig. 3 in (69)) plus supporting text). These findings formed the basis of a 1987 ACSM tutorial lecture, the publication (68) of which has been quite extensively referenced previously without major rebuttal. In response, Bassett and Howley briefly note that "Noakes (68,69) criticizes Hill, contending that he lacked the data to show a plateau in $\dot{V}O_{2max}$ (sic) with increasing running speeds. However, Table 1 and Figure 2 show the original data from A. V. Hill's paper (38). Clearly A. V. Hill did demonstrate a plateau in himself and also in subject J (whose O_2 was nearly identical at 4.25 and 4.98 $m \cdot s^{-1}$ despite a marked increase in oxygen requirement). In his 1988 article (68), Noakes chose to re-fit Hill's velocity versus $\dot{V}O_2$ data using a linear equation. We are puzzled by this reinterpretation of A. V. Hill's data since it appears to be biased toward the view that a plateau does not exist. Hill was not guilty of "circular reasoning" as Noakes suggests but rather conducted experiments that clearly demonstrated the $\dot{V}O_2$ plateau." Unfortunately Bassett and Howley have not applied due care in their analysis, nor was the contentious data correctly referenced. They supplied page numbers from an earlier companion paper by Hill et al. (37).

However, the contentious data (Table 1 and Figure 2 in their response) comprise 28 measurements of oxygen consumption ($\dot{V}O_2$) in seven different athletes. Of these 28 measurements, 14 were collected in Hill himself (subject H). The remaining 14 measurements were collected in six other subjects, three each in four subjects and one each from the final two subjects. Hill et al. (38) admit to modifying four of the 14 results in athletes other than Hill. In their words: "The observations on the two latter have been 'reduced' to the same body-weight as A. V. H. before plotting." They do not explain how these data were transformed, why such transformation was necessary, or whether that transformation influenced their conclusions.

For my original paper (68), I considered that only the 14 unmodified measurements on Hill provided sufficient material for reliable retrospective analysis. I remain unconvinced that one can reasonably expect to identify a "plateau

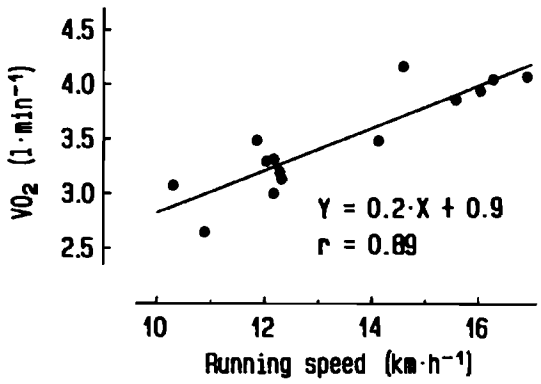

Figure 1—The 14 data points for $\dot{V}O_2$ measured at different running speeds in A. V. Hill (38). There is a linear relationship between $\dot{V}O_2$ and running speed without evidence of a "plateau phenomenon." Note the large (16%) variation in measured $\dot{V}O_2$ at 12 $km \cdot h^{-1}$ and the discrepantly high $\dot{V}O_2$ measured at 14.5 $km \cdot h^{-1}$. Notice also the discrepancy between the predicted $\dot{V}O_2$ with increasing running speed (Line A; Fig. 2) with the actually measured $\dot{V}O_2$ in Hill at increasing running speeds (this Figure). Reference 38. Hill, A. V., C. N. H. Long, and H. Lupton. Muscular exercise, lactic acid, and the supply and utilization of oxygen: parts VII-VIII. *Proc. R. Soc. B* 97:155–176, 1924.

phenomenon" and hence sustain an influential physiological theory from a total of three measurements of $\dot{V}O_2$ in each of four athletes, and one each in another two. However, it appears that Bassett and Howley have no such concerns. They accept these data as absolute proof of the "plateau phenomenon" because: 1) Hill's data showed a "plateau phenomenon," and 2) the $\dot{V}O_2$ of one athlete (J) increased by only 30 $mL \cdot min^{-1}$ when his running speed increased by 0.7 $m \cdot s^{-1}$. To arrive at this conclusion, they discarded: 1) the contrary evidence that the "plateau phenomenon" did not occur in the three other subjects (75% of the sample) in whom three data points were measured (subjects S, W, and C.N.H.L) and 2) my analysis of the other set of measurements (35) which irrefutably established that Hill did not exhibit a "plateau phenomenon" when running at 16 $km \cdot h^{-1}$ for 250 s (Fig. 2 in (68); Fig. 3 in (69)). Such selective analysis, in particular their reluctance to acknowledge, let alone refute, Figures 1–3 in the J. B. Wolffe lecture (69), does not provide adequate data for an observer of this debate to arrive at an informed decision.

We return to the 14 measurements made on Hill (Table 1 in (4). Those data are reproduced here in Figure 1. The relationship between $\dot{V}O_2$ and running speed is described by the linear equation ($y = 0.7x + 0.9$; $r = 0.89$) without evidence for a "plateau phenomenon," as originally argued (68). Therefore, I contend that Bassett and Howley have failed to provide evidence to support their contention that I erred and that Hill and his colleagues were "not guilty of circular reasoning" and "clearly demonstrated the $\dot{V}O_2$ plateau."

But there are additional concerns about the research methods common to Hill and his colleagues and subsequent researchers and should have been acknowledged by Bassett and Howley, given their interest in how a maximal effort is

identified (41). Were Hill and his colleagues to submit these data for publication today, an indifferent reviewer would inquire whether the "plateau phenomenon," detected by Bassett and Howley in those classic data, was an artifact of the specific methods used by Hill and his colleagues. For example, to prove the plateau phenomenon with an interrupted protocol in which a single $\dot{V}O_2$ is measured at each exercise load, that sample must capture the peak $\dot{V}O_2$ for that work rate. This is especially relevant at the highest work rates when the duration of exercise is shorter so that a true steady state may never be reached.

Hill and his colleagues sampled expired air for 30 s beginning about 220 s after the onset of exercise. They did not prove that this method captures the peak $\dot{V}O_2$ for each particular work rate (running speed). Hence additional samples measured later than 220 s after the onset of exercise might have revealed yet higher $\dot{V}O_2$ in Hill. A later study (97) suggests that this is unlikely at the range of work rates tested by Hill and his colleagues. Yet Hill and his colleagues did not exclude this possibility, which could certainly apply at the much higher work rates of which modern athletes are capable.

But Hill and Lupton (35) were well aware of an upward drift in $\dot{V}O_2$ during more prolonged steady-state exercise. When Hill ran at 240 m·min^{-1} (14.4 km·h^{-1}), his $\dot{V}O_2$ increased from 3590 to 3910 mL·min^{-1} from the third to the 26th minute. Hill concluded that this could probably be "attributed to a painful blister on the foot causing inefficient movement" ((35), p. 155) and hence did not consider alternate explanations. Interestingly, Hill's $\dot{V}O_2$ (53 mL·kg^{-1}·min^{-1}) at the end of that exercise was close to his supposed $\dot{V}O_{2max}$ of 57 mL·kg^{-1}·min^{-1} when he ran at 17 km·h^{-1} for only 250 s (Figs. 1 in (68, 69)). Hill almost certainly never established his true $\dot{V}O_{2max}$ (Fig. 2 in (68); Fig. 3 in (69)).

In their study Taylor et al. (97) identified two other factors that could interfere with the $\dot{V}O_{2max}$ measured with the methods of Hill and his colleagues. First, any reduction in the rate at which $\dot{V}O_2$ increased at the onset of exercise "may result in apparent declines in the maximal oxygen intake . . . which are in reality only the reflection of the fact (that) the rate of increase in oxygen intake is smaller than normal" (p. 79).

The second factor was improvements in running economy that would reduce the $\dot{V}O_2$ at any workload and hence the $\dot{V}O_{2max}$ and that could also theoretically induce an artifactual "plateau phenomenon," as discussed subsequently. But the major criticism, raised previously (68,69), was that Hill should have run at speeds faster than 17 km·h^{-1} if he wished to prove that his $\dot{V}O_2$ had indeed leveled off at either 16 km·h^{-1} (Figs. 1 in (68, 69)) or at 17 km·h^{-1} (Fig. 1). The reasons why Hill considered this unnecessary are discussed subsequently.

The question that begs an answer is: Why did Hill and his colleagues include all 28 measurements for their analysis and not just the 14 that I have included in Figure 1? The answer provides the astonishing realization, not previously identified, of what exactly Hill and his colleagues did conclude. For their conclusions were quite different from those that all others (11,53–55,67,82,83,97,101,103) have presented retrospectively.

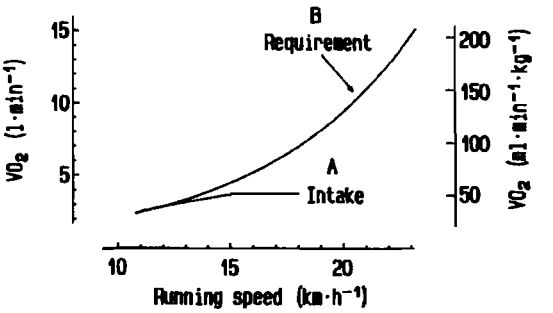

Figure 2—Hill and Lupton (35) predicted that the relationship between $\dot{V}O_2$ and running speed was exponential and comprised a limiting real oxygen consumption of 4 L·min^{-1} (Line A) and an accumulating oxygen debt. Together these reduced the renal oxygen cost of running at different speeds (Line B). The universal $\dot{V}O_{2max}$ of 4 L·min^{-1} was achieved at a running speed of 13.2 km·h^{-1}. Higher running speeds could be achieved only because of a large capacity for anaerobic metabolism in humans causing high rates of muscle glycogen use and heat accumulation. Because many athletes are able to run faster than 13.2 km·h^{-1} for prolonged periods, this model predicts that the "plateau phenomenon" can be present for extended periods (minutes to hours) before it causes the termination of exercise. Reference 35. Hill, A. V. and H. Lupton. Muscular exercise, lactic acid, and the supply and utilization of oxygen. *Q. J. Med.* 16:135–171, 1923.

For Hill and his colleagues did not search for the plateau phenomenon, as do modern exercise physiologists, by analyzing the successive measurements of $\dot{V}O_2$ in individual subjects as first suggested by Taylor et al. (97). Rather they considered the data as a collective and based their conclusion on the finding that no measured $\dot{V}O_2$ exceeded 4 L·min^{-1} in any of their studies. Hence their interpretation was that there is an absolute $\dot{V}O_{2max}$ of 4 L·min^{-1} in humans: "The oxygen intake attains its maximum value, which in athletic individuals of about 73 kilograms body weight *is strikingly constant (in the case of running) at about 4 L per minute*" (author's emphasis) ((38), p. 157); "The form, however, of the oxygen intake curve of Figure 1, *approaching a constant level of 4 L per minute*, makes it obvious that no useful purpose would be served by investigating higher speeds in this way" ((38), p. 157); and "The amount of work which the heart has to do is enormous, and it seems to reach its limit, in the case of athletic people, when *about 4 L of oxygen are taken in per minute*" ((31), pp. 230–231).

So I conclude that Hill et al. (38) interpreted the 28 measurements in their Figure 1 *as if all the data had come either from a single individual or from separate but physiologically identical individuals.* As no subject achieved a $\dot{V}O_2$ greater than 4 L·min^{-1}, they concluded that this was the universal limit (plateau) for *all* humans. Thus, paradoxically the authors of the very study that spawned the concept of the individual plateau phenomenon and the individuality of the $\dot{V}O_{2max}$ believed neither.

There were two contributory reasons for this fixation with a universal human $\dot{V}O_{2max}$ of 4 L·min^{-1}. The first was the

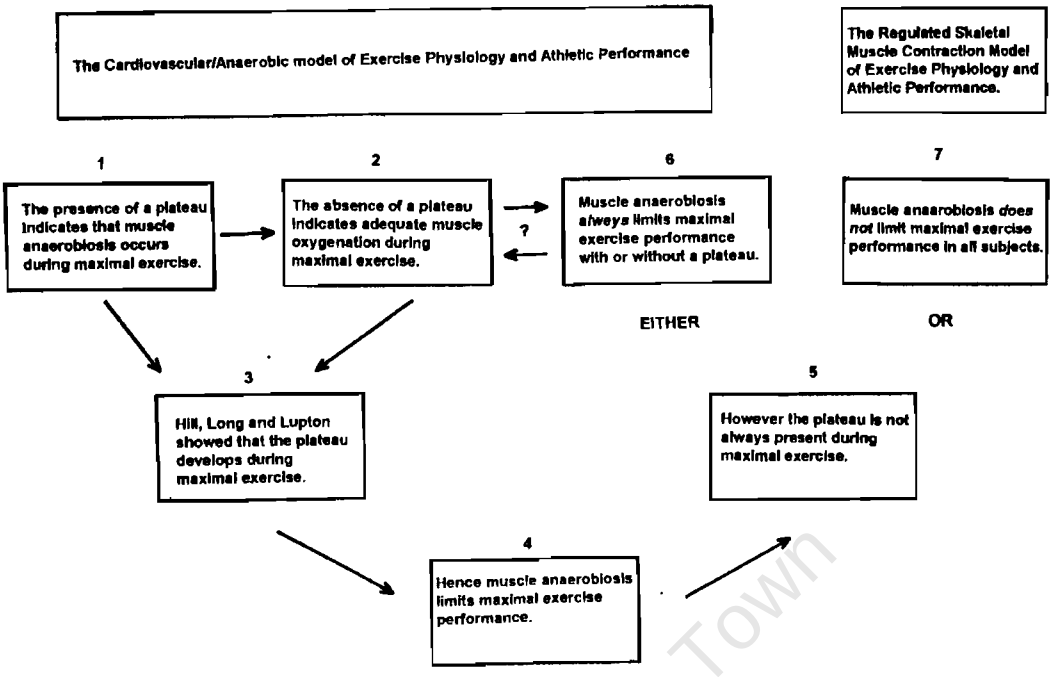

Figure 3—The logical conflict for the cardiovascular/anaerobic model caused by the finding that the plateau phenomenon does not occur in all subjects.

belief that $\dot{V}O_{2max}$ rises exponentially with increasing running speed as shown in Figure 2, reproduced from Figure 3 in Hill and Lupton (35). The figure incorporates their theory that the total oxygen demand of running (Line B) exceeds the measured $\dot{V}O_2$ (Line A) at speeds above 220 $m \cdot s^{-1}$ (13.2 $km \cdot h^{-1}$), this difference increased exponentially with further increments in speed. Hence they identified that the original "anaerobic threshold" or what became known as the "plateau phenomenon" began at a running speed of 13.2 $km \cdot h^{-1}$. Line A confirms their belief that the $\dot{V}O_{2max}$ in humans is 4 $L \cdot min^{-1}$. Interestingly, another publication (29) indicates that Hill knew that humans can run faster than 13.2 $km \cdot h^{-1}$ for many hours. The implication is that Hill and his colleagues must have concluded that skeletal muscle anaerobiosis can be present for hours before it causes the termination of exercise.

Interestingly, Bassett and Howley appear to misrepresent the original figure and the interpretation of Hill and his colleagues, because they write: "By measuring steady-state $\dot{V}O_2$ values at different speeds, (Hill and Lupton) demonstrated a linear relationship between running speed and $\dot{V}O_2$." In fact, their acceptance of the cardiovascular/anaerobic model made it impossible for Hill and his colleagues ever to consider a linear relationship between running speed and $\dot{V}O_2$, a logical inconsistency missed by Bassett and Howley. A similar inconsistency identified in the J. B. Wolffe lecture, concerns the absence of a plateau in $\dot{V}O_2$ at those submaximal work rates above the "anaerobic threshold" (Fig. 7 in (69)). Figure 2 shows that Hill and his colleagues were not similarly inconsistent because their line identifying the measured $\dot{V}O_2$ (Line A) does not increase at running speeds greater than their postulated "anaerobic threshold" at 13.2 $km \cdot h^{-1}$. But $\dot{V}O_2$ does increase linearly with increasing work rate (running speed) (14,68). As a result, the $\dot{V}O_2$ predicted by Hill and his colleagues becomes gravely inaccurate at faster running speeds and was close to 100 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ at 18 $km \cdot h^{-1}$ (Fig. 2) compared with the real value of about 62 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (Fig. 2 in (69)).

The effect of this error would be to implant the subconscious conclusion that it mattered not whether any individual's $\dot{V}O_{2max}$ was 4 (55 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ for the 73 kg Hill), 5 (68 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$), 6 (82 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$), or even 10 (134 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) $L \cdot min^{-1}$. For the unmeasured "anaerobic" contribution would exceed even that highest value at all running speeds above 20 $km \cdot h^{-1}$ (Fig. 2). Thus it would be pointless to measure $\dot{V}O_2$ (and hence $\dot{V}O_{2max}$) at faster running speeds, as the measured component would account for less than 50% of the "real" $\dot{V}O_2$. As Hill, Long and Lupton ((37), p. 135) wrote: "The maximum recorded oxygen intake in man, breathing air, and the total energy made available by the use of this amount in oxidizing foodstuffs is relatively *so small that no severe exercise of any kind could be taken were man limited, in his movements, to energy provided through the contemporary supply of oxygen*". Interestingly this is the precise model currently used to explain energy metabolism in exercising reptiles (5). But, unlike Hill and his colleagues, Bennett

realizes that this system does not allow activity other than of high intensity and short duration: "Anaerobic metabolism (in reptiles) appears to be particularly useful in and used for fueling intense activities of short duration but of great ecological importance (e.g., territorial defense, nest emergence" (p. 131).

Hill and his colleagues derived these incorrect conclusions exactly because their cardiovascular/anaerobic model predicts a running speed at which oxygen demand outstrips supply. Accordingly, they had to develop an elaborate method to predict the "anaerobic" contribution to energy consumption during running. They termed this anaerobic contribution the "oxygen debt" (30,35,37). More recently the term "excess postexercise oxygen consumption" (EPOC) has been preferred (20). As they found that the "oxygen debt" so measured increased as an exponential function of the work rate, so they were bound to conclude that the "real" oxygen cost of exercise rose exponentially with increasing running speed (Fig. 2). With the wrong model, they were bound to reach false conclusions.

Interestingly, Hill should have realized the enormity of his error and perhaps at some time later in his career he might have. For he used this model to extrapolate the durations for which different running speeds could be maintained by athletes with the universal $\dot{V}O_{2max}$ of 4 $L \cdot min^{-1}$ and an estimated "oxygen debt" capacity of 10–20 L. Whereas the model produced reasonable results for ordinary athletes running short distances (35), its predictions become progressively more inaccurate when applied to longer distances or to the world's best runners.

For example, his model forced Hill to predict that no athlete could sustain a running speed of 348 $yards \cdot min^{-1}$ (19.2 $km \cdot h^{-1}$) for much more than 10 min (31, p. 239). Yet another of his papers (29) showed that the world records for middle and long distance running events were held by athletes able to run faster and for longer than the limits imposed by Hill's model. For example, that model predicts that when running 10,000 m in 30 min, the then world record holder would have consumed 330 L of oxygen (Fig. 2) of which a maximum of 120 L (30 min at a $\dot{V}O_{2max}$ of 4 $L \cdot min^{-1}$) would have come from oxygen consumed during the event. This would leave an oxygen debt of 210 L as against their estimated maximum human oxygen debt of 10–20 L. Thus the model could not account for 200 L of oxygen, 60% of the total. The reptilian form of energy metabolism, surmised by Hill and his colleagues, was clearly unable to explain the performances of world-class human athletes of the 1920s.

This revelation could explain why Hill and his colleagues did not attempt to predict running speeds for races longer than 2 miles (35, p. 159) and why they did not discover the accepted physiological principle that athletes maintain different $\%\dot{V}O_{2max}$ at different racing distances (66,67). Rather they had to predict that speeds faster than 13.2 $km \cdot h^{-1}$ always required $100\%\dot{V}O_{2max}$ (Fig. 2).

Thermodynamic and metabolic considerations also indicate that, according to Hill's model, no world record holder could ever finish any running race lasting more than a few minutes. Standard calculations reveal that the body temperature of an athlete running at 18 $km \cdot h^{-1}$ would rise by 1°C every 2.8 min if the $\dot{V}O_2$ were 94 mL O_2 $kg^{-1} \cdot min^{-1}$ at that running pace. The rate of muscle glycogen use at that $\dot{V}O_2$ would have to be 46 $g \cdot min^{-1}$. Thus after 15 min of exercise, the athlete's core temperatures would have reached 42.5°C and his total body carbohydrate stores would have been depleted. The point is that these calculations could have alerted Hill to the magnitude of his error, particularly as he was conversant with the thermodynamics of muscle contraction (30,33,34). But Hill seems to have been more interested in formulating models than in verifying, or better refuting, their predictions (25). Perhaps the identification of these errors might have forced Hill to question his cardiovascular/anaerobic model of exercise physiology and human performance.

Figure 2 identifies a second discrepancy in the logic of Hill and his colleagues. For they had previously concluded that Hill's oxygen consumption equaled the oxygen demand at all running speeds below 16 $km \cdot h^{-1}$ (Figs. 1 in (68, 69) plus accompanying text). Indeed in Figure 1, Hill and his colleagues actually measured a linear increase in measured $\dot{V}O_2$ when Hill ran at speeds up to 17 $km \cdot h^{-1}$. Yet in their conceptual Figure 2, the oxygen demand exceeds supply at all running speeds above 13.2 $km \cdot h^{-1}$ so that at 16 $km \cdot h^{-1}$, the predicted "anaerobic" contribution contributes close to 50% of the expected $\dot{V}O_2$. These discrepancies result from the inconsistent logic used by Hill and his colleagues to identify the onset of "anaerobiosis" in their different studies.

Other factors that contributed to Hill and his colleagues' erroneous belief in a universal $\dot{V}O_{2max}$ of 4 $L \cdot min^{-1}$ resulted from the small size of the track on which their testing was performed, as well as the equipment they used. As reported previously (68,69), Hill acknowledged that their testing methods limited the peak running speeds they could study: "Greater speeds were not comfortable on our small track" ((38), p. 157); "We have been unable hitherto to continue the observations on H at the higher speeds, owing to the smallness of the track making faster running on it impossible" ((35), p. 159). Notable in their apparatus used to measure $\dot{V}O_2$ during exercise (Fig. 4 in (37)) is the small inlet aperture of the respiratory valve. The resistance to flow in that valve might have contributed to the feelings of breathlessness reported by Hill when he ran at 16 $km \cdot h^{-1}$ and which he erroneously considered to indicate that he had reached his $\dot{V}O_2$ plateau (Fig. 3 in (69)). Finally and facetiously, Hill may personally have believed in this universal maximum because his was the highest $\dot{V}O_{2max}$ that he and his colleagues ever reported (4172 $mL \cdot min^{-1}$; 57 $mL \cdot kg^{-1} \cdot min^{-1}$) (35).

In summary, Hill and his colleagues did not describe the "plateau phenomenon" as currently understood. Rather they believed there to be a universal $\dot{V}O_{2max}$ of 4 $L \cdot min^{-1}$. They drew this erroneous deduction because their original intellectual model was based on the belief that skeletal muscle anaerobiosis develops during exercise (Fig. 2 in (69)). As a result they concluded that an "oxygen debt" develops during exercise. Measurement of that "oxygen debt" led to the

erroneous conclusion that $\dot{V}O_2$ rises exponentially with increasing running speed. Accordingly they found no logical reason ever to test any athlete running faster than 17 $km \cdot h^{-1}$. For at that speed the measured oxygen intake comprised only 66% of the erroneously predicted total oxygen requirement (Fig. 2). Hill was the main subject for these studies. As Hill weighed 73 kg and as his $\dot{V}O_2$ at 17 $km \cdot h^{-1}$ was 57.7 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ (Fig. 1), so the conclusion was drawn circuitously that there is a universal $\dot{V}O_{2max}$ of 4 $L \cdot min^{-1}$ (73 kg × 57.7 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$).

The true relevance of the study of Myers et al. (60). In this response to Bassett and Howley, I provide another interpretation of the studies of Myers et al. (57,59,60). The interpretation of that study by Bassett and Howley was the following: "This was a rather unique and intricate approach to analyzing data, which had not previously been used. If the slope of the change in $\dot{V}O_2$ *were equal to zero, it meant a perfectly linear increase in* $\dot{V}O_2$ *over time*. A positive value meant that the rate of increase in $\dot{V}O_2$ was less than it had been previously, though $\dot{V}O_2$ could still be climbing. During submaximal exercise the slope of the change in $\dot{V}O_2$ varied about zero, suggesting a fairly linear increase in $\dot{V}O_2$. . . . However, in the final 1–2 min of the ramp test, some subjects had values that differed significantly from zero, indicative of a leveling off in $\dot{V}O_2$. Myers et al. (60) noted that only 33% of their subjects (2 of 6) met the criteria for a plateau established by Taylor et al. (97). This failure to demonstrate a plateau in all subjects is consistent with previous studies using more conventional open-circuit spirometry techniques. The authors concluded that the plateau is not a reliable physiological marker for maximal effort in all subjects. This is precisely the reason that investigators have spent considerable effort in finding other objective physiological criteria for the determination of $\dot{V}O_{2max}$ (41)."

However, Myers (57), the author of this research, provides the exact opposite explanation for a change in $\dot{V}O_2$ slope of zero: ". . . . If oxygen uptake were no longer increasing (while work increases continuously), the slope of the relationship between the two variables would not differ statistically from zero." Hence a zero slope indicates a plateau in oxygen consumption, not a "perfectly linear increase in $\dot{V}O_2$," as Bassett and Howley wish us to believe.

Correctly interpreted, the real value of the studies of Myers et al. (59,60) were that they have established for the first time that the "plateau phenomenon" occurs also during submaximal exercise. Myers (57) concludes: "It appears that the slope of the change in oxygen uptake throughout progressive exercise varies greatly despite a constant, consistent change in external work and the use of large, averaged samples. This degree of variability would appear to preclude the determination of a plateau by most definitions. . . Recent data from our laboratory (59,60) and others (68) suggest that the plateau concept has limitations for general application during standard exercise testing" ((57) pp. 102–103).

Thus I understand the work of Myers et al. (59,60) to show that the appropriate technology detects many "plateau phenomena" occurring randomly throughout progressive exercise to exhaustion. If the "plateau phenomenon" also occurs during submaximal exercise, it cannot indicate the onset of anaerobiosis as demanded by the cardiovascular/anaerobic model. Hence the really novel contribution of this work was to question further the physiological meaning of the "plateau phenomenon" and hence the essential foundation on which the cardiovascular/anaerobic model has been constructed. To suggest that this work simply rediscovers old knowledge that supports the cardiovascular/anaerobic model is not consistent with deductive reasoning.

The finding that the "plateau phenomenon" occurred randomly during both the submaximal and maximal segments of progressive ramp exercise identified another issue recently addressed by Duncan et al. (16). Interrupted testing of the kind used by Taylor et al. (97) and all the other "classical" workers (1,2,53,55,79,80,84,97,103) may be more likely to identify the "plateau phenomenon" than the progressive exercise protocols of the type used by Myers et al. (59,60) and others (14) which became popular when on-line, real-time measurements of $\dot{V}O_2$ first became feasible. As early as 1940, Taylor (95) noted: "The trend of oxygen consumption at maximal levels is of great significance because of the prevailing view that the ability to absorb oxygen is a limiting factor in individual physical performance. As summarized in Figure 3, oxygen consumption is by no means always deficient at exhaustion levels. In fact, in 50% of cases no deviation in the linear increase of oxygen intake occurs at exhaustion and in the remaining cases this value may accelerate more often than fall off."

One obvious difference between progressive and interrupted testing is that the latter occurs over a few days, as many as five in the original study of Taylor et al. (97). This invites the question: Is the "plateau phenomenon" an artifact, resulting from rapid physiological adaptations that develop in response to three to five exercise bouts on successive days? For example, rapid but quite small (~3%) adaptations in running economy in response especially to uphill treadmill running or walking on the previous test days could produce an artifactual "plateau" on the final test day when the highest work rate was achieved (Fig. 4).

Interestingly, Taylor et al. (97) acknowledged that changes in running economy did occur and might impact on the maximum oxygen consumption so measured: "Men have been able to complete the (same) work task in the presence of a 17% loss of maximal oxygen intake. It should be kept in mind, however, that there is good reason to believe *that repeated bouts of running on the treadmill result in improved skill for performing the task and reduced oxygen cost* (author's emphasis). If the workload chosen is close to workloads which fail to elicit a maximal oxygen intake in a given subject, then a substantial improvement in skill in running on the treadmill could result in a reduction of the apparent maximal oxygen intake . . . Such a situation could result in a lower oxygen intake which was not the result of any loss of performance by the cardiorespiratory system" (p. 77).

Thus, while Taylor et al. (97) concerned themselves with the effects of long-term changes in running economy that

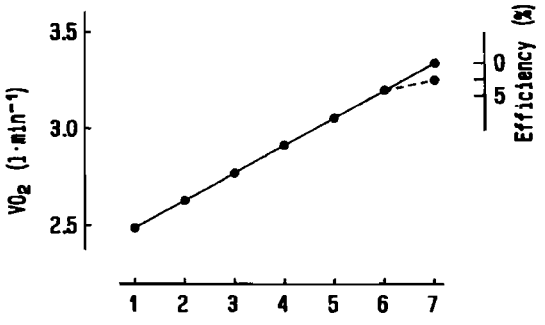

Figure 4—Small (~ 3%) changes in running economy induced by prior treadmill training could explain an apparent plateau phenomenon. The development of on-line, real time measurements of $\dot{V}O_2$ led to the introduction of progressive exercise testing which appears to produce the "plateau phenomenon" less frequently than does interrupted testing conducted on successive days (16,95). References: 16. Duncan, G. E., E. T. Howley, and B. N. Johnson. Applicability of $\dot{V}O_{2max}$ criteria: discontinuous versus continuous protocols. *Med. Sci. Sports Exerc.* 29:273–278, 1997; 95. Taylor, C. Studies in exercise physiology. *Am. J. Physiol.* 135:27–42, 1941.

would apparently lower the $\dot{V}O_{2max}$ measured at a previously determined maximal workload, they did not consider the effects of the previous exercise bouts on running economy on the final test day and hence the possibility that this might produce an artifactual "plateau phenomenon" (Fig. 4). But this remains a possibility that needs to be refuted.

Others have noted the converse difficulty, that of determining the "plateau phenomenon" when there are clear and progressive improvements in running economy, resulting from such interrupted testing on successive days. For example, Seeherman et al. (88) observed that the treadmill running economy of animals improved for 2–6 wk. Only thereafter could the "plateau phenomenon" be identified: "An average of 6 to 8 wk of daily treadmill exercise was required for each determination of $\dot{V}O_{2max}$" (p. 22). If limiting oxygen consumption always terminates maximal exercise, it is surprising that such a protracted process is required to establish that relationship. Finally, although Bassett and Howley (4) vigorously defend the existence of the "plateau phenomenon," a previous publication by Duncan et al. (16) concluded that: "... a $\dot{V}O_2$ plateau is not a prerequisite for defining $\dot{V}O_{2max}$ and is of limited use as a primary objective criterion for evaluating the quality of a graded exercise test." One is left to question what really is the significance of the "plateau phenomenon," if any.

FACTORS LIMITING $\dot{V}O_{2MAX}$

As they now admit that the "plateau phenomenon" is an occasional feature of maximal exercise (and also of submaximal exercise according to the findings of Myers et al. (59,60)) and hence of "limited" value, Bassett and Howley must present an alternate argument to sustain the cardiovascular/anaerobic model of exercise physiology and athletic performance. They thus argue that the "plateau phenomenon" is not critical to their model as "there is a tremendous body of evidence *suggesting* (author's emphasis) that oxygen transport is the limiting factor for $\dot{V}O_{2max}$" so that any contrary argument, more particularly that proposed by myself, is necessarily "flawed."

Accordingly, they begin their defense of this section with what has become the standard textbook statement: "Physiologists have closely examined a number of factors that may limit $\dot{V}O_{2max}$, including: 1) pulmonary diffusion capacity for oxygen, 2) maximal CO, 3) the peripheral circulation, and 4) the metabolic capacity of skeletal muscle. . . . Today most physiologists believe that the capacity of the central cardiovascular system to transport oxygen to the tissues is the principal determinant of $\dot{V}O_{2max}$ (82). The evidence for this view is not based on a plateau in oxygen intake, as Noakes asserts, but on a large number of scientific experiments that will be discussed."

But is it really true that the "plateau phenomenon" is irrelevant to the belief that limitations in oxygen transport determine the $\dot{V}O_{2max}$?

My readings suggests that Taylor et al. (97) were the first to interpret the "plateau phenomenon" as understood and described in the majority of current exercise physiology textbooks: "The classic work of Hill (30) has demonstrated that there is an upper limit to the capacity of the combined respiratory and cardiovascular system to transport oxygen to the muscles. There is a linear relationship between oxygen intake and workload until the maximum oxygen intake is reached. Further increases in workload beyond this point merely result in an increase in oxygen debt and a shortening of the time in which the work can be performed" (p. 78). But Figure 2 shows that Hill actually believed the relationship between running speed and $\dot{V}O_2$ to be exponential so that the universal $\dot{V}O_{2max}$ of 4 $L \cdot min^{-1}$ was reached at a running speed of 13.2 $km \cdot h^{-1}$ although, as shown in Figure 1, Hill reached this universal $\dot{V}O_{2max}$ at 17 $km \cdot h^{-1}$. Perhaps Taylor (97) are responsible for establishing the historic myth that Hill and his colleagues both searched for and identified a "plateau phenomenon." Taylor et al. (97) also concluded that the existence of the "plateau phenomenon" proves that the cardiovascular system limits oxygen delivery to the periphery and that skeletal muscle anaerobiosis limits maximal exercise performance.

The next substantive paper of Mitchell et al. (55) begins with the statement: "According to Hill, maximal oxygen intake is reached when oxygen intake per unit time has attained... its maximum and remains constant ... owing to the limitation of the circulatory and respiratory systems." In their subsequent classic review, Mitchell and Blomqvist (53) extend this interpretation: "If a person is subjected to progressively increasing workloads, there is a linear relationship between workload and oxygen uptake until the maximal oxygen uptake is reached. Heavier workloads can usually be achieved, but oxygen uptake levels off or may even decline .... Maximal oxygen uptake is the greatest amount of oxygen a person can take in during physical work and is a measure of his maximal capacity to transport oxygen to the tissues of the body. It is an index of maximal cardiovascular function .... and, therefore is valuable in the

evaluation of abnormal cardiovascular function." Clearly Mitchell and Blomqvist (53) also use the existence of the plateau phenomenon to conclude: 1) that exercise capacity is limited by factors relating exclusively to oxygen use and 2) that cardiovascular function limits the $\dot{V}O_{2max}$.

Other influential physiologists, Wyndham et al. (103) began their study of the "plateau phenomenon" with the following statement: "In a classic study of the physiology of exercise, Hill and Lupton (35) noted that: 1) each individual has a maximum level of oxygen uptake per minute, 2) the level varies from one individual to another, and 3) the extra work done above the maximum level of O_2 intake is by means of "anaerobic" metabolism, i.e., the oxygen requirement comprises O_2 intake plus an "O_2 debt."

Interestingly, these authors had great difficulty identifying the plateau phenomenon with repeated testing in their subjects. When they applied curve fitting equations to identify the "plateau," they were consistently left with calculated $\dot{V}O_{2max}$ values that were lower than the maximum values they had actually measured, clearly an impossible conclusion. Harris (25) has warned of the need to ensure that the facts fit the theory. The "plateau" exercise of Wyndham et al. (103) is a clear example of forcing the facts to fit a preconceived theory. Wyndham et al. (103) also concluded that the methods of neither Astrand (1) nor of Taylor et al. (97) could establish "the level of maximum oxygen uptake." Perhaps at the same time they might have asked whether they were studying something that does not exist.

As the authors also refer to the work of Rowell, it is appropriate also to review his opinions (82,83): "Hill and Lupton (1923) showed that oxygen uptake does not continuously increase with increasing work intensity until intolerable levels of effort are reached. Rather a plateau of oxygen uptake is eventually reached well before the effort becomes intolerable. Hill and his colleagues went on to show that individuals could exercise for brief periods at levels exceeding those required to elicit this plateau, that is, beyond $\dot{V}O_{2max}$. Our ability to define the functional limits of the cardiovascular system has provided a powerful scientific base from which to investigate many aspects of regulation. This functional limit occurs at the maximal oxygen uptake ($\dot{V}O_{2max}$) which, by definition, equals the product of maximal values of heart rate (HR), stroke volume, and arteriovenous oxygen difference (Fick principle)" ((82), p. 213). Finally Rowell concludes: "In summary, the capacity to increase oxygen uptake during exercise is limited in normal humans by the ability to raise the CO" (82, p. 246).

Thus Rowell uses the historically erroneous interpretation of Hill and his colleagues' work also to conclude that: 1) oxygen delivery limits maximal exercise because of a limited CO and 2) the $\dot{V}O_{2max}$ defines the functional limits of the cardiovascular system.

Similarly in a recent review, Wagner (99) writes: "The fundamental point is that a maximal rate of O_2 utilization can in fact be shown experimentally to exist in normal skeletal muscle. . . . Thus, in intact mammals at very high exercise levels, it can generally be shown that even if external power is increased, there is no significant further rise in $\dot{V}O_2$ (2,30,88). The positive linear relationship between external power and $\dot{V}O_2$ characteristic of submaximal exercise flattens out (or asymptotes) to define $\dot{V}O_{2max}$. . . . "

Thus Wagner argues that the "plateau phenomenon" proves that there is a maximal rate of oxygen consumption by muscle. Interestingly, his commitment to the "plateau phenomenon" is not entirely unconditional for he includes the enigmatic observation: "Even limiting oneself to a discussion of $\dot{V}O_{2max}$ does not preclude confusion because $\dot{V}O_{2max}$ is a somewhat elusive variable both conceptually and experimentally." Clearly something has happened more recently to produce doubts about the certainty of the "plateau phenomenon," at least in Wagner's mind. Yet he does not allow these doubts to undermine his certainty that an oxygen limitation can be identified during maximal exercise in humans. This begs the question: What additional direct (not inferential) information is available to sustain his belief in the face of such uncertainty?

Bassett and Howley's attempt to discount the pivotal importance of the plateau phenomenon as the foundation for the cardiovascular/anaerobic model is disingenuous in the extreme. Indeed the plateau phenomenon probably qualifies as the *single most influential concept in modern exercise physiology*. As shown by the extremely influential opinions of Taylor et al. (97), Rowell (82,83), Mitchell and Blomqvist (53), Wyndham et al. (103), and Wagner (99), it is the singular physiological observation that underpins the cardiovascular/anaerobic model of exercise physiology and its predictions. Indeed, had Hill and his colleagues not advocated the plateau phenomenon, there would have been no logical basis for the brace of studies quoted by Bassett and Howley as "proof" of the cardiovascular/anaerobic model of exercise physiology and athletic performance. For the simple reason that these is still no published evidence proving that muscles become anaerobic during exercise and that this anaerobiosis then limits maximal exercise performance. Were such direct evidence available, it would have been quoted extensively by these authors in preference to the indirect evidence provided by the "plateau phenomenon."

Hence there is no direct proof for the cardiovascular/anaerobic model of exercise physiology and athletic performance. Nor, indeed, as Mitchell et al. (55) warned four decades ago: "The view that cardiac capacity is the determinant of maximal oxygen intake is surmise, not established fact."

The studies reviewed by Bassett and Howley in this section of their response have produced results that are compatible with the cardiovascular/anaerobic model but which do not prove its truth. For none excludes the possibility that exercise performance and $\dot{V}O_{2max}$ might be limited by other factors that are also influenced by interventions that improve exercise performance or the $\dot{V}O_{2max}$, seemingly by increasing exclusively oxygen delivery to the exercising muscles. This represents the classic scientific dilemma of proving causation and excluding association between apparently related phenomena. Unequivocal proof of the cardiovascular/anaerobic model requires data show-

ing that the oxidative capacity of the mitochondria in the maximally exercising muscles is limited by an inadequate oxygen supply caused by a failure of the pumping capacity of the heart.

The cardinal point is that, without the "plateau phenomenon," the cardiovascular/anaerobic model has no greater claim to be the sole and authentic explanation of exercise physiology and athletic performance than does any other competing model. But such is the primacy enjoyed by the plateau phenomenon and the cardiovascular/anaerobic model of exercise physiology and athletic performance (1,2,30–32,35–38,41,53–55,82–85,97,99,101,103), that all other competing models have been rigorously ignored, perhaps even suppressed. The J. B. Wolffe lecture tried to encourage a broader, more inclusive perspective.

For example, the obvious point ignored by many is that muscles do not work by oxygen alone; they contract in response to activation of central and peripheral neural pathways with coupling of excitation to contraction by the complex processes leading to calcium release from the sarcoplasmic reticulum and its binding by the thin filament proteins. Nor is it prudent to ignore the possibility that the activity of the thick and thin filament proteins might contribute to skeletal muscle contractile activity during exercise, as occurs in the heart (43). The question that has to be asked is: Why have so few modern exercise physiologists championed these possibilities, preferring rather to accept the cardiovascular/anaerobic model as the sole reasonable explanation for human exercise physiology and athletic performance?

The only explanation I can offer is that most exercise physiologists have ignored any other possibility simply because of the oppressive hegemony of the cardiovascular/anaerobic model and the unusual vigor of its proponents in protecting their particular model. Consider Bassett and Howley's certitude: "(Noakes') view assumes that the cross-bridge cycling rate is the limiting factor in distance running. However, cross-bridge cycling cannot occur without adequate quantities of ATP supplied by aerobic metabolism. The majority of the evidence points to the cardiorespiratory system as being the limiting factor for oxygen uptake (which is the quantitative measure of aerobic metabolism)". Thus the only "evidence" these authors can provide to "prove" that cross-bridge cycling does not limit maximal exercise performance is not a body of published findings disproving a specific conjecture, for example, that myosin ATPase activity is related to exercise performance, but rather an uncritical devotion to an unproven model that, as I have now shown for the third time, is based on a mythical foundation (68,69).

Thus the J. B. Wolffe lecture included a series of examples in which there is clear evidence that maximal exercise is definitely not limited by skeletal muscle anaerobiosis and hence by a failure of the cardiac pumping capacity. These examples include exercise at extreme altitude (40,44), in the heat (63–65), and in persons with renal (45) and cardiac disease (102), especially following cardiac transplantation (15). In none of these conditions does the defect appear to be in either oxygen delivery to or oxygen utilization by the exercising muscles. Rather the primary defect is either in central recruitment of muscle contraction (definitely in exercise at moderate to extreme altitude (44) and possibly in other conditions) or because of impaired skeletal muscle contractile function resulting from changes either in excitation/contraction coupling or in the function of the thick or thin filament proteins. The crucial distinction is that the defect in these conditions is not in oxygen provision and energy production, but in the processes of skeletal muscle recruitment and contraction.

That many do not appreciate this crucial distinction is apparent in the traditional explanation that the poor exercise tolerance of patients with metabolic muscle diseases results from impaired oxygen utilization by their diseased muscles. Rather the primary defect, as suggested by the "lactate paradox" (69) is likely an inability of their diseased muscles to generate sufficient force for there to be a normal oxygen requirement. Thus the low $\dot{V}O_{2max}$ in these patients is the result, not the cause of their poor exercise tolerance, as also found in patients with renal (45) or cardiac disease (15,101). Abnormalities in skeletal muscle force generation, perhaps resulting also from a reduced total muscle mass, and not in oxygen delivery or utilization, explain the poor exercise tolerance of these patients.

Despite these arguments, there is indeed good reason to believe that the $\dot{V}O_{2max}$ must be regulated by the central cardiovascular function in healthy individuals. I contend that in contrast to the conventional arguments, the proof of this hypothesis requires the absence of a plateau in CO and in $\dot{V}O_2$. Furthermore if cardiovascular function regulates or limits the $\dot{V}O_{2max}$, then skeletal muscle anaerobiosis cannot develop during maximal exercise. The questions to be addressed are: 1) *Does the pumping capacity of the heart limit the $\dot{V}O_{2max}$? and, if so, 2) what are the consequences for the heart?*

Bassett and Howley (4) present another common conclusion in this section: "However, in the vast majority of healthy subjects the evidence points to the pumping capacity of the heart (CO) as being the major limiting factor for $\dot{V}O_{2max}$." Other highly influential exercise physiologists have concluded similarly (6,82,83,85). But the pumping capacity of the heart is seldom directly measured in healthy subjects during maximum exercise. Hence this conclusion must be based not on directly measured evidence but on inferences drawn from other information, perhaps from the measurement of the $\dot{V}O_2$ and from the (theoretical) existence of the "plateau phenomenon." Figure 5 has been redrawn from the classic paper of Mitchell and Blomqvist (53). It shows the clearly defined plateau in oxygen consumption in this subject when the work rate exceeds stage 4 of the test corresponding, interestingly, to Hill's universal $\dot{V}O_{2max}$ of 4 $L \cdot min^{-1}$. During the submaximal portions of the exercise test (stages 1 to 4), increases in work rate cause essentially linear increases in CO, stroke volume, and HR. When the $\dot{V}O_2$ plateaus at stages 4 and 5, these variables must also level off, hence proving that the pumping capacity of the heart limits the $\dot{V}O_{2max}$.

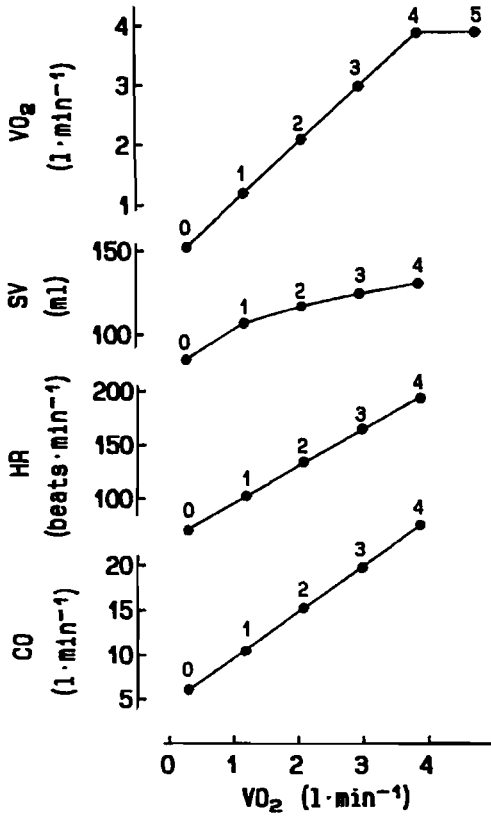

Figure 5—The classical diagram of Mitchell and Blomqvist (53) depicting the expected changes in $\dot{V}O_2$, stroke volume (SV), HR, and CO during progressive exercise to exhaustion. Note that whereas the "plateau" in $\dot{V}O_2$ is clearly identified, no plateau in SV, HR, and CO is sbown as data for these cardiovascular variables were not included at workloads beyond the $\dot{V}O_{2max}$. Reference 53. Mitchell, J. H. and G. Blomqvist. Maximal oxygen uptake. *New Engl. J. Med.* 284:1018–1022, 1971.

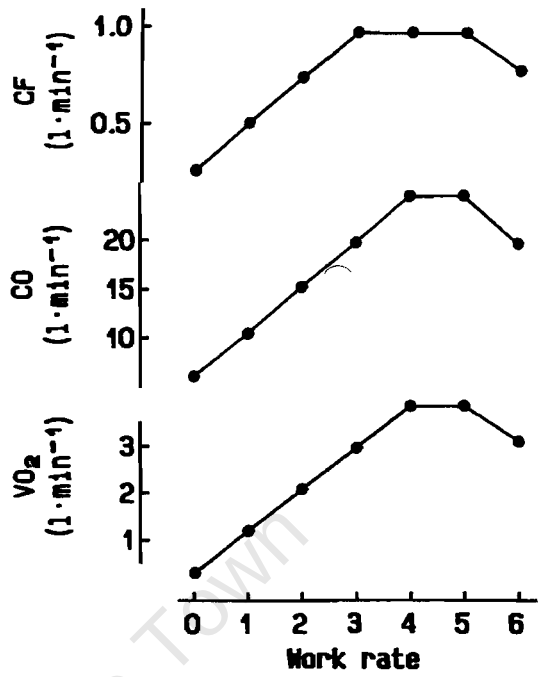

Figure 6—Diagram showing the expected cardiovascular changes that produce the "plateau phenomenon," if the cardiovascular/anaerobic model is correct. Note that a plateau in coronary blood flow (CF) causing myocardial ischemia must occur before the CO levels off, and well before skeletal muscle anaerobiosis develops at the plateau in $\dot{V}O_2$. Furthermore, continuing exercise after the plateau in CF and $\dot{V}O_2$ must cause a precipitous fall in CO as a result of progressively increasing myocardial ischemia.

Surprisingly, Mitchell and Blomqvist (53) do not provide data for these cardiovascular measures once the $\dot{V}O_{2max}$ has been reached (Fig. 5). A more recent review by Mitchell of that paper (54) also lacks such data. Perhaps as serious scientists they were correctly reluctant to speculate on what they had not measured. Or perhaps they realized the dilemma that such a conclusion posed, especially for the heart.

For the issue that must ultimately be addressed is: What are the consequences of the cardiovascular/anaerobic model for the heart itself? Or, alternatively, if the CO limits the $\dot{V}O_{2max}$, what limits the CO? For the heart is also a muscle. The cardiovascular/anaerobic model predicts that (skeletal) muscle function fails when its oxygen supply is inadequate. Hence if logic is to be preserved, the failure of the heart's pumping capacity, in Rowell's words "to raise the CO" at the $\dot{V}O_{2max}$ must result from an inadequate (myocardial) oxygen supply. Hence coronary blood flow must plateau sometime before the CO levels off at the $\dot{V}O_{2max}$. This limiting coronary blood flow induces myocardial "fatigue," causing the plateau in CO and hence in the $\dot{V}O_{2max}$, leading only thereafter to skeletal muscle anaerobiosis. Thus by this logic, the coronary blood flow must be the first physiological function to show a "plateau phenomenon" during progressive exercise to exhaustion (Fig. 6).

Hill et al. (36) anticipated this dilemma: "Certain it is that the capacity of the body for muscular exercise depends largely, if not mainly, on the capacity and output of the heart. It would obviously be very dangerous for that organ to be able, as the skeletal muscle is able, to exhaust itself very completely and rapidly, to take exercise far in excess of its capacity for recovery... The enormous output of the heart of an able-bodied man, maintained for considerable periods during vigorous exercise, requires a large contemporary supply of oxygen to meet the demand for energy... When the oxygen supply becomes inadequate, it is probable that the heart rapidly begins to diminish its output, so avoiding exhaustion; the evidence for this, however, is indirect, and an important field of research lies open in the study of the recovery process in heart muscle, on the lines of which it has been developed in skeletal muscle" (p. 443). As a result: "It would seem possible that a deciding factor in the capacity of a man for severe prolonged exercise may often be the efficiency of his coronary circulation" ((30), p. 108).

Hence the interpretation of Hill and his colleagues is unambiguous and internally consistent. Their model predicts that the first event leading to exhaustion during maximal exercise is an inadequate oxygen supply to the heart. This impairs myocardial function causing a leveling of the CO, a reduced skeletal muscle blood flow, and ultimately skeletal muscle fatigue as depicted in Figure 6. They postulate that the heart must reduce its CO specifically to prevent the development of a large "oxygen debt."

But even this explanation is unsatisfactory as it still fails to explain what physiological events terminate maximal exercise. For it is now known that the heart has no capacity to generate an "oxygen debt." Rather, an inadequate myocardial oxygen supply at the $\dot{V}O_{2max}$ would induce the symptoms of angina pectoris (43), which would terminate maximal exercise. But it is now also known that this does not occur, at least in healthy humans without coronary artery disease. Thus all the evidence shows that none of the markers of myocardial ischemia, including electrocardiographic ST-segment displacement (77), myocardial release of lactate (27), and increases in both the end-diastolic and end-systolic ventricular volumes with a reduction in stroke volume (82,83), has been measured in healthy athletes at maximum effort. Rather myocardial lactate uptake occurs across the myocardium at those high exercise intensities (21,27) which induce the highest rates of lactate release from the exercising muscles.

No modern physiologist has been sufficiently brave to tackle this intellectual dilemma inherited from Hill and his colleagues. For it is not appealing to suggest that myocardial ischemia limits maximal exercise in healthy individuals. Furthermore, all the published evidence refutes these logical predictions of the cardiovascular/anaerobic model.

Conclusions. There is an obvious discrepancy in the logic presented in the previous two sections by Bassett and Howley. For they initially argue with great conviction that the "plateau phenomenon" was indeed identified by Hill and his colleagues. Next they argue the opposite; that the "plateau phenomenon" is not universally present and can be identified in a variable proportion of subjects as shown in their own studies (16). Although this is an important admission, it is hardly novel. Taylor et al. (97) who were the first researchers after Hill and his colleagues specifically to analyze the "plateau phenomenon" wrote that "there are conditions under which a maximal oxygen uptake cannot be elicited" (p. 143). One wonders why it has taken so long for this admission to be forthcoming from some devotees of the cardiovascular/anaerobic model. Perhaps it is because this admission unearths another logical nightmare: If a subject terminates exercise without demonstrating a "plateau phenomenon," does this indicate that skeletal muscle anaerobiosis limited their exercise, according to the cardiovascular/anaerobic model? Proponents of the cardiovascular/anaerobic model must either respond in the affirmative or abandon their model. Yet in confirming their model, they commit the logical error revealed in Figure 3.

Statements 1–4 form the logical basis of the cardiovascular/anaerobic model of exercise physiology. Yet if statement 1 is true, then so too must be its converse, that is, that the absence of the plateau phenomenon indicates that skeletal muscle is adequately perfused and oxygenated during maximal exercise (statement 2).

Hence the finding (statement 5) that the plateau phenomenon is present in as few as 50% of subjects during maximal exercise (1,4,14,16,41,55,57,59,60,95–97,99,103) leads to the logical conclusion (statement 7) that factors other than skeletal muscle anaerobiosis must limit exercise in a sizable proportion of athletes or indeed in all athletes if one accepts the findings of Myers et al. (59,60). This was the essential conclusion of the J. B. Wolffe lecture which developed what might be termed "the regulated skeletal muscle contraction model of exercise physiology and athletic performance."

Denying this conclusion introduces the logical conflict between statements 2 and 6. But as I have argued earlier, it is the very absence of the plateau phenomenon that more likely proves that central cardiovascular function regulates or "limits" the $\dot{V}O_{2max}$.

ROLE OF OXYGEN DELIVERY IN DETERMINING ENDURANCE PERFORMANCE

In this section, Bassett and Howley set out to show that physiological variables relating to oxygen transport also predict endurance performance. They wish to prove that oxygen delivery determines endurance performance as, in their opinion, it also determines maximal exercise performance.

I would argue that it is essential to undertake research in the scientific area in which one professes expertise. Perhaps it is bold of me to suggest that the quotation of Thomas Huxley (42) is particularly appropriate to their presentation: "Science is organized common sense where many a beautiful theory was killed by an ugly fact." This section of Bassett and Howley's response produced a beautiful theory despite a host of ugly facts that disprove it. For example, the conceptual error that a statistical relationship proves causation was used as justification of their position. Furthermore, in proving statistical relationships it appeared that they selectively ignored a large body of evidence showing the opposite, namely, that these variables are either unrelated or only poorly related to endurance performance. For example, the studies Bassett and Howley quoted to "prove" that $\dot{V}O_{2max}$ and running economy predict racing performance included athletes whose performances differed by 18 min (38%) in a 16-km race (Fig. 10 in (4)) and by 9 min (20%) in a 10-km race (Fig. 12 in (4)). But in studies of athletes whose performances are more similar, neither $\dot{V}O_{2max}$ (9,10,12,13,71,74,75,87) nor running economy (71) was a good predictor of running performance. Even in their Figure 12, the running economy of the four fastest 10-km runners was identical, yet their performances differed by 4 min (9%). By their logic, this absence of statistical association must therefore disprove the theory that oxygen delivery determines endurance performance in elite athletes. In athletes with similar abilities the best predictor of performance

is usually a measure of the peak workload achieved during exercise (19,56,68,71,86,87). Indeed, the study of Morgan et al. (56) showed a significant negative correlation between $\dot{V}O_{2max}$ and 10-km racing speed in a group of runners with similar best 10-km times.

The second disagreement between Bassett and Howley and myself in this section is the absence of a valid conceptual framework to explain how oxygen delivery determines endurance performance. Bassett and Howley believe a link exists among oxygen delivery, exercise intensity, and changes in blood lactate concentrations: "However, what was needed was a single measurement that would incorporate all three variables and simplify the prediction of performance. The answer was provided by the classic study of Farrell et al. (18) dealing with the link between lactate accumulation and performance." In fact, that "classic" study (18) suffered from the very limitation, already identified, since it also concerned athletes whose performances varied substantially. The range of finishing times for 42 km in the 13 marathon runners in that study varied from 2 h 17 min to 3 h 49 min, a variation of 67%. Similarly the range of $\dot{V}O_{2max}$ values in the group ranged from 36–59 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$. When athletes of similar abilities are studied, the lactate threshold, however defined, and indeed any measurement derived from the blood lactate concentration, is of "negligible" value in predicting athletic performance (39).

But even if the blood lactate concentration is always an excellent predictor of endurance performance, this does not "prove" that oxygen delivery determines endurance performance. For the cardiovascular/anaerobic model provides the only conceptual link between oxygen consumption, exercise intensity and blood lactate concentration. Thus their Figure 13 provides another example of how Bassett and Howley interpret data exclusively according to the cardiovascular/anaerobic model, specifically to "prove" that model. The authors do not explain how they interpret their Figure 13. Presumably they would argue that the greater the running economy and the higher the $\dot{V}O_{2max}$, the faster the running speed at which "anaerobiosis" first develops and, hence, the greater the running speed that can be achieved before the blood lactate concentration rises. The rise in blood lactate concentration then determines endurance performance in an unspecified way.

However, this interpretation ignores the substantive section in the J. B. Wolffe lecture which dissociates skeletal muscle lactate production from skeletal muscle oxygen delivery (7,8,20,46–48,50,58,91). The onset of blood lactate accumulation is more likely related to the rate of carbohydrate oxidation (7,14,48) than the $\dot{V}O_2$, as required by the cardiovascular/anaerobic model. Thus, there is no longer any logical reason to interpret blood lactate concentrations as an index of skeletal muscle anaerobiosis according to the cardiovascular/anaerobic model. As already argued, it was this error that led Hill to draw all his erroneous conclusions. Modern exercise physiologists should not continue to repeat his errors if they wish to advance knowledge (25).

Bassett and Howley concluded this section with a critique of my view that a factor related to running speed over a shorter (sprint) distance may also predict performance at much longer distances of 5–50 km in groups of athletes who specialize in those long distances. I did not conclude that this means that sprinters would be the best distance runners. Rather I concluded that the best distance runners must have muscles that are both very powerful (and hence can generate a fast sprinting speed) and have superior fatigue resistance. The accuracy of this prediction is shown by our more recent work (9) which shows that the best distance runners (5–42 km) yet studied are almost as fast as superior milers at distances of 1–2 km. But the muscles of the distance runners have substantially greater fatigue resistance.

ROLE OF MUSCLE FACTORS IN DETERMINING ENDURANCE PERFORMANCE

I have argued that proponents of the cardiovascular/anaerobic model face key logical dilemmas when they propose factors that limit maximal exercise performance (Fig. 3). Not least is the logical inference that if CO limits the $\dot{V}O_{2max}$, then the limitation in CO must result from myocardial ischemia. But their challenge becomes even more daunting when the same model is used to explain endurance performance, as do Bassett and Howley: "In contrast to Noakes' assertion, the research literature provides considerable support for the hypothesis that performance in endurance events is limited by oxygen delivery ($mL \cdot kg^{-1} \cdot min^{-1}$), which is set by the subject's $\dot{V}O_{2max}$ and the percent of $\dot{V}O_{2max}$ that can be maintained."

First, why should prolonged endurance exercise in which the oxygen consumption is not maximal and therefore not limiting be determined by oxygen delivery to the active muscles? Besides their argument provided in the previous section, Bassett and Howley also quote this statement of Hill et al. (38) to support their belief: "Some individuals can naturally run or walk uphill for long periods without distress. This may be partly a matter of diffusion constant of the lungs for oxygen; largely, however, it is probably one of the capacity of the heart itself." But this interpretation invites the question: If the ability to exercise without fatigue during prolonged exercise results from the "capacity of the heart itself," then it follows that the onset of fatigue during prolonged exercise must be caused by heart fatigue, that is, by the onset of cardiac failure with a reduced capacity to pump blood to the active muscles. Hence the cardiovascular/anaerobic model can only explain endurance performance if the heart itself also limits that performance. Yet there is no logical physiological explanation for this proposed dependence. Rather one is forced to postulate that the progressive development of cardiac failure during prolonged exercise reduces skeletal muscle blood flow inducing anaerobiosis and skeletal muscle fatigue. But the development of cardiac failure during prolonged exercise is the exception, not the rule (52), and produces a unique set of symptoms and signs quite unlike those present in normally fatigued athletes.

Furthermore, blood lactate concentrations are low at exhaustion following very prolonged exercise (51), a further example of the "lactate paradox" discussed previously. I would note that Bassett and Howley's proposition that changes in muscle H^+ and glycogen concentrations affect exercise performance is extraneous to this discussion. These represent a different model of fatigue (70,72) separate from their cardiovascular/anaerobic model.

Second, the model fails to explain why exercise is impaired in the heat when the oxygen and blood supply and metabolism of the active muscles are normal (63–65) or at altitude when the "lactate paradox," as fully detailed in the J. B. Wolffe lecture, reveals itself as it does also in patients with various chronic diseases or in those exhausted by prolonged exercise. Third, this model cannot explain why treatment with dichloroacetate (DCA), a metabolic stimulator of the pyruvate dehydrogenase complex, increases $\dot{V}O_{2max}$ and maximal exercise performance (49), reduces the rise in blood lactate concentrations during submaximal (49,98) and maximal exercise (49), and maintains higher muscle PCr concentrations during exercise (98). These studies indicate that metabolic events in skeletal muscle can alter exercise performance and metabolism independent of changes in skeletal muscle oxygenation.

Fourth, the model cannot explain why elite black South African distance runners, the fastest group of distance runners yet studied, performed significantly better at distances beyond 5 km than did a group of middle distance runners whose $\dot{V}O_{2max}$ values were the same (9). The discrepancy in performance increased with increasing race distance. Nor can this model explain why women with either lower measured $\dot{V}O_{2max}$ values (89) or who are slower over racing distances of 10–42 km (3) begin to outperform men in races longer than 56 km.

Fifth, this model cannot explain why the form of muscle weakness which develops during the course of prolonged exercise like marathon racing (61,62,76) persists for at least 7 d after exercise and is characterized by impaired skeletal muscle contractile activity (62) and altered electromyographic activity (92). It would seem probable that this weakness is in some way linked to the development and expression of fatigue during prolonged exercise. Its persistence after exercise proves that it is not caused by the transient metabolic changes occurring during exercise.

Similarly, this model cannot explain the personal observations (68,69), common to all athletes, that the inability to train vigorously every day or to increase one's pace near the finish of an endurance running event is associated with discomfort in the leg muscles. Measurement of lower than maximum HRs under both conditions suggests that the symptoms result from factors other than cardiac fatigue and are most likely related to the changes in skeletal muscle function described by Nicol et al. (61,62), Pullinen et al. (76), and Strojnick and Komi (92).

It was precisely because of these discrepancies that I concluded that the cardiovascular/anaerobic model cannot explain fatigue and performance under all conditions. Hence another model was necessary. Initially I argued that a muscle factor alone must predict exercise performance (66–68). That a localized muscle factor is involved in the form of fatigue studied by Spriet et al. (90) is clear. They showed that force production by ischemic skeletal muscle contracting in response to external stimulation falls progressively, ceasing before the development of irreversible ATP depletion and skeletal muscle rigor.

But my original model was not entirely satisfactory, not least because it ignored the role of central neural factors which limit exercise performance at altitude and explain that form of the "lactate paradox" (22,44). The same mechanism might also explain why exercise terminates in the heat even though skeletal muscle blood flow and metabolism are unaffected (63,64). It also seems unlikely that precooling enhances endurance performance exclusively by a peripheral, skeletal muscular effect. Hence by the time of the J. B. Wolffe lecture, the model had been refined substantially. The model that I have now proposed is one in which "skeletal muscle contractile activity is regulated by a series of central, predominantly neural, and peripheral, predominantly chemical, regulators that act to prevent the development of organ damage or even death during exercise in both health and disease and under demanding environmental conditions" ((69), p. 571). Unfortunately, this model was not acknowledged by Bassett and Howley.

$\dot{V}O_{2MAX}$ PARADIGMS OF HILL VERSUS NOAKES

Bassett and Howley list the contributions made by Hill. I contend that the majority of Hill's ideas are now antiquated as argued here. Nor am I the first so to argue.

In 1969, Harris (25) published a classic paper describing how the "oxygen debt" also attributed to Hill and his colleagues achieved a mythical status in the exercise sciences even though the facts consistently showed that, like phlogiston, it did not exist: "Excess lactate represents the last major attempt on the part of physiologists to fit the facts into the classical conception that 'oxygen debt' is due to the metabolism of lactate. Two generations have been mesmerized by this conception and each has failed to fit the facts to the theory." He continued: "Much of the present-day exercise physiology is still based on the misconceptions of the past; and the time has come to call a halt to the over-earnest examination of largely fortuitous relationships between the concentrations of lactate or pyruvate in the blood and the recovery volume of oxygen . . . The theory of oxygen debt looks backwards from the premise that the muscle cell has to make good something which is lost during work, endowing the human cell with the all-to-human property of hindsight. We should now begin at the other end, start with the chemical disturbances produced by contraction and see how (not why) they cause the muscle cell and the body to increase its uptake of oxygen" (p. 389).

Perhaps Harris' sentiments about the "oxygen debt" apply equally to: 1) Hill and Lupton's 1923 concept of the universal $\dot{V}O_{2max}$, 2) the description by Taylor et al. (97) of a

mythical "plateau phenomenon" that was neither looked for nor ever identified by Hill and his colleagues, 3) Wasserman and McIlroy's (101) description of the "anaerobic threshold"; and 4) the cardiovascular/anaerobic model of exercise physiology and athletic performance (69), that all these erroneous ideas have spawned. Perhaps, as Harris concludes, "we have been looking . . . for something which is not there."

Indeed I continue to emphasize that it is the absence, not the presence of the plateau phenomenon, that is the stronger evidence that cardiovascular function regulates or "limits" the $\dot{V}O_{2max}$.

Conclusion: the common theory of Hill and Noakes. This more extended analysis of the work of Hill and his colleagues has discovered why the "plateau phenomenon," as currently understood, is implausible precisely because it predicts that exercise terminates when the oxygen demands of the exercising skeletal muscles exceed their supply.

For the inherent weakness in Hill's cardiovascular/anaerobic model is simply stated: The heart is a muscle, just as is skeletal muscle, dependent on an adequate oxygen supply for its contraction. But unlike skeletal muscle the heart is dependent on its own pumping capacity for its oxygen supply. Hence if the CO reaches a peak and can rise no further, the immediate cause will have been a plateau in (coronary) blood flow and the immediate effect will be a developing myocardial ischemia. The knock-on effect of this will be a further reduction in myocardial contractile function, a further fall in CO, and more severe myocardial ischemia. Thus, the inability of the heart "to raise its CO" at the $\dot{V}O_{2max}$ (83) must be both the result and the cause of a developing myocardial ischemia, according to the model that holds that oxygen deficiency impairs muscle function.

Hence according to the cardiovascular/anaerobic model, the logical end point of vigorous exercise must be a progressive and irreversible myocardial ischemia with the development of angina pectoris. As this does not occur in healthy human athletes, some other mechanism must intervene to prevent the CO reaching a maximum while the oxygen demands of the tissues continue to rise.

Proponents of the cardiovascular/anaerobic model have not acknowledged that Hill had himself realized that his model was fatally flawed. So he introduced modifications, unrecognized until again revealed here: "It would seem probable . . . that the heart is able to regulate its output, to some extent, in accordance with the degree of saturation of the arterial blood, either of that which reaches it through the coronary vessels or *by some reflex in other organs produced by a deficient oxygen supply* (author's italics). From the point of view of a well coordinated mechanism, some such arrangement is eminently desirable; *it would* clearly be useless for the heart to make an excessive effort if by so doing it merely produced a far lower degree of saturation of the arterial blood; and we suggest that, in the body (either in the heart muscle itself or in the nervous system), there is some mechanism which causes a slowing of the circulation as soon as a serious degree of unsaturation occurs, and vice versa. This mechanism would tend . . . to act as a "governor," maintaining a high degree of saturation of the blood" ((38), pp. 161–162).

Hence Hill and his colleagues realized that even if the ultimate limits for maximal exercise are set by the cardiovascular system, some mechanism (other than skeletal muscle anaerobiosis) must be present to terminate exercise before the heart is itself damaged by the very plateau in CO that is theoretically necessary to explain the "plateau phenomenon" and the development of skeletal muscle anaerobiosis (Fig. 6). Thus they proposed the existence of a "governor" in either the myocardium or nervous system, specifically to terminate exercise before myocardial damage developed.

Contrast this to my model proposed in the J. B. Wolffe lecture (69): "The alternate model proposes that skeletal muscle contractile function is regulated by a hierarchy of controls specifically to prevent damage to any of a number of different organs. Severe anaerobiosis is one specific end point that must be thwarted so that irreversible rigor and necrosis in the active muscles is prevented. The challenge for exercise scientists is to understand how the body anticipates potential for organ damage and how skeletal muscle contractile function is regulated specifically to preclude any such calamities" (p. 587).

Thus the more logical analysis of Hill and his colleagues, ignored by all modern exercise scientists, has exposed the one critical weakness of my model. It is that skeletal muscle anaerobiosis can only ever occur after myocardial ischemia has developed (Fig. 6).

Perhaps the strengths of my model and that of Hill and his colleagues can now be combined into an even more contemporary hypothesis: Skeletal muscle recruitment and contractile function are regulated by a hierarchy of controls, specifically to prevent damage to any of a number of different organs. During maximal exercise, progressive myocardial ischemia preceding skeletal muscle anaerobiosis must be thwarted so that neither the heart nor the skeletal muscle develops irreversible rigor and necrosis with fatal consequences.

CARDIOVASCULAR FUNCTION DURING EXERCISE AT ALTITUDE: A CRUCIAL TEST OF THE HILL/NOAKES MODEL

An important test of this combined model is provided by studies of the cardiovascular response to exercise at increasing altitude in which the progressive reduction in the arterial oxygen tension increases the probability that myocardial ischemia will develop during maximal exercise. If skeletal muscle function at altitude is limited by an inadequate oxygen delivery and is not regulated to prevent the development of myocardial ischemia, then the peak CO during maximum exercise must be the same or higher at altitude than at sea level. But if the heart is to be protected from myocardial ischemia during maximal exercise at increasing altitude, then the falling arterial oxygen content and hence

TABLE 1. Cardiorespiratory measures at different altitudes: Operation Everest II.

Altitude (m)	Sea level	6100 m	7620 m	8848 m
paO_2 (Torr)	87	34	33	28
Maximum work rate (Ws)	300–360	180–210	120	120
Ventilation ($L \cdot min^{-1}$)	125	161	162	184
Heart rate ($beats \cdot min^{-1}$)	168	137	122	118
Cardiac output ($L \cdot min^{-1}$)	24	20	16	16
avO_2 ($mL \cdot L^{-1}$)	154	106	89	67
PvO_2 (Torr)	19	12	14	14

avO_2, arterial minus venous oxygen difference; PVO_2, mixed venous oxygen tension; Data are from reference 94: Sutton, J. R., J. T. Reeves, P. D. Wagner, et al. Operation Everest II: oxygen transport during exercise at extreme simulated altitude. *J. Appl. Physiol.* 64:1309–1321, 1988.

the reduced potential for oxygen delivery to the myocardium must cause a progressive reduction in maximum CO with increasing altitude. Furthermore, the absence of myocardial ischemia during maximal exercise at extreme altitude when the arterial oxygen tension is barely sufficient to maintain cerebral function would be consistent with the presence of the governor proposed by Hill and his colleagues.

Table 1 lists peak cardiorespiratory measures at different altitudes measured during the epic Operation Everest II (24,40,78,81,93,94,100). As the arterial oxygen tension falls with increasing altitude, peak achieved work rate, HR, and, most significantly, CO fall substantially whereas maximum ventilation rises (94). No electrocardiographic evidence of myocardial ischemia was detected during maximum exercise at any altitude up to 8840 m (81,94). Indeed left ventricular systolic function was maintained and perhaps even enhanced during maximal exercise at a simulated altitude of 7620 m (78,93). Hence the authors concluded that "limitations of performance may have been caused by other factors, and reduced HRs and COs at maximum effort (at altitude) were the result rather than the cause of the reduced maximal O_2 uptake".

But a more insightful observation is that at any work rate CO was the same at sea level and at any higher altitude up to the highest tested (8840m) (40,94).

Hence at altitude CO is not increased during exercise to compensate for the reduced arterial oxygen content. Thus the body makes no attempt to increase CO to optimize oxygen delivery to the tissues at increasing altitude. The sole conclusion must be that the oxygen demands of skeletal muscle are not pre-eminent during exercise at altitude. Rather, skeletal muscle recruitment must be regulated, perhaps by the governor first proposed by Hill, probably to protect the heart from an hypoxia that would be inevitable were the oxygen demands of the skeletal muscles, not the heart, the priority. This governor is presumably responsible for reduced skeletal muscle recruitment and the lower than expected blood and muscle lactate concentrations during maximum exercise at altitude (44).

If skeletal muscle function is indeed regulated to prevent myocardial hypoxia at altitude, the question becomes: what physiological variable is sensed by the governor? Logic suggests that the variable must be related to oxygen delivery to, or use by, the myocardium. Table 1 shows that the oxygen tension in the mixed venous blood draining from the systemic circulation including skeletal muscle and from the heart in the coronary sinus is the only variable that is the same at maximal exercise at all altitudes. Hence one possibility is that the venous oxygen tension in either mixed venous or coronary sinus blood is the variable that is sensed.

But since myocardial and not skeletal muscle oxygenation is at risk during exercise at altitude, it would be more likely that the oxygen tension in the coronary vascular bed would be the monitored variable.

Indeed the study of Grover et al. (23) showed that the coronary sinus PO_2 is the same during submaximal exercise at all altitudes from sea level to 3100 m, suggesting that "the coronary circulation is autoregulated to maintain coronary sinus blood O_2 tension constant" (23). This would mean that, at altitude, coronary flow must increase in proportion to the reduction in the arterial PO_2 to maintain a constant coronary sinus oxygen tension.

Hence, the rate of either coronary flow or of myocardial oxygen delivery would provide the necessary input for the appropriate functioning of Hill's governor.

In summary, the evidence from these altitude studies shows that the heart is prevented from developing myocardial ischemia during maximal exercise even at extreme altitude in keeping with Hill and Noakes' model that skeletal muscle function is regulated to prevent organ, especially heart damage during exercise. The evidence further disproves the model which holds that the oxygen demands of the exercising muscle are preeminent and that exercise is limited only after oxygen delivery to the exercising skeletal muscles becomes inadequate (4).

As the ultimate source of all those controversial ideas that have so entranced his scientific progeny, Nobel Laureate A. V. Hill would hopefully have no option but to agree with this updated version of his original contributions. It would be in keeping with his pithy conclusion derived late in his career: "I have long believed, and am still inclined to believe, that all theories of muscle contraction are wrong. But they have been very useful in stimulating new research. In fact, many of the best theories are self destructive, by provoking fresh inquiry and leading to new facts which they cannot explain. The only useless theories are those than cannot be tested and can explain everything" ((34), pp. 362–363).

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Review Article

Physiological models to understand exercise fatigue and the adaptations that predict or enhance athletic performance

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A popular concept in the exercise sciences holds that fatigue develops during exercise of moderate to high intensity, when the capacity of the cardiorespiratory system to provide oxygen to the exercising muscles falls behind their demand inducing "anaerobic" metabolism. But this cardiovascular/anaerobic model is unsatisfactory because (i) a more rigorous analysis indicates that the first organ to be affected by anaerobiosis during maximal exercise would likely be the heart, not the skeletal muscles. This probability was fully appreciated by the pioneering exercise physiologists, A. V. Hill, A. Bock and D. B. Dill, but has been systematically ignored by modern exercise physiologists; (ii) no study has yet definitely established the presence of either anaerobiosis, hypoxia or ischaemia in skeletal muscle during maximal exercise; (iii) the model is unable to explain why exercise terminates in a variety of conditions including prolonged exercise, exercise in the heat and at altitude, and in those with chronic diseases of the heart and lungs, without any evidence for skeletal muscle anaerobiosis, hypoxia or ischaemia, and before there is full activation of the total skeletal muscle mass, and (iv) cardiovascular and other measures believed to relate to skeletal muscle anaerobiosis, including the maximum oxygen consumption (VO_2 max) and the "anaerobic threshold", are indifferent predictors of exercise capacity in athletes with similar abilities. This review considers four additional models that need to be considered when factors limiting either short duration, maximal or prolonged submaximal exercise are evaluated. These additional models are: (i) the energy supply/energy depletion model; (ii) the muscle power/muscle recruitment model; (iii) the biomechanical model and (iv) the psychological model. By reviewing features of these models, this review provides a broad overview of the physiological, metabolic and biomechanical factors that may limit exercise performance under different exercise conditions. A more complete understanding of fatigue during exercise, and the relevance of the adaptations that develop with training, requires that the potential relevance of each model to fatigue under different conditions of exercise must be considered.

The nature of the physiological and biochemical adaptations that occur in response to physical training has been extensively studied in humans and other mammals. This information is readily available and is likely to be well known to most exercise scientists (Saltin & Gollnick 1983, Holloszy & Coyle 1984). Similarly there is an extensive literature on the cellular mechanisms believed to cause the fatigue that develops during exercise (Fitts 1994).

In contrast, fewer studies have evaluated the extent to which these adaptations explain the improvements in performance that occur with different types of physical training (Acevedo & Goldfarb 1989, Daniels et al. 1978, Hawley et al. 1997, Houston et al. 1979, Moore et al. 1997, Ramsbottom et al. 1989, Westgarth-Taylor et al. 1997, Weston et al. 1997) and which presumably result from changes that delay the onset or development of fatigue. There are at least three probable reasons for this.

First, many exercise physiologists may consider this to be the work of the coach, not of the scientist. Or, accustomed to the tightly controlled conditions of laboratory research, some scientists may be reluctant to undertake field-based studies of performance in which all the different variables influencing human performance are not easily controlled. Human performance is influenced by many variables, not least those involving the psyche. Many scientists may feel,

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perhaps justifiably, that these variables cannot be sufficiently well controlled in field studies for there to be meaningful findings.

Second, there is a dearth of tools to measure accurately human performance in the laboratory. If sports performance cannot be measured frequently with a high degree of precision in the laboratory, then training-induced changes in exercise performance are not quantifiable. As a result, most studies use physiological surrogates to predict changes in exercise performance. The most widely used performance surrogate is the maximum oxygen consumption (VO_2 max). But, the very use of this specific measure has helped to entrench a particular and, perhaps, unquestioning dogma of the factors that likely determine human exercise performance (Noakes 1988, 1997, 1998).

As a result, most of the training studies reported in the literature have measured the physiological and biochemical responses of the human to training and have paid less attention (i) to the extent to which human exercise performance is altered by different training programmes and (ii) to the specific physiological adaptations which explain training-induced changes in athletic performance.

Indeed, an important weakness in our current thinking in exercise physiology is that we lack certain knowledge of the precise factors that determine fatigue and hence limit performance in different types of exercise under a range of environmental conditions. In part, this is because some scientists remain unaware that their research is based on the (subconscious) acceptance usually of one specific model of human exercise physiology (Noakes 1997, 1998). But it would be very surprising if one single physiological model adequately explains human exercise performance under all conditions.

Accordingly, the aim of this review is not to describe how the body adapts to physical training. This information is freely available, largely descriptive and not particularly contentious, so that its review is unlikely to challenge how we think about our science. Rather I will use this opportunity to pose two questions: What physiological models have exercise scientists developed (and subconsciously accepted) for the study of the physiological and biochemical determinants of fatigue during exercise? And which specific physiological, metabolic or biomechanical attributes might explain superior athletic performance and enhanced resistance to the development of fatigue?

Table 1. Current physiological models to understand the physiology of training for enhanced endurance performance

(a) The cardiovascular/anaerobic model
(b) The energy supply/energy depletion model
(c) The muscle recruitment (central fatigue)/muscle power model
(d) The biomechanical model
(e) The psychological/motivational model

Current physiological models to understand the physiology of training for enhanced endurance performance

Table 1 lists five different models that are commonly used to study and explain the likely physiological and other training-induced changes that may improve, especially, endurance performance, probably by delaying or preventing the onset of fatigue. Each model has its own proponents, usually those with a special expertise in the specific areas embraced by the model. Thus, the cardiovascular/anaerobic model is promoted usually by cardiovascular and respiratory physiologists; the energy supply/energy depletion model is favoured by the exercise biochemists; the muscle power/muscle recruitment model is advocated by muscle physiologists, and some biomechanists and neuro-physiologists; the biomechanical model by biomechanists, and the psychological/motivational model by sports psychologists.

Yet it is highly improbable that the factors explaining human exercise performance under all conditions are restricted to one physiological system or to one scientific discipline. Thus, human performance is unlikely to be adequately defined by any of these unitary models that are often presented as if they are mutually exclusive. The complexity of the physiological and other factors determining human performance is emphasized when the limitations of each of these models are exposed.

The cardiovascular/anaerobic model

Maximal exercise

This model holds that endurance performance is determined by the capacity of the athlete's large heart to pump unusually large volumes of blood and oxygen to the muscles. This allows the muscles to achieve higher work rates before they outstrip the available oxygen supply, developing skeletal muscle anaerobiosis (Fig. 1) (Noakes 1988, 1997, 1998, Bassett & Howley 1997). This model remains the most popular for explaining why fatigue develops during exercise; how the body adapts to training; how these adaptations enhance performance and, as a consequence, how effective exercise training programmes should be structured.

This model predicts that training increases "cardiovascular fitness" especially by increasing the body's maximum capacity to consume oxygen, measured as the maximum oxygen consumption (VO_2 max). This effect results from an increased maximum capacity of the heart to pump blood (the cardiac output) and an enhanced capacity of the muscles to consume that

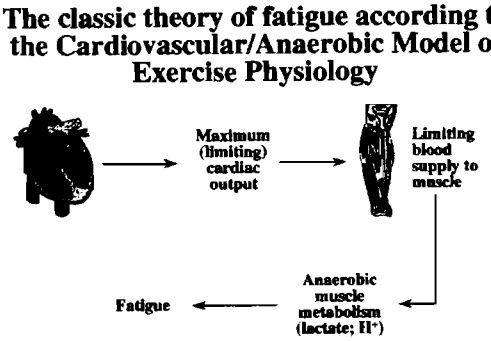


Fig. 1. The Cardiovascular/Anaerobic Model of Exercise Physiology and Athletic Performance holds that the heart has a limiting maximum cardiac output that is reached at the onset of a "plateau phenomenon", ascribed incorrectly to the work of Hill and colleagues (Hill et al. 1924, Hill 1927). As a result, blood and hence oxygen flow to the exercising muscles falls behind demand, inducing anaerobic metabolism. Metabolites of anaerobic metabolism, in particular hydrogen ions, then inhibit muscle contraction, inducing fatigue.

oxygen, the latter by increasing skeletal muscle capillarization and mitochondrial mass. It is argued that these adaptations delay the onset of skeletal muscle anaerobiosis during vigorous exercise, thereby reducing blood lactate concentrations in muscle and blood at all exercise intensities above the so-called "anaerobic threshold". The delayed onset of this blood lactate accumulation then allows the exercising muscles to continue contracting for longer at higher intensities before the onset of fatigue.

In addition, these changes increase the capacity of the muscles to use fat as a fuel during exercise, thereby enhancing endurance performance (according to the Energy Depletion model, described subsequently) (Saltin & Gollnick 1983, Holloszy & Coyle 1984). An important but unrecognized prediction of this model is that increases in coronary blood flow must be an essential adaptation to training (Noakes 1998). The higher coronary blood flow allows a greater pumping capacity of the heart producing a greater cardiac output to perfuse the exercising muscles, which can then achieve a higher exercise capacity.

This model finds strong support from the confirmation that these changes, with the exception of a greater coronary flow which is inferred, not proven, do indeed result from training, as fully documented in the literature. The key question is whether these changes are causally linked; that is, do these changes cause the change in exercise performance or do they occur pari-passu with other adaptation(s) that are the real cause of changes in exercise performance. For there are important deficiencies in this model which are fully argued (Noakes 1988, 1997) and counter-argued (Noakes 1998, Bassett & Howley 1997) elsewhere and will not be repeated here.

Perhaps the major but overlooked limitation of this model is that, if the pumping capacity of the heart does indeed limit oxygen utilization by the exercising skeletal muscle, then the heart itself will be the first organ affected by any postulated oxygen deficiency (Noakes 1998). This was first recognized by Hill and his colleagues as early as 1925 (Hill et al. 1924). Paradoxically it was the incorrect interpretation, by others, of the work of Hill and his colleagues, in particular their supposed description of a plateau phenomenon (Noakes 1998), that forms the (mythical) foundation for the cardiovascular/anaerobic model of exercise physiology. Yet those who popularized this mythical interpretation of the work of Hill and his colleagues, failed also to record what Hill considered to be the physiological cause (and equally the consequence) of the fatigue that develops during maximal exercise.

For the interpretation of Hill and his colleagues was unequivocal: "Certain it is that the capacity of the body for muscular exercise depends largely, if not mainly, on the capacity and output of the heart. It would obviously be very dangerous for the organ to be able, as the skeletal muscle is able, to exhaust itself very completely and rapidly, to take exercise far in excess of its capacity for recovery ... When the oxygen supply becomes inadequate, it is probable that the

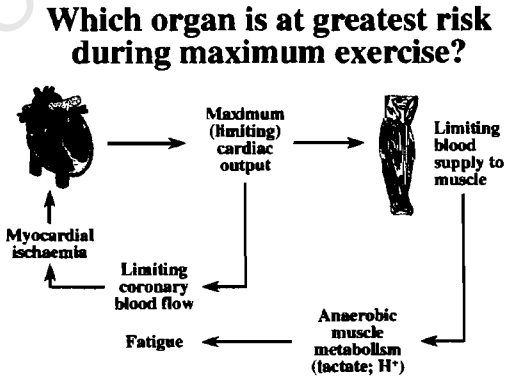


Fig. 2. The weakness of the Cardiovascular/Anaerobic Model of Exercise Physiology and Athletic Performance is that the attainment of a maximum cardiac output has more serious consequences for the heart than it does for the skeletal muscles as the first organ to be affected by a maximum cardiac output would be the heart itself. Continuing to exercise with a fixed (maximum) cardiac output would cause myocardial ischaemia. The heart, unable to increase coronary flow (dependant on an increase in cardiac output), would be unable to balance the increased myocardial oxygen demand caused by the very increase in workrate, theoretically necessary to define the mythical "plateau phenomenon" of Hill and his colleagues. Many early researchers believed that the heart did indeed develop ischaemia during maximal exercise, leading to a fall in cardiac output (Hill et al. 1924, Bainbridge 1931, Hill 1927, Dill 1938).

heart rapidly begins to diminish its output, so avoiding exhaustion ...".

The point identified by Hill and his colleagues, and since ignored by all subsequent generations of exercise physiologists, is that the heart is also a muscle, dependent for its function on an adequate blood and oxygen supply. But, unlike skeletal muscle, the heart is dependent for its blood supply on its own pumping capacity. Hence any intervention that reduces the pumping capacity of the heart, or demands the heart somehow to sustain an increased work output by the exercising muscles without any increase in cardiac output and coronary flow (as theoretically occurs when the "plateau phenomenon" develops), imperils the heart's own blood supply. Any reduction in coronary blood flow will consequently reduce the heart's pumping capacity, thereby inducing a vicious cycle of progressive and irreversible myocardial ischaemia (Fig. 2). It would seem logical that human design should include controls to protect the heart from ever entering this vicious circle.

Hence if (skeletal) muscle function fails when its oxygen demand exceeds supply then, for logical consistency, the inability of the pumping capacity of the heart to "raise the cardiac output" at the VO_2 max (Rowell 1993), must also result from an inadequate (myocardial) oxygen supply caused by a plateau in coronary flow. This limiting coronary blood flow induces myocardial "fatigue", causing the plateau in cardiac output and hence in the VO_2 max leading, finally, to skeletal muscle anaerobiosis. Thus, by this logic, the coronary blood flow must be the first physiological function to show a "plateau phenomenon" during progressive exercise to exhaustion (Fig. 3). All subsequent physiological "plateaus" must result from this limiting coronary flow (Noakes 1998).

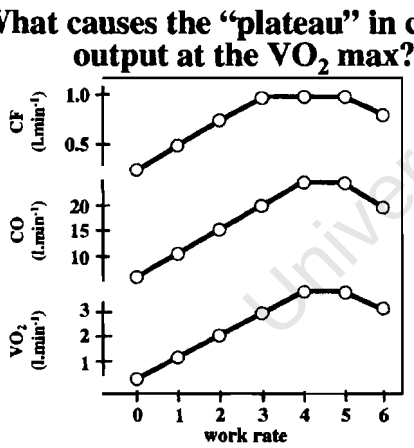


Fig. 3. According to the logic of the Cardiovascular/Anaerobic Model of Exercise Physiology and Athletic Performance, coronary flow must be the first physiological variable to "plateau" during progressive exercise to exhaustion. The peak in coronary flow would then induce a plateau in cardiac output as a result of a progressive myocardial ischaemia. Continuing to exercise with a fixed cardiac output and coronary flow would rapidly cause an ischaemia-induced fall in cardiac output and in coronary flow, and hence in whole body oxygen consumption. This logic was accepted by the early proponents of this model (Hill et al. 1924, Bainbridge 1931, Hill 1927, Dill 1938) but has since been overlooked by exercise physiologists for the past 75 years.

Whereas the most influential modern exercise physiologists have enthusiastically embraced this mythical basis for a "plateau phenomenon" for the past 75 years, none seems to have grasped this logical prediction of the "plateau phenomenon", which is that the "plateau phenomenon" requires the heart to fatigue first before skeletal muscle fatigue can develop. But this was clearly a concept with which the pioneering exercise physiologists were entirely comfortable. Thus, in addition to the conclusion of Hill and his colleagues, already quoted, both Bock and Dill (Bainbridge 1931) also believed that myocardial hypoxia causes a fall in the cardiac output at the point of fatigue during high intensity exercise:

"The blood supply to the heart, in many men, may be the weak link in the chain of circulatory adjustments during muscular exercise, and as the intensity of muscular exertion increases, a point is probably reached in most individuals at which the supply of oxygen to the heart falls short of its demands, and the continued performance of work becomes difficult or impossible" (p. 15). Hence they proposed that: "Another factor, which may contribute to the production of this type of fatigue, is fatigue of the heart itself" (p. 229).

"Although the occurrence of fatigue of the heart in health is not very clearly established, a temporary lowering of the functional capacity of the heart, induced by fatigue of its muscular fibres, might gradually bring about during exercise an insufficient blood supply to the skeletal muscles and brain. The lassitude and disinclination for exertion, often experienced on the day after a strenuous bout of exercise, has been ascribed to fatigue of the heart as its primary cause" (p. 229). Hence they concluded: "The heart, as a rule, reaches the limit of its powers earlier than the skeletal muscles, and determines a man's capability for exertion".

In summary, the early physiologists who believed that skeletal muscle anaerobiosis limits maximal exercise clearly understood that any plateau in cardiac output, necessary for there to be a limiting skeletal muscle blood flow, must result from a plateau in coronary blood flow which would expose the heart to a progressive myocardial ischaemia that would worsen as exercise was prolonged.

Perhaps the reluctance of modern physiologists to acknowledge these concepts stems from the current

appreciation that progressive myocardial ischaemia does not occur during maximal exercise in healthy athletes (Raskoff et al. 1976), even though there is good evidence that it is a limiting cardiac output that probably determines the VO_2 max (Rowell 1993). Thus, one postulate might be that even if cardiac output limits maximal exercise as seems likely (Noakes 1997), termination of exercise must occur before the heart actually reaches that maximum and hence well before skeletal muscle anaerobiosis can develop (Noakes 1998). Hence for 75 years, exercise physiologists may have focused on the incorrect organ as the site of any potential anaerobiosis that may develop during maximal exercise (Hill et al. 1924, Bainbridge 1931, Hill 1927, Hill et al. 1924).

How might a maximal cardiac output be reached without the development of myocardial ischaemia? The argument that the rate of cardiac filling, due either to a limiting venous return or the effects of a restrictive pericardium (Stray-Gundersen et al. 1986) may limit the maximal cardiac output, whilst superficially attractive, is still unable satisfactorily to explain which physiological events terminates exercise. Such an argument fails for the reason that the continuation of exercise beyond that (however limited) maximal cardiac output must still cause a progressive myocardial ischaemia to develop (Fig. 2). Hence, even if the cardiac output is limited by factors unrelated to the development of myocardial ischaemia (for example, a limiting venous return), the continuation of exercise beyond that point of limitation must induce myocardial ischaemia and the development of chest pain (angina pectoris) that would terminate exercise.

Perhaps it is more logical to speculate that maximal exercise terminates as part of a regulated process before the absolute maximum cardiac output and coronary blood flow are achieved. Interestingly Hill and his colleagues seem to have been the first to suggest a solution to this dilemma as early as 1924: "From the point of view of a well co-ordinated mechanism, ... it would clearly be useless for the heart to make an excessive effort if by doing so it merely produced a far lower degree of saturation of the arterial blood; and we suggest that, in the body (either in the heart muscle itself or in the nervous system), there is some mechanism which causes a slowing of the circulation as soon as a serious degree of unsaturation occurs, and vice versa. This mechanism would tend to act as a governor maintaining a high degree of saturation of the blood" (Hill et al. 1924, p. 161–162).

Clearly no such governor has yet been discovered, perhaps because no physiologists have yet searched for it. But there is clear physiological evidence for the existence of such a governor. The evidence comes from studies of skeletal and cardiac muscle function at altitude. For if oxygen deficiency really does develop in either heart or skeletal muscle during maximum exercise, its appearance will likely be more easily identifiable during exercise at altitude under conditions of hypobaric hypoxia. Furthermore, such experiments should identify in which organ – heart or skeletal muscle – anaerobiosis first becomes apparent; the heart, according to the ideas of the pioneering British and North American exercise physiologists, or the skeletal muscles, according to the influential group of modern exercise physiologists (Noakes 1998).

The original studies of exercise at altitude were undertaken by a research group co-ordinated by Dill and his colleagues from the Harvard fatigue laboratory. This research established two crucial findings. First, that peak blood lactate concentrations during maximum exercise fell with increasing altitude (Edwards 1936), a phenomenon since labelled the "lactate paradox" (Hochachka 1989). Second, that maximum heart rate and cardiac output likewise fell during exercise at increasing altitude (Christensen 1938, Dill 1938).

Edwards (1936) interpreted the "lactate paradox" at altitude accordingly: "The inability to accumulate large amounts of lactate at high altitudes suggests a protective mechanism preventing an already low arterial saturation from becoming markedly lower ... It may be that the protective mechanism lies in an inadequate oxygen supply to essential muscles, e.g. the diaphragm or the muscles".

The existence of the "lactate paradox" was confirmed during the epic laboratory experiment of exercise and acclimatization at simulated high altitude, Operation Everest II (Green et al. 1989). That study found that muscle lactate concentrations achieved during maximal exercise at the highest equivalent altitude achieved during that experiment (8848 m – equivalent to the summit of Mount Everest) were no higher than when at rest at sea level.

Hence, in as much as high muscle lactate concentrations would have to be present if the exercising muscles were contracting "anaerobically", this study proves that exercise at extreme altitude terminates when the exercising muscles are contracting in fully aerobic conditions.

Similarly Operation Everest II (Sutton et al. 1988) confirmed these original and subsequent studies (Pugh 1964, Vogel et al. 1974) showing that heart rate and cardiac output are substantially reduced during exercise at extreme altitude. The key observation is that the peak cardiac output falls with increasing altitude. This response is equally paradoxical for those who believe that the delivery of an adequate oxygen supply to the exercising muscles is the cardinal priority during exercise (Noakes 1998). For logic demands that *if* the principal responsibility of the cardiovascular system during exercise is the achievement of an (ultimately inadequate) oxygen supply to skeletal

muscle, then the maximum cardiac output during exercise at increasing altitude must either stay the same or even increase at increasing altitude in order to limit the effects of the progressive reduction in the arterial oxygen content.

Yet the evidence is absolutely clear. The heart makes the exactly opposite adjustment - maximum cardiac output falls with increasing altitude (Sutton et al. 1988). The reduction is due to the reduction in heart rate; stroke volume and myocardial contractility are, if anything, enhanced during peak exercise at altitude (Reeves et al. 1987, Suarez et al. 1987). Hence the conclusion must be that some currently unrecognized mechanism must exist to insure that the heart does not become "anaerobic" during maximal exercise at any altitude – from sea level to the summit of Mount Everest – in healthy humans.

Interestingly Christensen, but not Dill, interpreted this phenomenon correctly: "Christensen and I differed in our interpretation of his measurements of respiratory and circulatory function in exercise (at altitude). In his opinion, the chief limiting factor is the ventilation of the lungs. In the hardest grade of work at any station, the pulmonary ventilation reached about as high a value as at sea level, while the maximal cardiac output became less as the altitude increased. He thinks this means that the heart has an untapped reserve; it is circulating blood fast enough to carry to the tissues all the oxygen supplied by the lungs" (Dill 1938, p. 170–171).

These studies invite two precise conclusions. First, that the oxygen demands of the skeletal muscles are not the cardinal priority and hence are not "protected" during maximum exercise, at least at extreme altitude. Second, neither the skeletal muscles nor the heart becomes "anaerobic" during maximal exercise under conditions of hypobaric hypoxia. The sole conclusion must be that some type of "governor", as originally proposed by A.V. Hill, must limit maximum exercise at altitude. Furthermore, it would be difficult to explain why the same control mechanism should not act similarly during maximum exercise at sea level.

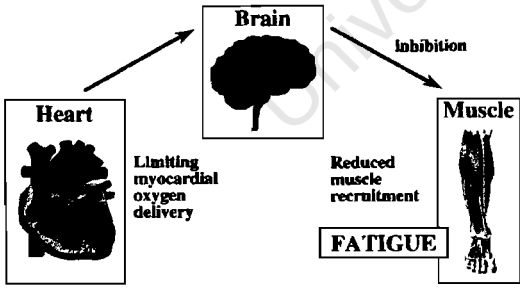


Fig. 4. The "governor" postulated by Hill could be activated by a limiting myocardial oxygen delivery. As a result, there would be a reduced activation of the exercising skeletal muscle by the cerebral motor cortex. There is compelling evidence for the presence of this reflex during exercise at altitude (Kayser et al. 1994) with the result that neither the heart (Sutton et al. 1988, Reeves et al. 1987, Suzrez et al. 1987) nor the skeletal muscles (Green et al. 1989) develop "anaerobiosis" during maximal exercise at extreme altitude.

In summary, a number of famous studies have shown that under the precise conditions likely to induce anaerobiosis in either the heart or skeletal muscles – maximal exercise at altitude – neither the heart nor the skeletal muscle show any evidence whatsoever for "anaerobic" metabolism. This unexpected finding can be explained only if there is a "governor", probably in the central nervous system, whose function is likely to prevent the development of myocardial ischaemia. The same governor could also serve the identical function also at sea level, thereby preventing the development of myocardial ischaemia during maximum exercise at sea level, according to Fig. 2. As Dill (1938) concluded, probably correctly: "The capacity of the heart, as has already been suggested, is restricted at high altitude because of the deficiency in supply of oxygen to it" (p. 15). But the important point is that the heart never actually develops an oxygen deficiency at altitude or at sea level; the governor acts to terminate exercise before that deficiency becomes apparent.

The final confirmation for the presence of this theoretical governor comes from the study of Kayser et al. (1994). They showed that skeletal muscle recruitment, measured as skeletal muscle EMG activity at peak exercise, falls with increasing altitude, but increases acutely with oxygen administration. They conclude: "during chronic hypobaric hypoxia, the central nervous system may play a primary role in limiting exhaustive exercise and maximum accumulation of lactate in blood". This study therefore proves the existence of the neural effector limb of Hill's postulated governor (Fig. 4) and its activity during exercise at altitude.

Interestingly, had the human body been designed to function according to the modern physiologists' cardiovascular/anaerobic model, which requires that anaerobiosis first develops in skeletal muscle before maximal exercise is terminated, no climber would ever have reached the summit of Mount Everest or other high mountains, even with the use of supplemental oxygen. Rather, all would have succumbed to a combination of myocardial ischaemia and cerebral hypoxia whilst their skeletal muscles were exercising vigorously and unrestrainedly, in pursuit of anaerobiosis and fatigue, according to the model depicted in Fig. 1.

Figure 4 therefore summarizes the hypothetical existence and action of the "governor", first proposed by A.V. Hill. It is postulated that receptor(s) exist in

the heart, to assess the adequacy of any of all of the following: coronary blood flow, coronary oxygen delivery or myocardial or coronary venous oxygen tension. Before any of these reach some predetermined limit, the motor cortex in the brain reduces skeletal muscle activation. As a consequence, skeletal muscle recruitment either fails to rise further or it falls, limiting the work output of the body, indicating the onset of "fatigue". The fall in work output by the body reduces myocardial oxygen demand and, as a consequence, the threat of myocardial ischaemia is averted.

Alternatively it may be that myocardial adenosine triphosphate (ATP) concentrations are sensed and "defended" in much the same way as appears to be the case for skeletal muscle, as discussed subsequently (Fitts 1994, Spriet et al. 1987). Reduction of myocardial ATP concentrations could lead directly to a reduction in myocardial contractile force as occurs in "myocardial stunning" (Braunwald & Kloner 1982). This could explain the onset of cardiac failure during maximal exercise in persons with coronary artery disease but could not explain why, at altitude, left ventricular function is enhanced during maximal exercise and shows no evidence for "fatigue".

Accordingly, it is proposed that maximal exercise is limited by a regulated process that terminates exercise before the development of a progressive myocardial ischaemia, that would precede the development of skeletal muscle anaerobiosis. This model further predicts that peak coronary blood flow is an important determinant of maximum exercise performance, and that interventions, including exercise training, that increase the maximum cardiac output probably also increase the maximum coronary blood flow, as their more important effect.

But this model does not exclude the possibility that interventions could also improve exercise performance by altering either skeletal muscle or myocardial contractile function or the efficiency of oxygen utilization, or both (Fig. 5).

Interestingly, the presence of a "governor" preventing the development of anaerobiosis in either heart or skeletal muscle during exercise at altitude has interesting implications for theories of the value of exercise training at altitude. For its presence means that any beneficial effect of altitude training cannot result from repeated exposure of either the heart or exercising skeletal muscle to greater levels of "anaerobiosis" than can be achieved during maximal exercise at sea level. This might explain why there remains considerable controversy about the proven value of high intensity training at altitude (Boning 1997).

The additional paradoxes that (i) adaptation to extreme altitude is associated with reduced skeletal muscle mitochondrial volume and enzyme content (Green et al. 1989, Oelz et al. 1986, Hoppeler et al. 1990); (ii) the skeletal muscle morphology of altitude-

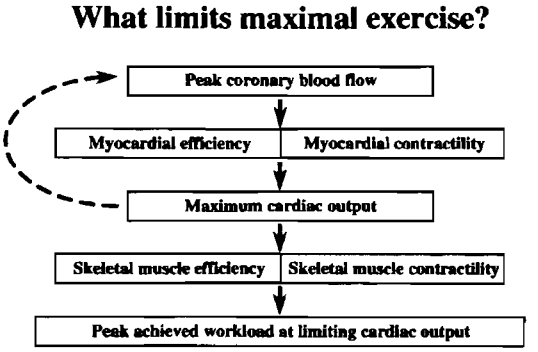


Fig. 5. According to the Hill/Noakes Cardiovascular/Neural Model of Exercise Physiology and Athletic Performance, performance during maximal exercise is ultimately limited by the peak coronary blood flow. However, the actual workrate achieved at that peak coronary blood flow would be determined by the efficiency and contractility of both the heart and the active skeletal muscles.

adapted Nepalese Sherpas is not different from that of acclimatized Caucasian climbers (Kayser et al. 1991) except that (iii) the volume density of skeletal muscle mitochondria is significantly smaller in Sherpas than in untrained sedentary subjects (Kayser et al. 1991), can best be explained if exercise performance at altitude is more likely determined by factors producing superior oxygenation of the heart, than of the skeletal muscles. This model therefore predicts that coronary blood flow and perhaps cardiac mitochondrial mass would be higher in high altitude natives and superior performers at high altitude. This would explain why high altitude natives achieve almost similar cardiac outputs at sea level and at altitude (Vogel et al. 1974), indicating a lesser activation of the "governor" during exercise at altitude.

Indeed the ability of high altitude natives to achieve high heart rates and cardiac outputs during exercise at altitude is associated with "relatively high oxygen tension and saturation" (Vogel et al. 1974) compatible with this postulate that superior myocardial oxygenation might be an important factor determining exercise capacity at altitude.

Prolonged submaximal (endurance) exercise

Many physiologists, notably in the past (Bainbridge 1931, Hill 1927, Dill 1938) but even today (Bassett & Howley 1997), have used this cardiovascular/anaerobic model also to explain the fatigue that develops during prolonged submaximal exercise and consequently have evoked changes in cardiovascular function to explain the mechanisms by which exercise training improves (endurance) performance during prolonged submaximal exercise.

Yet it is not entirely apparent why changes in the

Table 2. World rankings of male Kenyan runners in 1996

Distance	Rankings in world top 10
800 m	1*, 4, 6, 7, 10
1500 m	4, 5, 7, 8
5000 m	1, 7, 8, 9, 10
10 000 m	3, 4, 5, 6
3000 m steeplechase	1, 2, 3, 4, 5, 6, 8, 9, 10
3000 m	1, 3, 4, 5
Marathon	4, 6

* The naturalized Dane, Wilson Kipketer, is considered a Kenyan for the purposes of this analysis.

Table 3. Performances of Kenyans in the I.A.A.F. world cross-country championships (1986–1997)

Kenyan Senior Men, 1st for the last 12 years (1986–1997)
Kenyan Junior Men, 1st for the last 10 years (1988–1997)
Kenyan Senior Women, 1st 5 times in the last 7 years
Kenyan Junior Women, 1st 8 times in the last 9 years
Total: 35 Championships in 49 competitions including 24 individual championships.

maximum capacity to transport and utilize oxygen must also explain alterations in performance during *submaximal* exercise when oxygen transport cannot be limiting. An early proponent of this (il)logic was Sir Roger Bannister who wrote in 1956 that: "The muscular effort in long-distance running appears to be limited by cardio-respiratory failure as a whole and not by premature failure of any part of the integration" (Bannister 1956).

The obvious point is that, whereas the cardiovascular system could indeed set the limit for maximal exercise performance because of a limiting capacity to increase blood flow first to the heart, and then to the active muscles, it is not clear why cardiovascular function should limit prolonged submaximal exercise when blood flow and oxygen supply to muscle must be adequate. An Olympic analogy from my (African) continent highlights the issues that require debate.

In the years since Wilson Kiprugut won Kenya's first Olympic medal by finishing third in the 800 m at the 1964 Olympic Games, the dominance by Africans, especially Kenyans, in distance running has become a phenomenon unequalled in any other sport in the world (Bale & Sang 1996, Tanser 1997). Two measures of that dominance are provided by the world rankings of male Kenyan track runners in 1996 (Tanser 1997) (Table 2) and of the performances of the men and women's team, both senior and junior, in the World Cross-Country championships over the past 12 years (Tanser 1997) (Table 3). Of particular interest is the almost total dominance of the 3000 m steeplechase by Kenyans (Table 2). Indeed in excess of 90% of the 100 fastest-ever 3000 m steeplechase times in the world have been set by Kenyans. Any physiological explanation for the Kenyan's success must be able also to explain why these physiological attributes, uniquely common in Kenyan runners, offer an even greater advantage in cross-country events and in the steeplechase, rather than at other distances in which repeated jumping and changes in speed do not occur.

Two studies of Kenyan runners failed to provide a definitive physiological answer for their manifest superiority as distance runners although two of the best Kenyan runners were the most efficient runners yet studied (Saltin 1996, Saltin et al. 1995a,b) (Fig. 6). The overriding conclusion was that the Kenyans' VO_2 max values were not inordinately high; hence, a superior capacity for oxygen consumption during *maximum* exercise did not explain the Kenyans' manifest superiority during more prolonged *submaximal* exercise. In the words of Bengt Saltin, the senior author: "A comparison of some data on some of the very best runners in Kenya during the last decades and world class runners in Scandinavia does not reveal much that was not already known or could be anticipated" (Saltin 1996).

The only other study of elite (South) African distance runners is that of Coetzer et al. (1993). That study, which reported physiological data in the best group of distance runners yet evaluated anywhere in the world, has been largely ignored, for reasons that are not immediately clear. The sole weakness of the study was that the physiological characteristics of el-

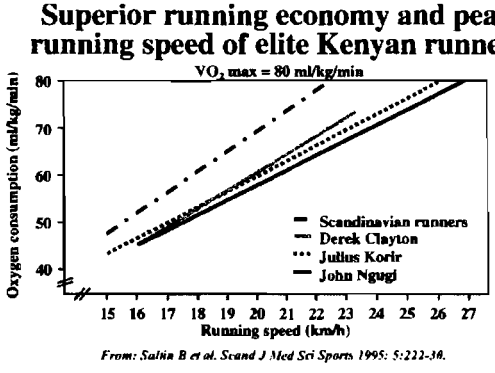


Fig. 6. In comparison to a group of elite Scandinavian runners (the highest running curve), the running economy (VO_2 at any running speed) of former world marathon record holder, Derek Clayton, and two of the greatest Kenyan runners, Julius Korir and John Ngugi, is substantially better. The Biomechanical Model of Exercise Physiology and Athletic Performance predicts that superior running economy would aid elite athletic performance by reducing both the rate at which heat is produced during exercise as well as the extent to which Stretch Shortening Cycle Fatigue develops during both training and racing. This theory predicts that the superior running ability of the Kenyans may relate, at least in part, to characteristics of their skeletal muscle and tendon elasticity (see also Fig. 12).

Table 4. Characteristics of elite South African distance runners

	Middle distance	Long distance
Height (cm)	181	169*
Weight (kg)	70	56*
Aerobic capacity (ml/kg/min)	72	71
Fatigue resistance (% VO_2 max for 21 km)	82	90*
Muscle fibre composition (% Type I)	63	53

*$P=<0.05$.
Data from Coetzer et al. 1993.

ite black South African distance runners were, perforce, compared to those of white South African middle distance runners. This comparison group was not ideal but was necessary because no other readily available group could match the performances of the black distance runners at any distance over 5 km. But the performances of the black and white runners in that study were at least equal in races of 1–3 km. Table 4 lists the important findings of that study.

The black distance runners were lighter and smaller, as also reported by Saltin (1996), with a slightly lower proportion of type I muscle fibres. But the key finding was that the black runners were able to run substantially faster at all distances beyond 5 km despite VO_2 max values that were the same as those of the middle distance runners. Hence the cardiovascular/anaerobic model failed to explain the superior endurance capacity of the black distance runners in that study and perhaps also in the studies of Saltin and colleagues (Saltin 1996, Saltin et al. 1995a,b).

Rather, the important difference was that the black runners were able to sustain a substantially higher proportion of their VO_2 max when racing. This is shown graphically in Fig. 7, which compares the % VO_2 max sustained by the black and white runners at different racing distances. At distances beyond 5 km, black runners sustained a significantly higher % VO_2 max than did the white runners and the difference increased with increasing racing distance. Thus, the crucial finding was that the black distance runners have superior fatigue resistance, not a higher aerobic capacity (VO_2 max). Hence factors distal to the heart, perhaps in the brain or in the muscles, appear to distinguish the very best runners in the world from those who are almost as good.

Interestingly, physiologists have known for at least two decades that the % VO_2 max that athletes can sustain during exercise is an important predictor of performance (Costill et al. 1973, Davies & Thompson 1979). Yet we have perhaps failed to emphasize, probably because of a devotion to the cardiovascular/anaerobic model, that this is likely to be a more important determinant of performance in prolonged exercise than is the VO_2 max alone. Furthermore, it has not been appreciated that the % VO_2 max sustained during exercise is a measure of the athlete's resistance to fatigue.

Hence, the important finding of that study was to show that the cardiovascular/anaerobic model may be unable to discriminate between very good and superior performance in events lasting more than a few minutes and which constitute the bulk of sporting events. It is consistent with the finding that the VO_2 max is a relatively poor predictor of endurance performance in athletes whose abilities are relatively homogenous (Noakes 1988, 1997, 1998, Davies & Thompson 1979, Noakes et al. 1990). The failure stems from the inability of this model to measure or predict fatigue resistance during prolonged *submaximal* exercise on the basis of physiological variables and performance measured during a single bout of progressive, maximal exercise to exhaustion. This confirms that the VO_2 max test does not measure *all* the physiological variables determining success during more prolonged exercise.

Further support for this explanation can be surmised from other information in Fig. 7, which shows that these athletes run at 100% or greater of their VO_2 max in race distances of 1–2 km. Yet it is not at those distances that the Kenyans' dominance is most apparent. If the Kenyans' success was due to their unusually high VO_2 max values, one would expect Kenyans also to be dominant at race distances of 800 m to the mile, which is not the case (Table 2).

Indeed, comparison of the performances of the

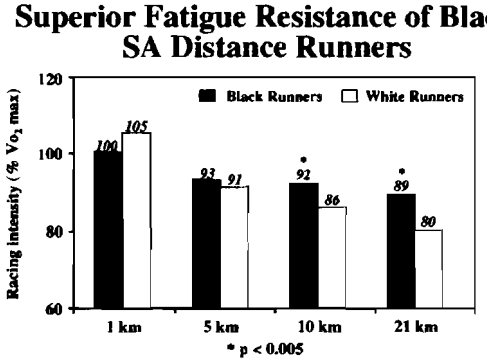


Fig. 7. The % VO_2 max sustained by elite South African black and white distance runners falls with increasing racing distance. However, black runners sustain a significantly higher % VO_2 max at race distances of 10 km and 21 km, indicating superior fatigue resistance. Such superiority cannot be explained by the Cardiovascular/Anaerobic Model of Exercise Physiology and Athletic Performance as VO_2 max values of black and white athletes in this study (Coetzer et al. 1993) were the same.

great British runner, Sebastian Coe, with those of a current Kenyan champion, Daniel Komen, provides further evidence for this interpretation. Remarkably, Komen's best time for the mile is 1 s faster than Coe's best. Yet the real performance difference occurs at 5 km: Komen's best time is 83 s faster than Coe's best, a performance difference of 10%.

In summary, there are serious theoretical flaws in the proposed cardiovascular/anaerobic model of exercise physiology and athletic performance (Noakes 1998), not least because the model predicts that a "plateau" in cardiac output must develop before skeletal muscle anaerobiosis can begin to occur. But any "plateau" in cardiac output requires that myocardial ischaemia be present either to cause that plateau (according to the theory that anaerobiosis limits muscle function) or as a result of it, as the cardiac output determines both coronary and skeletal muscle blood flow. As myocardial ischaemia has never been shown to develop during maximal exercise in healthy humans, so it would seem unlikely that skeletal muscle anaerobiosis can develop during progressive exercise to exhaustion (Noakes 1998). Rather, it would seem that "fatigue" during maximal exercise of short duration is part of a regulated neural process that prevents the development of myocardial ischaemia during maximal exercise.

Whilst this mechanism is designed to protect the heart from myocardial ischaemia, only indirectly does it determine the actual peak work rate achieved during maximal exercise (Fig. 5). The actual peak workrate achieved will depend on the "quality" of the skeletal and cardiac muscle. Superior myocardial contractility and efficiency of oxygen use would increase the maximum cardiac output achieved at any maximum (limiting) coronary flow. Similarly at any maximum skeletal muscle blood flow, superior contractility and efficiency of skeletal muscle contraction would increase the peak workrate achieved at that maximum cardiac output. This hypothesis forms what might be called the Cardiovascular/Neural Recruitment Model of Exercise Physiology and Athletic Performance.

Thus, this analysis of the traditional cardiovascular/anaerobic model of exercise performance leads to the alternate hypothesis that superior fatigue resistance, determined perhaps by the central nervous system or skeletal muscle contractile function, might explain superior performance in events lasting more than a few minutes. This superior fatigue resistance cannot be predicted by the cardiovascular/anaerobic model which uses exercise tests of short duration and in which the fatigue resistance component of endurance performance is not measured. By extension, it would seem that fatigue resistance is not causally determined by the magnitude of the athlete's cardiovascular capacity. There is also no logical reason to believe that fatigue resistance during *submaximal* exercise is determined by either the presence or absence of skeletal muscle anaerobiosis.

Accordingly, changes in exercise performance that result from endurance training are unlikely to be determined solely by changes in cardiovascular function, with the exception that increases in maximum coronary blood flow would likely be crucial for any increases in maximal cardiac output and hence in VO_2 max. It is of interest that the vasodilator capacity of the major epicardial coronary vessel is greatly increased in veteran long distance runners (Haskell et al. 1993). Perhaps this indicates that an important effect of endurance training, possibly at some critical growth periods, may be to increase maximum coronary blood flow as shown in animal models (Scheuer & Tipton 1997).

The energy supply/energy depletion model

The energy supply model

The central premise in the cardiovascular/anaerobic model is that it is the provision of a substrate (oxygen) to muscle that limits exercise performance so that fatigue is a direct consequence of a failure of oxygen delivery to the exercising muscles. A subtle extension of this idea produces a second model which proposes that fatigue during high intensity exercise may, alternatively, result from the inability to supply another substrate (ATP) at rates sufficiently fast to sustain exercise. Nobel Laureate A. V. Hill, whose research in the 1920s was directly responsible for the development of the cardiovascular/anaerobic model of exercise performance, also wrote: "The fact remains, however, that the chief factor in many forms of athletic achievement is the supply of energy and its proper and economic utilization" (Hill 1927, p. 237). Dr Peter Snell, Olympic Gold medallist in the 800 and 1500 m and former world record holder has stated similarly: "Performance in middle and (long) distance running ultimately depends upon the runner's capacity to produce energy for the duration of the event, and on the efficiency with which that energy is translated to running velocity. Thus the purpose of training is to improve the energy delivery systems, according to the demands of the event and to improve running economy" (Snell 1997).

Thus, this model predicts that performance in events of different durations is determined by the capacity to produce energy (ATP) by the different metabolic pathways including the phosphagens, oxygen-independent glycolysis, aerobic glycolysis and aerobic lipolysis. Superior performance is then explained by a greater capacity to generate ATP in the specific metabolic pathway(s) that predominates during that activity. Thus, the sprinter is assumed to have a greater capacity to generate ATP from the intramuscular phosphagen stores and from oxygen-indepen-

dent glycolysis, whereas the ultramarathon runner has a superior capacity to oxidize fat (aerobic lipolysis) (Hawley & Hopkins 1995).

Whether this hypothesis is true is uncertain as it has yet to be systematically evaluated. To prove this model would require (i) that the metabolic capacities of these different pathways be shown to be causally related to performance in events lasting the different durations; (ii) that the specific metabolic pathways be shown to adapt predictably with specific training, and (iii) that these adaptations alone explain the changes in performance that result from training with exercises lasting the different durations. Until these studies are completed, this model remains hypothetical, but interesting. It must be remembered that the truth of this model would need to disprove the opposing model, described in the previous section, which holds that maximal exercise performance is a regulated process limited by a failure of central neural recruitment. Fatigue at exhaustion, caused by a failure of central recruitment, will always *appear* to be due to a failure of ATP production unless the alternate possibility is studied (and excluded) simultaneously.

The argument against this model has been introduced elsewhere (Noakes 1997). In short, the prediction of this model is that exercise must terminate when muscle ATP depletion occurs (Fitts 1994), that is when the muscle develops rigor. Yet here again, the evidence appears clear. ATP concentrations, even in muscles forced to contract under ischaemic conditions, do not drop below about 60% of resting values (Fitts 1994, Spriet et al. 1987, Hochachka 1994) indicating that muscle ATP concentrations are "defended" in order to prevent the development of skeletal muscle rigor. As Fitts (1994) has concluded: "The overriding evidence suggests that (the high energy phosphates) do not participate in the fatigue process; that fatigue produced by other factors reduces the ATP utilization rate before ATP becomes limiting. The most compelling evidence for this conclusion is that cell ATP rarely falls below 70% of the pre-exercise level, even in cases of exercise fatigue" (p. 82).

Hence, is appears that the rate of ATP demand by the contracting muscles can never exceed the maximum rate of ATP supply because of the close matching of ATP demand to the available ATP supply (Spriet et al. 1987, Hochachka 1994).

There is an obvious analogy to the centrally situated neural "governor" that prevents the development of myocardial ischaemia during maximal exercise at either sea level or altitude. The difference is that the "governor" identified by Spriet et al. (1987) is clearly located in the periphery and acts even in muscles stimulated to contract with an externally applied current.

It is of interest that the presence of this peripheral "governor" is an essential component of the cardiovascular/anaerobic model as originally conceived from the work of Hill and his colleagues, and still widely promoted (Fig. 1). This hypothesis holds that when the rate of ATP production by oxidative sources becomes inadequate, high rates of "anaerobic" glycolytic ATP production produce metabolites, particularly H^+, which interfere with energy production and cross-bridge cycling causing fatigue and a failure of muscle contraction (Fitts 1994). In this way, muscle contraction fails not because of a failure of central recruitment (as predicted by the Cardiovascular/Neural Recruitment Model – previous section), but because of a peripherally located inhibition of muscular contraction. Proponents of this model can cite a large body of evidence showing that a number of metabolites can interfere with muscle cross-bridge cycling measured *in vitro* in isolated muscle fibres (Fitts 1994). The necessary assumption is that skeletal muscle contracting *in vitro* in the absence of an intact neural system behaves exactly as it would *in vivo* when the influences from the central nervous system are intact. But there is a body of evidence that is not compatible with these assumptions and conclusions.

For example, one of the few studies to evaluate critically this hypothesis that metabolites, particularly H^+, can induce skeletal muscle fatigue, is that of Mannion et al. (1995). They found that there is a wide range of muscle pH concentrations reached at exhaustion during intense exercise showing that if an accumulation of H^+ limits high intensity exercise *in vivo*, then "considerable interindividual differences must exist in the pH sensitivities of the various processes involved" (Mannion et al. 1995, p. 98).

Next, they found that in contrast to the prediction from *in vitro* studies, subjects with the highest proportion of type II muscle fibres were able to exercise to the lowest muscle pH concentrations. In contrast, *in vitro* studies have suggested that type I muscle fibres are more resistant to acidosis than are type II fibres. Finally, the authors found that subjects with a greater skeletal muscle buffering capacity did not accumulate more lactate during maximal exercise; nor were they able to exercise for longer than did those with lesser muscle buffering capacity. They concluded that "if acidosis makes any contribution to the fatigue during performance of this (high intensity) type of exercise, it is an indirect one ...".

One possibility is that such exercise is terminated by a central governor responding to factors other than skeletal muscle pH. Under these circumstances there would be no relationship between the onset of fatigue and muscle acidosis. This would not negate the established finding that *in vivo*, acidosis inhibits crossbridge cycling (Fitts 1994). It would mean only that this mechanism is not relevant in exercising

humans, perhaps because exercise terminates for other reasons, in particular to prevent the development of myocardial ischaemia, before the limiting skeletal muscle pH is reached.

Other relevant findings include the study of Bogdanis et al. (1995), who showed that recovery of muscle function following maximal sprint cycling exercise was related to recovery of muscle phosphocreatine concentrations and unrelated to muscle pH concentrations during recovery. In addition, Vollestad et al. (1988) showed that the gradual decline in maximum force generation in subjects performing repeated submaximal contractions for 40–70 min was "not due to lactacidosis or lack of substrates for ATP resynthesis and must have resulted from excitation/contraction coupling failure ...". Yet terminal exhaustion was associated with depletion of intramuscular phosphagen stores, but without evidence for acidosis.

In summary, a metabolic basis limiting high intensity exercise of short duration is widely assumed but incompletely documented. There is a need to establish whether those metabolic factors that appear to limit muscle function *in vitro* also play a role *in vivo* when the muscle is also under the influence of the central nervous system. Thus, the possible contribution of neural factors to this form of fatigue needs to be excluded before results from *in vitro* studies are extrapolated, without qualification, to the *in vivo* condition.

The energy depletion model

The related energy depletion model of exercise performance is specific for exercise lasting more than 2–3 h. It holds, in essence, that: "Depletion of endogenous carbohydrate stores has been shown to be a limiting factor in the ability to perform long term exercise" (Costill et al. 1973). The findings that support this conclusion are (i) that fatigue during prolonged exercise is *associated* with depletion of liver (causing hypoglycaemia) or muscle glycogen stores (Fitts 1994, Bosch et al. 1993, Coggan & Coyle 1987, Coyle et al. 1986, Tsintzas et al. 1996), or both; (ii) that reversal of hypoglycaemia allows exercise to continue (Coggan & Coyle 1987, Coyle et al. 1986, Tsintzas et al. 1996, Christensen & Hansen 1939) and (iii) that pre-exercise muscle glycogen supercompensation (carbohydrate-loading) (Hawley et al. 1997) or carbohydrate ingestion during exercise (Coyle et al. 1986), or both (Bosch et al. 1996), delays the onset of fatigue and improves exercise performance.

However, it must be remembered that relatively few carbohydrate-loading studies have been conducted with an adequate placebo control group. It seems highly improbable that neither athletes nor researchers are completely unaware of the widely reported benefits of carbohydrate-loading and that such knowledge is without effect on the findings of these trials. Indeed, two of the first such trials which included adequate placebo-controlled groups have both failed to find any ergogenic effect of pre-exercise carbohydrate loading (Burke et al. 1999, Hawley et al. 1997) under experimental conditions when such an effect might have been expected.

The finding that the reversal of hypoglycaemia alone allows exercise performance to continue (Coggan & Coyle 1987, Christensen & Hansen 1939) proves conclusively that liver glycogen depletion is one form of energy (carbohydrate) depletion that can definitely limit exercise performance. Interestingly, the rapidity with which the reversal of hypoglycaemia restores exercise performance indicates that a central neural "governor" must be active, similar to that activated during high intensity exercise at altitude. However, this control would be activated by changes in blood glucose concentrations and would act to prevent continuing high rates of muscle contraction and blood glucose oxidation that would further reduce the blood glucose concentration, risking hypoglycaemic cerebral damage.

But, in as much as no technique has yet been devised that will instantly reverse muscle glycogen depletion, in the same way that intravenous glucose infusion or oral glucose ingestion rapidly reverses hypoglycaemia, so it is impossible to prove conclusively that muscle glycogen depletion *alone* limits prolonged exercise performance. It needs to be remembered that there are many physiological changes besides muscle glycogen depletion that develop during exercise, and that any or all of these could contribute to, or cause fatigue during prolonged exercise. In addition, relatively little attention has been paid to the possible role of central (neural) fatigue (Davis & Bailey 1997) as *the* factor limiting prolonged exercise when muscle glycogen concentrations are also very low. Future studies of the energy depletion model need to show that central neural factors do not cause the fatigue currently ascribed to the development of muscle glycogen depletion during prolonged exercise.

Thus, the belief that muscle glycogen depletion causes fatigue is an interesting hypothesis that is supported logically by the findings that subjects who are exhausted during prolonged exercise develop very low muscle glycogen content (Fitts 1994, Bosch et al. 1993, Tsintzas et al. 1996, Burke et al. 1999), and that muscle glycogen is the metabolic fuel required for sustained high intensity exercise (Bosch et al. 1993). It would seem logical to assume that the two are causally linked at exhaustion during prolonged exercise; namely, that the near absence of muscle glycogen in exhausted subjects explains why they are unable to maintain, let alone increase, their exercise intensity at exhaustion. The finding that the vast majority of the modern and historical carbohydrate-loading studies show that this technique improves endurance per-

formance, presumably by increasing muscle glycogen utilization and delaying the onset of terminal muscle glycogen depletion, strongly supports the theory (Hawley et al. 1997). However, the possibility that part or all of these findings could also result from a placebo effect, acting through the central nervous system, needs to be considered (Burke et al. 1999). In addition, it is unclear how the inability to produce ATP at sufficiently high rates from one fuel source can explain this form of fatigue, given that skeletal muscle ATP concentrations remain high at exhaustion (as they do in all other forms of exhaustion (Fitts 1994)).

Nevertheless, there is a body of evidence that conflicts with the predictions of this hypothesis. For example, the classic study of Coyle et al. (1986) showed that athletes ingesting carbohydrate terminated exercise after 4 h when their muscle glycogen concentrations and rates of carbohydrate oxidation were the same as values measured 1 h earlier when the athletes were not exhausted. Another study found that athletes who adapted to a high fat diet were able to exercise to significantly lower muscle glycogen concentrations at exhaustion than when they were carbohydrate adapted (Lambert et al. 1994).

Conversely, Helge et al. (1996) showed that previously untrained subjects who trained on a high fat diet for 7 weeks before switching to a high carbohydrate diet for one week increased their pre-exercise muscle glycogen concentrations by 44% with only a small further increase in performance between the seventh and eighth weeks of the trial. Furthermore, performance was still substantially worse in fat-adapted subjects than it was in subjects who trained for 8 weeks on a high carbohydrate diet and whose pre-exercise muscle glycogen concentrations were 32% lower than fat-adapted athletes exposed to a high carbohydrate diet for one week.

In addition, exercise performance evaluated on 3 occasions in both dietary groups terminated before there was marked muscle glycogen depletion. The authors concluded: "Factors other than carbohydrate availability are responsible for the differences in endurance time between the groups" (p. 303); and "These observations also indicate that fatigue during prolonged moderately intense exercise does not always seem to be closely related to glycogen depletion, as is usually stated" (Christensen & Hansen 1939, Bergstrom et al. 1967). In his extensive review, Fitts (1994) similarly concludes: "It seems unlikely that muscle glycogen depletion, low blood glucose, and the resultant decline in carbohydrate oxidation is an exclusive fatigue factor during prolonged exercise". He does, however, acknowledge that "a possibility exists that muscle glycogen depletion is causative in fatigue via a mechanism independent of its role in energy production" (p. 83).

In addition, to my knowledge, no study has yet established that training improves endurance performance exclusively by increasing body carbohydrate stores and by delaying the onset of carbohydrate depletion during prolonged exercise in humans, although this finding has been reported in rats (Fitts et al. 1975) whose metabolism is substantially different from that of humans.

Similarly, it is currently difficult to explain performance in ultra-endurance events, especially the final 42 km running leg of the 226 km Ironman triathlon events according to this model, which holds that exercise of moderately high intensity is not possible once there is marked muscle glycogen depletion. After cycling at 40 $km \cdot h^{-1}$ for 4.5 h, the lead cyclists would be expected to have near total muscle glycogen depletion according to data from laboratory studies (Bosch et al. 1993). Yet the best performers in that event are able to run at close to 16 $km \cdot h^{-1}$ for a further 160 min. This probably represents an exercise intensity of >66% VO_2 max. The studies of Rauch et al. (1998) and O'Brien et al. (1993) suggest that total carbohydrate oxidation during very prolonged exercise of up to 6 h duration exceeds the estimated carbohydrate stores in liver and active muscle by up to 100%. Either these calculations are incorrect, or other sources of carbohydrate, in addition to those in the active muscles and liver, must contribute to fuel oxidation in events lasting more than 4–6 h. One possibility is that lactate oxidation of glycogen stored in the inactive skeletal muscles contributes a substantial additional amount to fuel use during very prolonged exercise (Rauch et al. 1998). How increased lactate oxidation contributes to performance is not known.

Similarly, provision of carbohydrate at high rates intravenously (Coggan & Coyle 1987) cannot extend exercise performance indefinitely. Whilst this could support the argument that muscle glycogen is *the* important carbohydrate source limiting exercise performance, the alternate possibility is that another factor, unrelated to depletion of body carbohydrate stores, perhaps a rising body temperature discussed subsequently, or central neural fatigue induced by other factors, may also limit endurance performance.

Perhaps there is a necessary *rate* of carbohydrate oxidation that is required to sustain a specific exercise intensity and that progressive whole body carbohydrate depletion lowers that rate, inducing fatigue. If this is correct, then fatigue resistance during prolonged exercise could be due to the capacity to sustain a higher rate of carbohydrate oxidation, and hence a *higher* respiratory quotient (RQ) during prolonged exercise. Again, this model suffers from the persisting logical impasse that a failure to generate ATP sufficiently rapidly must cause exercise to terminate because of muscle ATP depletion and rigor, a phenomenon which does not occur (Fitts 1994).

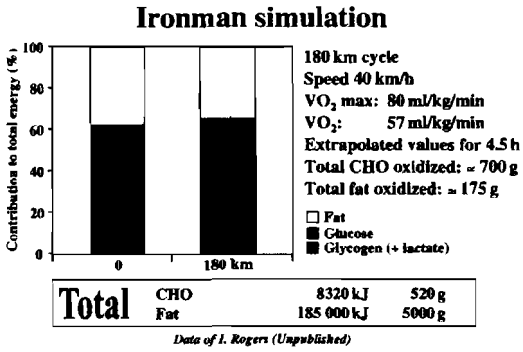


Fig. 8. Laboratory simulation suggests that an elite cyclist cycling 180 km in 4 h 30 min would cycle at an oxygen consumption of 57 ml/kg/min. Based on the measured contribution of fat and carbohydrate oxidation to this energy requirement (columns on the left of the figure), this would require the oxidation of about 700 g of carbohydrate and 175 g of fat. This compares to the predicted maximum body stores of 520 g of carbohydrate and 5000 g of fat in an elite triathlete. Hence this model predicts that the elite triathlete must commence the running leg of the triathlon with very low or absent whole body carbohydrate stores.

An equally plausible alternate theory postulates that superior endurance capacity may be determined by the exact opposite; by a superior capacity to oxidize fat and hence maintain a *lower* RQ during prolonged exercise. The latter possibility is supported by at least some evidence. In the studies of Bosch et al. (1993), those athletes unable to complete 3 h of exercise at 70% VO_2 max after carbohydrate-loading had significantly higher RQ during exercise and were therefore characterized by an inability to sustain high rates of fat oxidation during prolonged exercise. Indeed, simulated metabolic balance studies for the 226 km Hawaiian Ironman triathlon suggest it to be very likely that the capacity to oxidize fat at high rates will influence running speed late in the race when calculations suggest that muscle glycogen stores are likely to be depleted.

Figure 8 shows the expected energy metabolism during 4.5 h cycling at an oxygen consumption of 57 ml/kg/min. This is equivalent to cycling at 40 km/h and completing the 180 km cycle leg of the Ironman triathlon in the time necessary to be amongst the race leaders. The data for this simulation come from laboratory data measured on elite South African cyclists (I. Rodger. Unpublished data).

The simulation predicts that after 4.5 h of cycling an elite male Ironman triathlete would be expected to have oxidized about 700 g of carbohydrate and 175 g of fat. This compares to predicted whole body carbohydrate and fat stores of 520 g and 5000 g, respectively. Hence this model predicts that, at the end of the cycle leg, an elite athlete would have depleted his body carbohydrate stores, yet must still run 42.2 km at close to 16 km/h if he wishes to be successful.

Our other laboratory data suggest that after 4.5 h of such exercise, the carbohydrate contribution to whole body energy metabolism would comprise a blood glucose oxidation rate of 1.2 g/min (21 kJ/min) and a lactate oxidation rate of 0.6 g/min (10.5 kJ/min). Together with the average maximum rate of fat oxidation that we have measured after 6 h of laboratory cycling (0.76 g/min; 28 kJ/min), this provides a total rate of energy production of 59.5 kJ/min. This would provide energy at a rate sufficient to sustain a running speed of approximately 12 km/h, sufficient to complete the 42 km marathon leg of the Ironman triathlon in 3 h 30 min (Fig. 9). To equal the best marathon time yet run in that race, the athlete would be required to oxidize fat at a rate of 1.15 g/min (Fig. 10). This rate is approximately 50% faster than we have measured in cyclists in our laboratory.

Accordingly, if this metabolic model of fatigue in the Ironman triathlon is correct, then the difference between running the final marathon in 2 h 40 min versus 3 h 30 min may simply be a 51% (0.4 g/min)

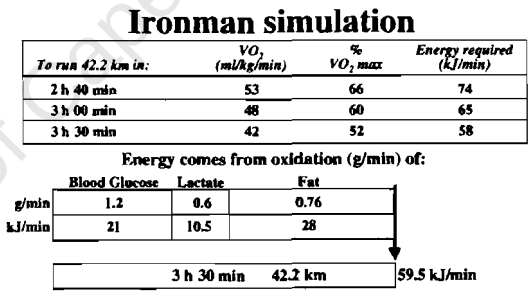


Fig. 9. The top panel of this figure shows the oxygen requirement (VO_2), the exercise intensity (% VO_2 max) and the rates of energy expenditure that would be sustained by a world-class athlete completing the final 42.2 km marathon running leg of the Ironman triathlon in times of either 2 h 40 min; 3 h 00 min; or 3 h 30 min. Laboratory studies suggest that after a 3.8 km swim and a 180 km cycle, the athlete's body carbohydrate stores would be depleted so that energy for the running leg would come from oxidation of (mainly ingested) blood glucose, blood lactate and from circulating free fatty acids derived from muscle and adipose tissue triglyceride. To complete the marathon running leg of the Ironman triathlon in 3 h 30 min, the athlete would have to sustain a VO_2 of 42 ml/kg/min (52% VO_2 max), equivalent to an energy expenditure of 59.5 kJ/min. Laboratory simulations (Fig. 8) suggest that under these conditions of near total carbohydrate depletion, peak glucose oxidation rates are 1.2 g/min and peak lactate (from glycogen) oxidation rates are 0.6 g/min. If these data for the maximum capacity to oxidize glucose and lactate in the carbohydrate-depleted state are correct, then to sustain the rate of energy expenditure necessary to run the marathon in 03:30:00, the carbohydrate-depleted triathlete must oxidize fat at a rate of 0.76 g/min.

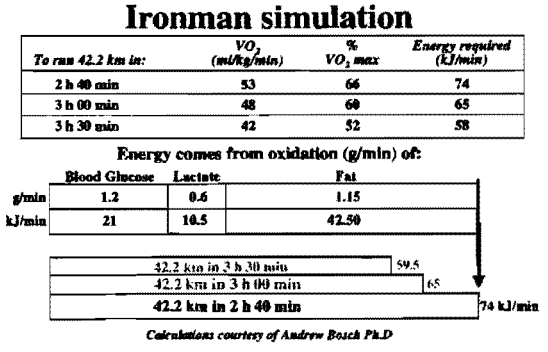


Fig. 10. To complete the marathon running leg of the Ironman triathlon in 2 h 40 min, currently the fastest running time yet recorded in the Hawaiian Ironman triathlon, the athlete would have to sustain a VO_2 of 53 ml/kg/min (66% VO_2 max), equivalent to an energy expenditure of 74 kJ/min. If the maximum capacity to oxidize glucose and lactate in the carbohydrate-depleted state is unchanged from values given in Fig. 9, then to sustain such a high rate of energy expenditure, the athlete must oxidize fat at a rate of 1.15 g/min. This model predicts that the superior ability of the elite Ironman triathlete may result from a much greater (approximately 50%) capacity to oxidize fat than has been measured in our laboratory experiments of very prolonged laboratory exercise involving sub-elite athletes (Rauch et al. 1998).

greater capacity to oxidize fat when body carbohydrate and, especially, muscle glycogen stores are depleted. Of course, this model does not negate the requirement that such high rates of fat oxidation can only be achieved if the central nervous system continues to recruit an appropriately large number of muscle fibres able to produce an appropriate force.

In summary, the human body has a limited capacity to store carbohydrates. In addition, high rates of carbohydrate oxidation are necessary to sustain high rates of energy expenditure (in the fed state). Furthermore, studies of very prolonged exercise (6 h) show that rates of carbohydrate oxidation remain high in athletes who ingest appropriate amounts of carbohydrate during exercise (Rauch et al. 1998). As both muscle and liver glycogen depletion occur in the fatigued state, it has popularly been assumed that there is a direct causal relationship between, especially, muscle glycogen depletion and the development of fatigue during prolonged exercise. Yet some findings suggest that this relationship may not be strictly causal under all circumstances. In addition is the logical impasse which requires that any energy depletion model predicts that exercise must terminate when muscle ATP depletion occurs, leading to muscle rigor. In the absence of such evidence, it would seem that factors in addition to depletion of body carbohydrate store may contribute to, or even cause, fatigue during prolonged exercise.

At present, no study has conclusively established that training-induced changes in the capacity to store and metabolize carbohydrate during prolonged exercise are causally related to training-induced changes in performance in humans, although this relationship is frequently assumed. The alternate possibility is that the capacity to oxidize fat at high rates when body carbohydrate stores are depleted, may delay fatigue and determine performance during exercise of moderately high intensity that lasts more than 4 h and is typified by ultradistance running and triathlon events (Fig. 8–10).

In this regard, the "crossover" concept of Brooks and Mercier (1994) is of particular interest. These authors argue that fuel choice during exercise "crosses over" from predominantly fat to exclusively carbohydrate at exercise intensities above about 80% VO_2 max. They conclude that training produces different effects depending on the intensity of the exercise being evaluated. At exercise intensities below their "crossover" point, training increases fat oxidation whereas at higher exercise intensities, training increases the capacity to burn carbohydrates. According to their concept, exercise at higher intensities (>70% VO_2 max) would be limited as an example of energy supply limitations (an inability to sustain high rates of carbohydrate oxidation), whereas exercise at lower intensities would be limited by muscle glycogen depletion. In fact the models are identical – according to the energy (muscle glycogen) depletion model, fatigue results from an inability to supply ATP sufficiently rapidly from fat oxidation (failure of energy supply from fat oxidation). The opposite pertains during high intensity exercise. In fact, as argued here and elsewhere (Fitts 1994), both the energy supply and the energy depletion models predict that muscle ATP depletion limits exercise. This does not occur; hence, the models must be too simplistic to explain what has been found.

The muscle recruitment (central fatigue)/muscle power model

The two previous models are based on the assumption that it is either the delivery of substrate either in blood (oxygen) or via the glycolytic and oxidative pathways (ATP) that limits exercise performance. The steps of (il)logic that have influenced these assumptions have been described (Noakes 1997, 1998). It remains difficult to prove whether or not either of these models is correct. Yet both continue to dominate, perhaps subconsciously, research and teaching in the exercise sciences, often to the exclusion of competing possibilities.

An alternate view is that it is not the rate of supply of substrate, either oxygen or fuel, to muscle that limits its performance but rather the processes involved

in skeletal muscle recruitment, excitation and contraction.

A failure of central nervous system recruitment of skeletal muscle forms the basis for the "central (nervous system) fatigue" hypothesis (Davis & Bailey 1997). This model holds that the brain concentration of serotonin (and perhaps other neurotransmitters, including dopamine and acetylcholine) alters the density of the neural impulses reaching the exercising muscles, thereby influencing the rate at which fatigue develops, especially during exercise. Alternatively, there may be inhibitory reflexes arising from the exercising muscles and which feedback to the spinal cord, reducing skeletal muscle recruitment at the level of the α-motoneuron. The evidence for both mechanisms has been extensively reviewed (Davis & Bailey 1997).

In brief, a number of studies indicate that manipulation of central nervous system neurotransmitter concentrations, in particular increasing dopamine and reducing serotonin concentrations, can enhance exercise performance whereas the opposite impairs performance. In addition, there is direct evidence for reduced central neural drive to muscle after fatiguing muscle contractions (Behm & St-Pierre 1997, Baker et al. 1993, Newham et al. 1991). This evidence is sufficiently persuasive to believe that central nervous system fatigue contributes to fatigue during prolonged exercise lasting tens of minutes to hours.

The clear evidence that fatigue at high altitude is caused by reduced central nervous system recruitment of the exercising muscles has been described. It is very likely that the fatigue that occurs during exercise in the heat is also likely limited by a failure of central recruitment as this form of fatigue cannot be explained by any other model. Thus, there is now substantive evidence that each athlete can store only some limiting amount of heat before being forced to reduce the exercise intensity or alternatively cease exercising altogether (Nielsen et al. 1990, 1993, 1997). There is no evidence from these studies that exhaustion under these conditions is associated with either skeletal muscle "anaerobiosis" or energy depletion. Rather, that it is either the total heat accumulated or its rate of accumulation that limits exercise is confirmed by intervention studies which show that precooling improves performance (Nielsen et al. 1997, Booth et al. 1997) whereas pre-heating has the opposite effect (Gongalez-Alonso et al. 1999).

In summary, there is sufficient evidence to suggest that a reduced central nervous system recruitment of the active muscles terminates maximum exercise at high altitudes (and probably also at sea level). The same mechanism likely terminates exercise in the heat when the body temperature reaches some limiting maximum and also when hypoglycaemia develops. In all these examples, reduced central recruitment of muscle would function to prevent organ damage (Noakes 1997).

However, the contrasting finding that skeletal muscle recruitment, measured as skeletal muscle electromyographic activity, rises during exercise at the same workload (Takaishi et al. 1994), is usually interpreted as evidence for a progressive failure of muscle fibre contractile function requiring additional fibre recruitment if the required force is to be sustained. Thus, this model holds that there is a progressive peripheral fatigue for which the central nervous system makes an appropriate adjustment.

Yet these studies usually impose a constant workload on the subject for the duration of the activity. But competitive sport does not usually involve such constant workrates; workrates tend to vary in a random, stochastic way (Palmer et al. 1994). We found that during prolonged exercise, which includes bouts of self-chosen high intensity exercise designed to simulate stochastic exercise, there is a progressive reduction in power output during the bouts of high intensity exercise (Burke et al. 1999). This strongly suggests central fatigue in which, during bouts of exercise requiring a near maximum effort, there is an inadequate increase in central neural drive to compensate for the expected reduction in the power output of the fatiguing skeletal muscle fibres (peripheral fatigue). That a relatively small percentage of the available muscle mass is ever recruited, even during maximal exercise (Sloniger et al. 1997), remains a perplexing but relatively underrecognized enigma. Proponents of any model of peripheral limitations for exercise performance need to explain why the body does not recruit all its available muscle mass to produce the necessary force under varying exercise conditions as so-called "peripheral fatigue" develops.

In summary, one interpretation of the muscle recruitment (central fatigue) model is that changes in central neurotransmitters induce fatigue simply as a natural consequence of prolonged exercise and changes in the relative balance of the different (ergogenic and ergolytic) neurotransmitters in the brain. No specific physiological value or importance is assigned to this phenomenon.

Alternatively, I have argued that a reduced central activation of the exercising muscles may be necessary to protect the human under specific conditions (Noakes 1997, 1998). It is postulated that these control mechanisms are necessary (i) to prevent myocardial ischaemia during exercise at high intensity; (ii) to prevent the development of muscle ATP depletion and muscle rigor during high intensity exercise; (iii) to prevent myocardial ischaemia or cerebral hypoxia during exercise at altitude; (iv) to prevent a fall in blood pressure during exercise in patients with chronic heart failure; (v) to prevent heatstroke during

prolonged exercise in the heat, and (vi) to prevent glucopaenic brain damage during prolonged exercise when hypoglycaemia results from liver glycogen depletion. The likely mechanism of control is through the regulation either of skeletal muscle recruitment or of excitation/contraction coupling in the muscle.

Muscle power model

This model holds that muscle contractile capacity, that is the ability of individual muscle cross-bridges to generate force, is not the same in the muscles of all humans, so that those with superior athletic ability have muscles with a superior capacity to generate force (superior contractility) by the individual cross-bridges of the different muscle fibres. This model is well accepted by cardiac physiologists, the majority of whom would argue that calcium delivery to the myofibres and the activity of the enzyme involved in ATP hydrolysis, myosin ATPase, rather than substrate supply, determine the contractile state of the myocardium in both health and disease (Opie 1998).

I could find only one recent statement using this model to explain superior athletic performance, specifically in swimming: "First, the strength of the muscles used in swimming is a major determinant of success in events from 50 m to 1500 m. Though this may not seem surprising, it must be remembered that strength *per se* does not dictate fast swimming. The forces generated by the muscle must be effectively applied to the water if they are to propel the body. Thus, strength specificity is the key to swimming success" (Costill et al. 1992).

There are rather few studies of the contractility of skeletal muscle isolated from athletes. These studies generally show that endurance training reduces skeletal muscle contractility (Fitts et al. 1989, Widrick et al. 1996). This establishes that skeletal muscle contractility is not an immutable characteristic of the different muscle fibre types (Fitss & Widrick 1996). By extension, one might speculate that the contractility of the specific muscle fibre types might differ between athletes of different abilities in different sporting disciplines, compatible with this muscle power model.

In summary, these two models of exercise performance predict that changes in exercise performance may result from increased skeletal muscle recruitment resulting from enhanced central neural drive, or from increased muscle contractile function resulting from biochemical adaptations in muscle that increase either force production or the rate of sarcomere shortening, or both.

However, the increase in performance resulting from these adaptations would occur only to the extent that the cardiovascular limits for exercise performance were not exceeded, according to the Cardiovascular/Neural Model.

The biomechanical model

There is growing interest in the role of muscles as elastic energy return systems which function both as springs and torque producers during exercise (Pennisi 1997, Roberts et al. 1997). Central to this model is the prediction that the greater the muscle's capacity to act as a spring, the less torque it must produce and hence the more efficient it is. The more efficient, more elastic muscle will enhance exercise performance, especially in weight-bearing activities, by slowing (i) the rate of accumulation of those metabolites that may cause fatigue during exercise, and (ii) the rate of rise of body temperature, thereby delaying the achievement of the core temperature that prevents the continuation of exercise.

This new information underscores another important logical weakness of the cardiovascular/anaerobic model for explaining enhanced endurance performance. For that model predicts that superior performance during prolonged exercise results from an *increased* oxygen delivery to muscle and an *increased* rate of energy and hence heat production. Thus, according to that model, the price of running faster is that more heat must be produced. But a higher rate of heat production would induce fatigue prematurely due to excessive heat accumulation, according to the findings of Nielsen and colleagues (Nielsen et al. 1993, 1997). A more logical biological adaptation would be to *reduce* the rate of oxygen consumption and hence the rate of heat production by increasing the athlete's efficiency (economy) of movement.

Indeed, if the rate of heat accumulation limits exercise performance under specific conditions, then factors that slow the rate at which heat accumulates when running fast should enhance performance. Two such factors are small size (Dennis & Noakes 1999) and superior running economy. A smaller size reduces the amount of heat produced when running at any speed. When environmental conditions limit the capacity for heat loss, smaller runners will be favoured (Dennis & Noakes 1999).

Further evidence supporting this argument that heat accumulation is a factor limiting endurance performance, is the finding that race times in both the marathon (Noakes 1992) and the longer distance track races including the 3000 m steeplechase and the 10000 m (McCann & Adams 1997) deteriorate as the environmental heat load increases. Thus, there is an inverse relationship between the environmental heat load, measured as the Wet Bulb Globe Temperature Index, and the reduction in race performance.

Therefore, according to this model, the more economical the athlete, the faster he or she will be able to run before reaching a limiting body temperature. A number of studies indicate that the best endurance athletes are also frequently the most economical

(Noakes 1992; Fig. 6). Indeed, most training studies show that improvements in running economy are perhaps the most likely response to training, especially in those who are already well-trained (Svedenhag & Sjodin 1985). This adaptation allows the athlete to run faster at the same oxygen consumption; thus, he or she completes a given distance more rapidly for the same average rate of heat accumulation but a reduced overall heat expenditure. This would be advantageous under conditions in which the heat load on the athlete increases (during the day).

Figure 11 shows that this adaptation may indeed exist. In a cross-sectional study of recreational (not elite) ultramarathon runners, it was found that those who trained more were more economical and hence could run faster at the same oxygen consumption or % VO_2 max. During competition, the better trained athletes ran at the same or a slightly lower % VO_2 max but completed the races in a shorter time (Scrimgeour et al. 1986). Hence being more economical, not having a higher VO_2 max, appears to be a more logical technique to enhance endurance performance.

In contrast, a high aerobic capacity, often a marker of poor running economy (Noakes 1988, 1992), would likely cause more rapid rates of heat accumulation and hence the more rapid onset of fatigue during prolonged exercise. This finding alone could explain why the best marathon runners usually have VO_2 max values in the range of 63–74 ml/kg/min. Less economical runners with higher VO_2 max values (Noakes 1988) have not necessarily been more successful (Noakes et al. 1990, Noakes 1992).

Thus, this model predicts that success in endurance events is not likely to result from training that makes the athlete ever more powerful with a larger muscle mass and greater VO_2 max. A more likely adaptation would be to reduce the athlete's size and increase his or her running efficiency. That runners believe they run better when lighter, is well known.

Another African analogy for this prediction is provided by the physiological strategy that the cheetah has evolved to survive as a successful predator. The cheetah, whose chase is terminated by an elevated rectal temperature after running at up to 100 km · h^{-1} for less than a minute (Taylor & Rowntree 1973), succeeds because of the animal's small size and probably a high degree of running economy (due to elasticity provided by the flexible spine). Thus, laboratory experiments showed that when the cheetah's rectal temperature reached 40.5–41°C, "the cheetahs refused to run ... They would simply turn over with their feet in the air and slide on the tread(mill) surface" (Taylor & Rowntree 1973).

The small size of the cheetah and its likely high running economy slows its rate of heat accumulation just sufficiently for it to outrun the smaller gazelles (≈25 kg) on which it preys and whose escape is also restrained by a rising body temperature (Taylor & Lyman 1972). Thus the chase between the gazelle and the cheetah is probably decided by which individual animal accumulates heat more slowly during the chase. In contrast, the heavier, more muscular lion has evolved a different co-operative, hunting strategy, targeting larger but slower mammals.

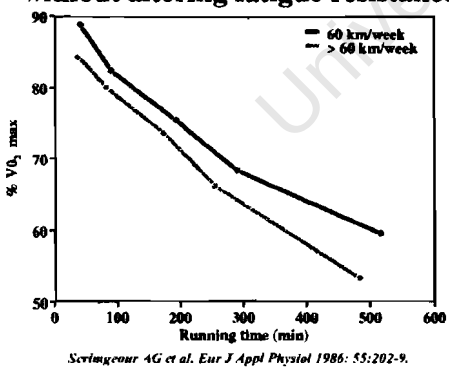
Perhaps the point is that smallness and greater running economy would seem to be a technique used to increase endurance capacity in one animal, the cheetah. Logic suggests that this technique may also be applicable to elite human athletes.

A second component of the biomechanical models stems from the accumulating evidence that repeated high velocity, short duration eccentric muscle contractions, as occur during running, induce a specific form of fatigue that develops during running races and is measurable for at least 7 days after a marathon race (Komi & Nicol 1998; Nicol et al. 1991).

Characteristics of this fatigue are a failure of the contractile capacity of the exercised muscles with a reduced tolerance to muscle stretch and a delayed transfer from muscle stretch to muscle shortening in the stretch/shortening cycle. As a result, the durations of both the braking and push-off phases in the running stride are increased, leading to mechanical changes in the stride with landing occurring on a more extended leg but with greater subsequent knee flexion.

As these abnormalities persist for many days after the race (Fig. 12), they cannot be explained by acute changes in oxygen or substrate delivery to the muscles, or by the elevated body temperature during

Training may improve racing performance without altering fatigue resistance



Scrimgeour AG et al. Eur J Appl Physiol 1986; 55:202-9.

Fig. 11. Ultramarathon athletes who trained more than 60 km · $week^{-1}$ (the lower running curve) outperformed less well trained athletes with similar VO_2 max values because their superior running economy allowed them to race faster but at a lower % VO_2 max, thereby finishing races of 10–90 km in shorter times. Hence changes in running economy with training allow athletes to run faster and at a *lower* exercise intensity, the opposite of what is usually assumed.

exercise, as required by the first 3 models. Rather, Komi and Nicol (1998) conclude that: "Stretch shortening fatigue results usually in a reversible muscle damage process and has considerable influence on muscle mechanics, joint and muscle stiffness as well as on reflex intervention". Thus any evaluation of fatigue resistance, especially in weight-bearing activities like running, needs to consider this specific form of stretch/shortening cycle fatigue.

To return to the African analogy, empirical observation of the running stride and the anatomical structure of the lower limb of Kenyan runners suggests, at least to this author, that an evaluation of the elastic elements of the legs of elite Kenyan runners and their resistance to stretch/shortening cycle fatigue would likely be very rewarding.

For example, it appears that African athletes generally train harder than do Caucasian runners (Tanser 1997, Coetzer et al. 1993). Especially the training volumes and intensities of the Kenyan runners (Tanser 1997) are unmatched by other athletes. But to achieve such training volumes, there must be superior resistance to the stretch/shortening cycle damage proposed by Komi & Nicol (1998), both in training and in marathon racing.

Hence, another possibility is that the more elastic muscles of elite distance runners are better able to resist eccentrically induced damage in training. This may allow more intensive daily training and hence superior adaptations to training. That same superiority would also enhance performance during competitive racing by delaying the onset of the stretch/shortening cycle fatigue that is an inevitable consequence of repeated eccentric muscle contractions.

In summary, the biomechanical model predicts that superior performance, especially in a weight-bearing activity like running, may be influenced by the capacity of the muscles to act as elastic energy return systems. Changes in the efficiency and durability of this process would (i) enhance movement economy and reduce the rate of heat production during exercise, thereby enhancing exercise capacity by slowing the rate at which the body temperature rises when environmental conditions are severe; (ii) enhance the quality of training by allowing more rapid recovery from stretch/shortening cycle fatigue so that more frequent bouts of intensive training can be undertaken and (iii) enhance fatigue resistance during competition by increasing resistance to that form of muscle damage that develops during repeated cycles of stretch/shortening contractions.

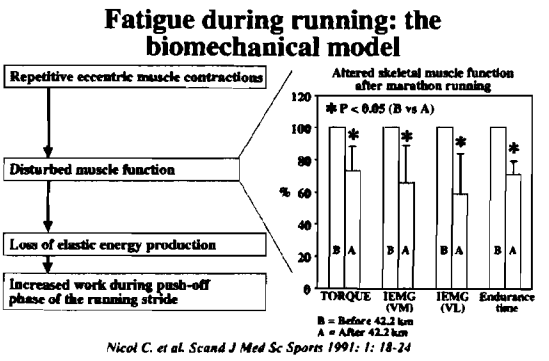


Fig. 12. According to the Biomechanical Model of Exercise Physiology and Athletic Performance, repetitive eccentric muscle contractions, as occurs in the quadriceps and calf muscles during running, produces altered muscle function with a loss of elastic energy production, requiring an increased work during the push-off phase of the running stride. The studies of Komi & Nicol (1998) and Nicol et al. (1991) show that there is a persistent reduction in peak torque and endurance performance time of the quadriceps muscle of subjects after they completed a 42.2 km marathon race. Integrated electromyographic activity (IEMG) in both the vastus medialis (VM) and the vastus lateralis (VL) was also reduced after the marathon. These studies show that there is a long-term effect of marathon running on skeletal muscle performance that persists after the muscle's energy stores are replaced, indicating that this abnormality is not explained by the Energy Depletion Model. It seems probable that the marathon "wall" (Noakes 1992) is probably explained by these alterations in skeletal muscle function.

The psychological/motivational model

This model holds that the ability to sustain exercise performance results from a conscious effort and is often included as a component of the central fatigue hypothesis (Davis & Bailey1997). But it conflicts with one proposal of the muscle recruitment model, which holds that exercise performance is regulated at a subconscious level and which exists, in part, to prevent conscious override that might damage the human.

It would seem that exercise performance must include at least some component that can be influenced by conscious effort. The dichotomy of physiology and psychology has generally prevented adequate laboratory evaluation of this model. Any studies showing an ergogenic effect of any placebo intervention on exercise performance would prove that this model contributes, in part, to athletic performance. Any detailed discussion of this model is beyond the scope of this author's expertise.

Summary

This paper has reviewed some of the models currently promoted to describe how exercise performance is limited by fatigue and enhanced by training. The argument advanced here is that until the factors determining both fatigue and athletic performance are established more definitely, it remains difficult to define which training adaptations are the most important for enhancing exercise performance, or how training

should be structured to maximize those adaptations. This remains a serious weakness for the practical application of much research in the exercise sciences.

However, within the constraints provided by these models, it would seem that the following training adaptations would contribute to enhanced exercise performance with training.

(a) *Cardiovascular/neural recruitment model*: Relevant training adaptations would be those that result in an increased VO_2 max and skeletal muscle blood flow during both maximal and prolonged submaximal exercise.

According to the model I have presented here, a plateau in coronary flow would appear to be the factor that limits the cardiac output, and hence the VO_2 max. Thus, an essential component of training would be to increase the maximal coronary flow.

However, even if the maximal coronary blood flow limits the maximal cardiac output, the actual peak workrate or peak VO_2 max that is achieved will depend on the contractile state of the myocardium and the efficiency with which the heart is able to convert that maximum coronary flow into a peak cardiac output. Similarly, the actual maximum work of which the muscles are capable at the VO_2 max, will equally depend on the economy and contractility of the skeletal muscles. Thus, optimum training would not only maximize coronary flow but also the efficiency and contractility of both the heart and skeletal muscles.

Incidentally, according to this model, interventions such as EPO therapy, blood re-infusion, or the administration of oxygen, all of which improve performance, would act in part by increasing oxygenation of the myocardium at maximal exercise, thereby allowing a greater cardiac output and hence a higher VO_2 max.

(b) *Energy supply model*: The important training adaptation would be an increased capacity to store and utilize metabolic substrates during exercise with a greater capacity to produce ATP and prevent a reduction in muscle phosphagen concentrations under all exercise conditions. Adaptations in different metabolic pathways would be necessary for optimizing performance in activities of different durations and intensities.

(c) *Energy depletion model*: A reduced rate of carbohydrate utilization during prolonged exercise would enhance performance by delaying the onset of whole body carbohydrate depletion. This model predicts that an increased capacity to burn fat during prolonged exercise would enhance endurance performance. That this model can also be considered as an "energy supply" model was described above.

(d) *Muscle recruitment and muscle power models*: These models predict that increased skeletal muscle contractile function, a peripheral effect, or increased neural recruitment, a central nervous system effect, would be advantageous for performance during exercise.

(e) *The biomechanical model*: A key predictor of the biomechanical model is that increased movement economy would improve performance by reducing the rate of heat accumulation during exercise. This model also explains why a reduced body mass would improve performance during prolonged exercise as it slows the rate of heat accumulation.

The importance of elastic return energy, especially in weight-bearing sports, and the identification of stretch/shortening cycle fatigue suggests that training may improve elasticity and delay stretch/shortening cycle fatigue, perhaps by altering the elastic component of skeletal muscle, tendons and ligaments.

Conclusion

The importance of these conceptual models is that they indicate that different physiological systems may determine performance under different exercise conditions. Hence, exercise physiologists need to consider all these models when they design studies to determine which are the most important physiological, biochemical, neural and other factors determining the changes in exercise performance that result from training.

More importantly, this review shows that many findings are incompatible with the predictions of one or more of these models. Rather than simply continuing to accept these inconsistencies uncritically, the modern generation of exercise physiologists should challenge old dogmas and so approach more closely the unattainable truth (Noakes 1997, 1998).

Key words: fatigue; VO_2 max; heart; skeletal muscle; glycogen; fat metabolism; muscle recruitment; contractility.

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CHAPTER 7

The Limits of Exercise for the Heart — a New Hypothesis

T D (Tim) Noakes

In the early 1920s, Archibald Vivian Hill, Nobel Laureate in Medicine and former Professor of Physiology at the University College, London, together with his colleagues C.N.H. Long and Hartley Lupton, developed the concept that the heart has a limiting maximum capacity, which is reached during maximal all-out exercise lasting between 3–7 minutes. This limiting cardiac output determines the peak exercise capacity by establishing the peak rate of oxygen delivery to the exercising muscles. This theory has been the single most enduring feature of the exercise sciences for the past 75 years.

But perhaps the more remarkable realisation is that, on the basis of a minimum of data and a surfeit of interpretation, Hill and his colleagues developed a model of cardiac function during exercise that included both the exceptionally clever and the profoundly incorrect. Worse, that part of the theory which is probably the most incorrect, is the one that has survived. Their more revolutionary concept has been forgotten. These ideas, dormant for 75 years, provide a completely novel understanding of how the heart's function may be limited during maximum exercise, specifically to ensure that myocardial ischaemia cannot develop, at least in health. Hill's concept can be extended to provide a novel understanding of the physiological basis of fatigue during exercise under a variety of conditions.

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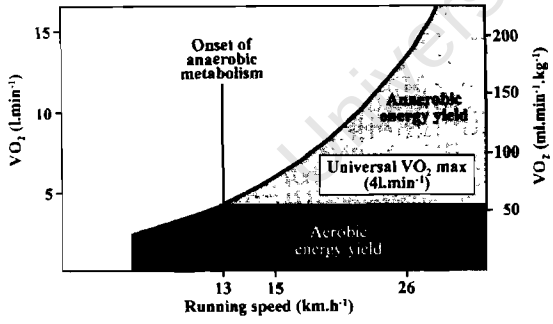
THE ORIGINAL STUDIES OF A.V. HILL

The legacy of Hill and his colleagues arises from a series of experiments undertaken between 1923 and 1925, shortly after Hill had assumed the Chair of Physiology at the University College, London. In these experiments Hill, and his associates, Hartley Lupton and Henry Long, repeatedly measured the oxygen consumption of subjects who ran for 3 minutes at different speeds on a circular grass track, 85 m in circumference; the use of laboratory treadmills was still in its infancy. On the basis of these experiments, the

authors concluded: "Considering the case of running there is clearly some critical speed for each individual above which, the maximum oxygen intake is inadequate, lactic acid accumulating, a continuously increasing oxygen debt being incurred, fatigue and exhaustion setting in".[1] Hill[2] further concluded that: "The oxygen intake may attain its maximum and remain constant merely because it cannot go any higher owing to the limitations of the circulatory and respiratory systems."

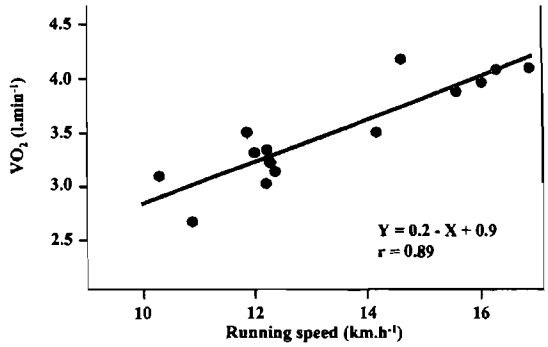
The Hill hypothesis. Hence the enduring hypothesis[3-7] proposed by Hill and his colleagues was that, during exercise, there is a workrate, the whole body oxygen demand of which exceeds the heart's capacity to supply. As a result, oxygen consumption (VO_2) "plateaus" at that workrate, defining the maximum whole body oxygen consumption (VO_2 max). Increasing the workrate beyond the VO_2 max requires an increasing "anaerobic" metabolism. Ultimately exercise terminates when the metabolic by-products of anaerobic metabolism, especially lactate and H^+, interfere with both energy production and muscle contractile activity, terminating exercise. Or in the words of a contemporary: "the valuable glycogen inside the muscle-fibres is turned into poisonous lactic acid, the muscles become stiff and tired, dwindle in power, and finally refuse to function until the lactic acid has been turned back into glycogen during the recuperative process of rest".[8] Hence this model predicts that rising muscle and blood lactate concentrations and falling pH, act to terminate or "constrain" further exercise.

Furthermore, Hill and his colleagues believed there to be an absolute and universal VO_2 max of 4L.min^{-1} that occurred at a running speed of 13 km.hr^{-1} [9] (Figure 7-1). This interpretation was made even though none of their studies actually showed an unambiguously identified VO_2 "plateau".[9-12] In fact their most frequently studied subject, Hill himself, showed a progressive linear increase in VO_2 even at the highest running speed of which he was capable without rapid exhaustion (17 km.hr^{-1}) (Figure 7-2). In as much as a continuously rising VO_2 must indicate a progressive rise in cardiac output, these early findings cannot be interpreted as conclusive evidence that the cardiac output reaches a limiting maximum during peak exercise such that a further increase in workrate could not elicit any further rise in cardiac output.



Redrawn from A.V. Hill and H. Lupton Quarterly Journal of Medicine 16; 157, 1923.

Figure 7-1. Hill and his colleagues believed that oxygen consumption (VO_2) rose as an exponential function of running speed and comprised aerobic and anaerobic components. The aerobic component peaked at 13 km.h^{-1} which constituted the "universal" maximum oxygen consumption (VO_2 max) of 4 L.min^{-1}. Anaerobic metabolism increased at running speeds above 13 km.h^{-1} and was the predominant energy source for all running speeds above about 18 km.h^{-1}.



A.V. Hill, C.N. Long and H. Lupton. Proceedings of the Royal Society B 97: 157, 1924.

Figure 7-2. In contrast to their theoretical prediction (Figure 7-1), the actual data for all experiments on A.V. Hill show that his oxygen consumption rose linearly to the highest running speed of which he was capable (17 km.h^{-1}). This anomaly between Figures 7-1 and 7-2 was not recognised in Hill's lifetime.

In 1955, a section of Hill's work was selectively rediscovered and incorrectly interpreted as proof that there is "an upper limit to the capacity of the combined respiratory and cardiovascular system to transport oxygen to the muscles. Further increases in workload merely result in an increase in oxygen debt and a shortening of the time in which the work can be performed".[13] Hence by 1955, the work of Hill and his colleagues had been interpreted as proof that maximal exercise of short duration (3–15 minutes) is constrained by a *limiting* capacity for oxygen transport in the body due, most likely, to the attainment of a limiting, maximum cardiac output.

In fact, Hill and his colleagues did not ever show conclusively that VO_2 "plateaus" during maximum exercise,[9-12] nor did they even believe that VO_2 rises as a linear function of an increasing workrate. Rather this was described as an exponential function[14] as shown in Figure 7-1. The reasons for his error have been detailed previously.[9]

By 1955 a linear relationship between VO_2 and (submaximal) exercising workrate had been established.[15] Perhaps as a result, the first diagrams representing what Hill and his colleagues were supposed to have found, took the charac-

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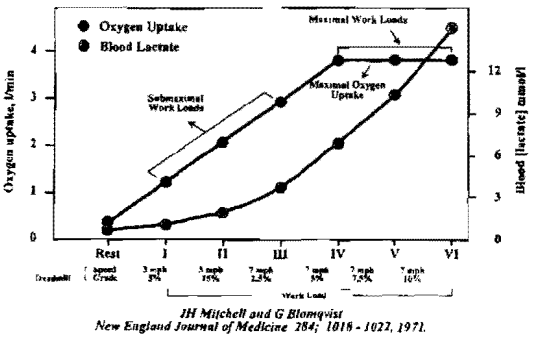

Figure 7-3. On the basis of Taylor et al's[13] 1955 interpretation of Hill's work, the more modern interpretation of the "plateau phenomenon" is shown in this figure. Note that oxygen consumption increases linearly up to a "plateau" value of 4 L.min^{-1}; further increases in workrate do not cause any further increase in VO_2. The exponential increase in blood lactate concentrations with increasing workrate has been interpreted to indicate the onset of "anaerobic" metabolism even during submaximal exercise. This contrasts with Hill's original teaching that "anaerobic" metabolism began only after the VO_2 max had been reached (Figure 7-1).

teristics of that shown in Figure 7-3.[16] Here VO_2 rises linearly up to a clearly defined "plateau" (contrast to Figure 7-1). Note that the VO_2 max in this 1972 diagram is 4L.min^{-1}, perhaps revealing the subliminal influence of the universal 4L.min^{-1} VO_2 max concept formulated nearly 50 years earlier by Hill and his colleagues.

Role of the heart. But this 1955 re-interpretation of work completed 30 years earlier, ignored two of the core tennants of Hill's evolving (Cardiovascular/Anaerobic) model of exercise physiology. The first was his realisation that if the rate of oxygen delivery to skeletal muscle does indeed reach a maximum that can be sustained for some variable time – the "plateau" shown in Figure 7-3 – then this must result from some form of cardiac failure that prevents any further rise in cardiac output during the "anaerobic" exercise that occurs at workrates requiring more than the VO_2 max. Thus he proposed that: "The enormous output of the heart of an able-bodied man, maintained for considerable periods during vigorous exercise, requires a large contemporary supply of oxygen to meet the demands for energy. When the oxygen supply becomes inadequate, it is probable that the heart rapidly begins to diminish its output, so avoiding exhaustion."[17] This interpretation was not confined exclusively to the hallowed lecture halls of the University College, London but crossed the North Atlantic to be included in the writings of Arlie Bock and David Dill co-founders of the Harvard Fatigue Laboratory in Cambridge, Massachusetts:[18] "The blood supply to the heart, in many men, may be the weak link in the chain of circulatory adjustments during muscular exercise, and as the intensity of muscular exertion increases, a point is probably reached in most individuals at which the supply of oxygen to the

heart falls short of its demands, and the continued performance of work becomes difficult or impossible."[18] As a result: "The heart, as a rule, reaches the limit of its powers earlier than the skeletal muscles, and determines a man's capability for exertion."[18]

Perhaps the reason why this interpretation has been ignored is because most now accept the converse; that is, that cardiac fatigue or failure does not develop during maximum exercise,[19] even at extreme altitude under conditions of profound hypoxia.[20,21] But none appear willing to have asked the question: If not, why not?

Plateau phenomenon. For logic demands that if cardiac output and oxygen consumption reach maximum values at the VO_2 plateau, then so too must muscle blood flow and total peripheral resistance. In other words, if the "plateau phenomenon" is real, a mechanism must exist that allows the active skeletal muscles to increase their work output (stage V and VI in Figure 7-3) without any further alteration in central or peripheral circulation. For any such alteration, for example, either a rise or fall in total peripheral resistance, will increase myocardial oxygen demand by increasing either the cardiac pre- or afterload. But, by definition, myocardial oxygen consumption cannot increase when the exercising workrate rises beyond the "VO_2 max" Hence any alteration in central or peripheral circulation during exercise at intensities beyond the VO_2 max "plateau" must cause an imbalance between myocardial oxygen demand and oxygen supply, inducing myocardial ischaemia, according to the very definition of the "plateau" phenomenon which requires that the workrate should increase without any further rise in myocardial or skeletal muscle VO_2.

Interestingly, one of the original diagrams depicting the expected cardiovascular changes during exercise at workrates up to, and beyond those eliciting the "plateau phenomenon", included information on changes in heart rate, stroke volume and cardiac output, only up to the workrate eliciting the VO_2 max. Figure 7-4 has been redrawn from the classic paper of Mitchell and Blomqvist.[16] It shows the clearly defined plateau in oxygen consumption in this subject when the work rate exceeds stage 4 of the test corresponding to Hill's universal VO_2 max of 4 L.min^{-1}. During the submaximal portions of the exercise test (stages 1 to 4), increases in work rate cause essentially linear increases in cardiac output, stroke volume, and heart rate. When the VO_2 plateaus at stages 5 and 6, these variables must also level off, hence proving that the pumping capacity of the heart limits the VO_2 max.

Surprisingly, Mitchell and Blomqvist[16] did not provide data for these cardiovascular measures once the VO_2 max has been reached (Figure 7-4). A more recent review by Mitchell of that paper[22] also lacks such data. Perhaps as serious scientists they were correctly reluctant to speculate on what they had not measured. Or perhaps they realized the

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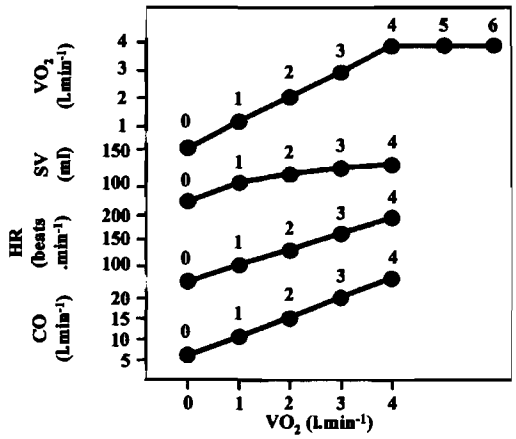

Redrawn from J.H. Mitchell and G. Blomqvist. New England Journal of Medicine 284: 1018 - 1022, 1971.

Figure 7-4. An original diagram depicting the plateau phenomenon in VO_2 (top panel; also Figure 7-3), included predicted changes in stroke volume (SV), heart rate (HR) and cardiac output (CO). Note that although the plateau in VO_2 at 4 L.min^{-1} was identified with no further increases during workrate stages 5 and 6, no data are included for predicted changes in SV, HR, and CO during work stages 5 and 6, "beyond the plateau phenomenon". Logic suggests that, if the "plateau phenomenon" is real, then cardiac output should begin to fall shortly after the attainment of VO_2 max, as a consequence of myocardial ischaemia. A.V. Hill and others believed that myocardial ischaemia develops during maximum exercise (for details, see text).

dilemma that such a conclusion posed, especially for the heart.

For the issue that must ultimately be addressed is: What are the consequences of the cardiovascular/anaerobic model for the heart itself? Or, alternatively, if the cardiac output limits the VO_2 max, what limits the cardiac output? For the heart is also a muscle. The cardiovascular/anaerobic model predicts that (skeletal) muscle function fails when its oxygen supply is inadequate. Hence if logic is to be preserved, this failure of the heart's pumping capacity, in Rowell's words "to raise the cardiac output" at the VO_2 max,[23] must result from an inadequate (myocardial) oxygen supply. Hence coronary blood flow must plateau sometime before the cardiac output levels off at the VO_2 max. This limiting coronary blood flow induces myocardial "fatigue", causing the plateau in cardiac output and hence in the VO_2 max, leading only thereafter to skeletal muscle anaerobiosis. Thus by this logic, the coronary blood flow must be the first physiological function to show a "plateau phenomenon" during progressive exercise to exhaustion.

Proposed "governor". When Hill and his colleagues realised that myocardial ischaemia must occur if the "plateau phenomenon" is real, they proposed a genuinely novel con-

Hill's original "governor" of heart function:

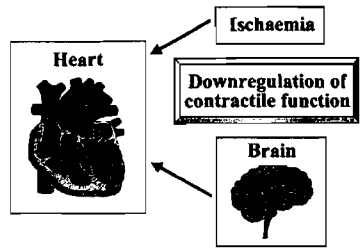

Figure 7-5. Hill proposed the need for a "governor", in either the heart or the brain, to reduce the extent to which myocardial ischaemia would develop during maximum exercise. This governor would act directly on the heart itself, to reduce its contractile state, thereby reducing myocardial oxygen demand and protecting the heart from damage during a developing "oxygen debt".

cept that has escaped the critical attention of subsequent generations of cardiologists and exercise physiologists: "It would seem probable that the heart is able to regulate its output, to some extent, in accordance with the degree of saturation of the arterial blood, either of that which reaches it through the coronary vessels or by some reflex in other organs produced by a deficient oxygen supply. From the point of view of a well co-ordinated mechanism, some such arrangement is imminently desirable; it would clearly be useless for the heart to make an excessive effort if by so doing it nearly produced a far lower degree of saturation of the arterial blood; and we suggest that, in the body (either in the heart muscle itself or in the nervous system), there is some mechanism which causes a slowing of the circulation as soon as a serious degree of unsaturation occurs, and vice versa. This mechanism would tend to act as a "governor", maintaining a high degree of saturation of blood".[17]

Thus, the physiological model of cardiovascular function during maximum exercise developed by A.V. Hill and his colleagues, requires that a limiting maximum cardiac output is reached sometime before the onset of fatigue and the termination of exercise. This causes a plateau in blood flow to the exercising muscles inducing skeletal muscle anaerobiosis. Such anaerobiosis then causes metabolic changes in the exercising muscles which lead to the rapid termination of exercise.

Myocardial ischaemia vs skeletal muscle anaerobiosis. But, with respect to maximal cardiac function, the far more interesting point is that the plateau in cardiac output necessary to induce skeletal muscle anaerobiosis, must cause myocardial ischaemia to develop *before* skeletal muscle anaerobiosis. Hill and his colleagues as well as their proteges at the Harvard Fatigue Laboratory, David Dill and Arlie Bock, did indeed teach that cardiac fatigue or failure must develop during maximum exercise at workrates be-

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yond the VO_2 max. But the novel insight of Hill and his colleagues was their proposal that some controlling mechanism – a "governor" – must exist in either the heart or the brain to limit the extent of this myocardial ischaemia (Figure 7-5).

In contrast, the major contribution for which Hill and his colleagues have been remembered is to the effect that "there is an upper limit to the capacity of the combined respiratory and cardiovascular system to transport oxygen to the muscle. Further increases in workload beyond this point merely result in an increase in oxygen debt and a shortening of the time in which the work can be performed.".[13]

The consequence of this interpretation has been that exercise physiologists have, for the past 75 years, favoured the belief that oxygen transport and its use exclusively determine maximum exercise capacity in humans and other mammals and any alteration thereof, whether due to disease, training, or other interventions.[3,13,16,24-26] This interpretation has recently been reaffirmed.[4-7] Indeed, for the past 50 years the focus of argument has not been to test the fundamental veracity of this hypothesis. Rather the debate has centered on the factors that determine the oxygen limitation this is supposed to occur at the VO_2 "plateau" – either the inability of the heart to increase oxygen delivery to the muscles[27] or a limiting capacity for oxygen uptake by the maximally exercising skeletal muscles.[28]

But not only did Hill and his colleagues fail to provide the experimental evidence underpinning any hypothesis that an oxygen limitation develops during exercise causing fatigue[9-12] but they understood the implications, at least for the heart, of this model. What is more, they proposed a unique controller, a governor, that would limit the extent to which myocardial ischaemia would develop, once the VO_2 "plateau" had been reached.

CHALLENGES POSED BY THIS INTERPRETATION OF THE WORK OF HILL

A number of important intellectual challenges arise from this interpretation of what Hill and his colleagues actually believed. The first is whether or not there is any evidence that cardiac output reaches a "plateau" or maximum value during intensive exercise, prior to the onset of fatigue, as predicted in Figure 7-4. This is an essential component of the traditional model.[1-7,13,14,16-18] Yet, to my knowledge, no study has yet actively evaluated this prediction of the model, which is surprising.

A number of studies have measured changes in cardiac output with increasing workrate up to those that elicit the VO_2 max.[29-34] These show that cardiac output rises linearly with increasing workrate and none suggest any evidence for the plateau in cardiac output predicted by the original model

of A.V. Hill and his colleagues (Figure 7-4). However, no study has looked specifically for a plateau in cardiac output that might occur, for example, in the last few minutes of exercise of progressively increasing intensity to exhaustion. Perhaps the really interesting question is why none have yet actively searched for the presence or absence of this phenomenon, given the centrality of this postulate to the Hill model.

The second intellectual challenge is to establish whether or not there is any published evidence suggesting the presence of either a cardiac or neural "governor". I propose that this evidence can be found in the phenomenon of the "lactate paradox" that develops in healthy humans during maximum exercise at increasing altitude but also during maximum exercise at sea level in patients with various chronic diseases of the heart or lungs.[9,10] Especially the "lactate paradox" at altitude provides the unambiguous test (a) of which organ, either heart or skeletal muscle, is at greatest risk for developing anaerobiosis or ischaemia during maximum exercise and (b) for the possible existence of a cardiac "governor".

For if, according to Hill's original model, myocardial ischaemia develops as the necessary precursor for skeletal muscle anaerobiosis during maximum exercise, then maximum exercise at altitude should identify this response even more readily than exercise at sea level. Three findings from a series of studies of cardiorespiratory and metabolic responses during maximal exercise at extreme altitude would appear to provide the definitive answer to these speculations.

Maximal exercise at extreme altitudes. Thus it has been found that peak muscle and blood lactate concentrations *fall* at increasing altitude[35-37] such that "above an altitude of 7500 m, no blood lactate is predicted even for maximal exercise. If this extrapolation held good, a well-acclimatized climber who reached the summit of Mount Everest without supplementary oxygen would have no blood lactate. This is a paradox indeed, because such a climber is apparently more hypoxic during maximal exercise than is any other known situation".[36] This phenomenon is paradoxical because blood and muscle lactate concentrations should, according to the traditional Cardiovascular/Anaerobic Model of Exercise Physiology,[12] increase under the conditions of increasing hypoxia or anaerobiosis that would be expected during maximum exercise at increasing altitude when arterial PO_2 is substantially reduced.

The most obvious explanation for the "lactate paradox" is simply the very low workrates achieved at extreme altitude. Skeletal muscle lactate production is most clearly related to the external workrate[38] so that any reduction in work rate would be expected to produce lower muscle and blood lactate concentrations. Nevertheless the lactate paradox at altitude must indicate (a) that skeletal muscle anaerobiosis is not present and (b) that something other than skeletal muscle hypoxia or anaerobiosis "constrains" the work output of

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the skeletal muscles at extreme altitude. But as the traditional model also requires that lactate or other metabolic by-products of "anaerobic" metabolism be the "constrainer" that limits maximal exercise, so that old model is quite unable to explain this additional paradox, which is therefore conveniently ignored.[5-7] Yet something other than elevated blood lactate concentrations or tissue hypoxia act to "constrain" maximum exercise at increasing altitude. Could this be the elusive governor proposed by Hill?

The second crucial finding is that, with acclimatisation, the maximum cardiac output *falls* during maximum exercise at altitude.[39] This is the opposite of the expected result.

Figure 7-6 shows that a reduction in the arterial PO_2 will have 2 effects on oxygen transport during exercise. The first has been the more readily grasped by exercise physiologists – a reduced capacity for oxygen delivery to the exercising skeletal muscles. Hence it has been assumed that the principal effect of a reduced arterial PO_2 will be to increase *skeletal muscle* anaerobiosis/hypoxia during exercise.[40]

But this interpretation has ignored the second obvious effect which is a simultaneous reduction in the capacity for oxygen transport to the heart itself (Figure 7-6). Hence when the arterial PO_2 is reduced, there is also an increased probability that myocardial anaerobiosis, hypoxia or ischemia may also develop.

As a result, the model of maximum exercise at altitude provides the test of whether it is the heart or skeletal muscles that is protected during exercise in an hypoxic environment. Thus if the traditional (Cardiovascular/Anaerobic) model is correct, then the oxygen demands of skeletal muscles will

Does the oxygen supply to the exercising muscles or to the heart limit exercise at altitude?

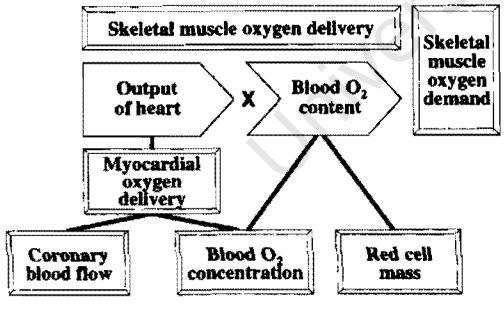

Figure 7-6. During ascent to increasing altitude, the arterial oxygen tension falls. Exercise physiologists have consistently assumed that the crucial effect of this would be to reduce the potential for oxygen delivery to the exercising muscles. An equally relevant effect is also to reduce myocardial oxygen delivery. If myocardial ischaemia is likely to develop during maximum exercise, then maximum exercise at altitude will increase the probability that this will happen unless alternate control mechanisms exist to terminate exercise before myocardial ischaemia develops.

Does the oxygen supply to the exercising muscles or to the heart limit exercise at altitude?

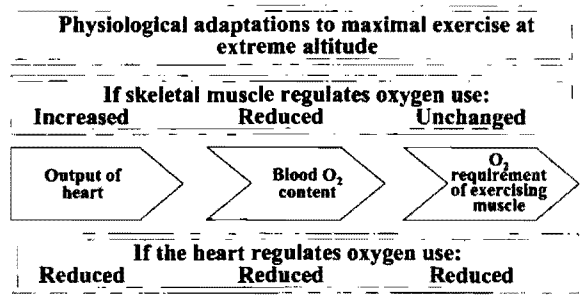

Figure 7-7. Maximum exercise at extreme altitude offers the opportunity to determine whether or not oxygen delivery to the exercising skeletal muscles drives cardiovascular function during such exercise. This would be the case if the cardiac output rises as the arterial oxygen tension falls (in order to maximise oxygen delivery to the exercising muscles). In contrast, if oxygen delivery to the heart determines the maximum (allowed) cardiac output during exercise, then the cardiac output during maximum exercise will fall at increasing altitude, as the arterial oxygen tension and, hence, maximum myocardial oxygen delivery falls.

take primacy during maximum exercise under conditions of hypoxia. As a result, cardiac output must always be the same or greater during maximum exercise at increasing altitude with progressively lower arterial PO_2 (Figure 7-7).

In contrast, if some other mechanism exists, for example if it is a limiting myocardial oxygen delivery that "constrains" myocardial function according to the proposal of Hill and his colleagues, then maximum cardiac output will fall as the arterial PO_2 is reduced at increasing altitude (Figure 7-7).

Hence the finding that the maximum cardiac output falls with increasing altitude[39] establishes that, when the arterial PO_2 is reduced, the skeletal muscles are unable to maximize their potential oxygen supply by forcing the heart to achieve its maximum (sea level) cardiac output (Figure 7-8). Rather the progressively lower maximum cardiac outputs achieved during maximum exercise at increasing altitude suggest that whatever "constrains" skeletal muscle activity at altitude, also "constrains" cardiac function, probably as a direct consequence.

The lower maximal cardiac outputs at altitude are also not the result of a myocardial ischaemia that could develop during maximum exercise at altitude.[20,21] For example, from their study showing that left ventricular systolic function measured either as the ejection fraction or as the ratio of the peak left ventricular systolic pressure to the end systolic volume, was the same during peak exercise and at altitude (7620 m), Suarez et al.[21] concluded that: "Left ventricular systolic function is not a limiting factor in compromising the exercise capacity of normal humans on ascent to high altitude, even to the peak of Mount Everest".

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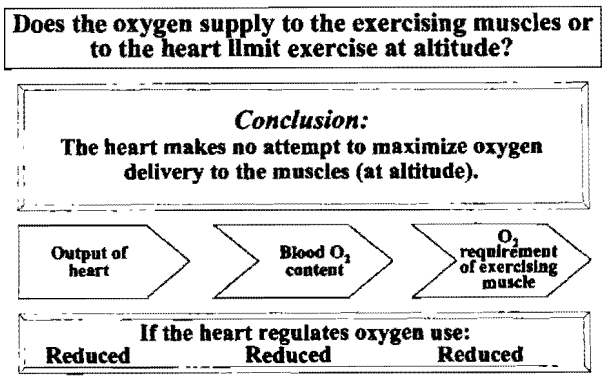

Figure 7-8. The finding that the maximum cardiac output falls with progressive reductions in arterial oxygen tension at increasing altitude, proves that oxygen delivery to organs other than skeletal muscle determines the maximum oxygen consumption and peak workrate achieved during exercise (at altitude).

Hence the conclusions from these studies are that:

Maximum exercise at extreme altitude is terminated before anaerobiosis develops in either heart or skeletal muscle.

The heart makes no attempt to increase cardiac output and therefore maximize 0_2 delivery to skeletal muscle during maximum exercise at extreme altitude.

Hence something other than tissue hypoxia and the by-products of "anaerobic" metabolism in the exercising muscles "constrains" maximum exercise at extreme altitude.

What prevents muscle anaerobiosis? Hence the third intellectual challenge posed by this novel interpretation is: What acts to "constrain" both cardiac and skeletal muscle function at extreme altitude such that neither organ becomes anaerobic, hypoxic or ischaemic during maximum exercise under those extreme conditions? The allied question is whether the same "constrainer" also acts during maximum exercise at sea level.

The study of Kayser et al[41] suggests, in my view, the most reasonable solution. They showed that skeletal muscle electromyographic (EMG) activity was lower at exhaustion during maximum exercise at moderate altitude compared to sea level. Furthermore, when subjects inhaled 100% oxygen during maximum exercise at altitude, the peak exercise workrate and muscle EMG activity increased but still did not reach sea level values. This suggests that the variable constraining skeletal muscle recruitment at altitude responds to alterations in the oxygen tension either of the inhaled air or, as a result, of one or more of the tissues involved in the exercise response.

The findings of these studies can best be explained by the mechanisms proposed in Figure 7-9.

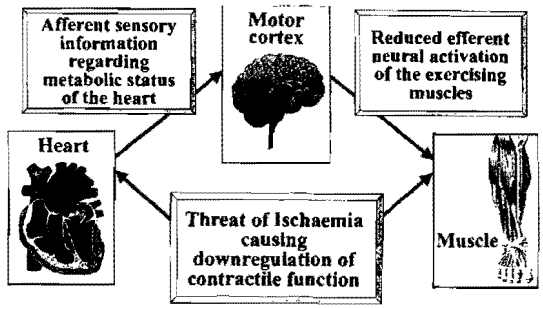

Figure 7-9. A postulated model in which governors in the brain and the active muscles act to ensure that neither cardiac nor skeletal muscle anaerobiosis develops during maximum exercise. Postulated receptors in the heart anticipating perhaps the onset of myocardial ischaemia, act to reduce the central, neural recruitment of the exercising muscles, thereby preventing any further increase in the oxygen demands of the active skeletal muscles and, consequently, the heart.

ROLE OF GOVERNORS

It is postulated that one "governor" exists in the brain. The function of that governor is to prevent the development of myocardial ischemia whenever a limiting myocardial oxygen delivery is approached. This might occur, for example, at the very high cardiac outputs (and coronary flows) achieved during maximum exercise, or the expectedly high and perhaps limiting coronary flows achieved under conditions of exercise at low arterial PO_2 as occurs at extreme altitude. Alternatively, at extreme altitude, an added or perhaps primary function of the governor may be to prevent hypoxia of the brain.

Afferent input to the governor may arise from oxygen-sensitive receptors in the heart, either in the myocardium or the coronary vessels, in the brain, and perhaps also in skeletal muscle. Alternatively, these receptors may monitor changes in intracellular metabolites, perhaps the phosphagens. These governors would forestall the development of hypoxia or ischemia in heart, brain or muscle by reducing the central (neural) recruitment of the exercising muscle mass whenever a limiting myocardial or cerebral oxygen delivery is approached. Reduced skeletal muscle recruitment would prevent further increases in peripheral and, as a consequence, also myocardial oxygen demands. At extreme altitude, reduced skeletal muscle recruitment would prevent arterial PO_2 from falling to levels that would induce cerebral hypoxia and unconsciousness.

The action of these neural governors would explain why the peak cardiac output is "constrained" whenever the arterial PO_2 is reduced[39,42,43] and alternatively why cardiac output increases when this constraint is removed as occurs, for example, when patients with chronic obstructive lung

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disease exercise whilst inhaling oxygen that increases the arterial PO_2.[44]

This model would also explain why there is as yet no evidence that (i) either cardiac output[16] or skeletal muscle blood flow[45] reach limiting "plateau" values during maximum exercise at sea level or (ii) that skeletal muscle anaerobiosis develops during maximum exercise at sea level,[43, 46–49] or (iii) that skeletal muscle or myocardial anaerobiosis develops during maximum exercise at extreme altitude.[20,21,35-37,39] Indeed the fundamentally more interesting question is why (and how) the intracellular PO_2 remains constant despite large changes in the external workrates of both skeletal muscle and heart.[43,47-49] But the action of the governor would ensure this outcome.

Figure 7-9 also suggests the existence of another governor, foreseen by Hill and his colleagues, and localised to both myocardium and skeletal muscle. This "governor" clearly established by the studies of Heyndrickx et al.[50] in cardiac muscle and by Spriet et al[51] and Hogan et al[52] in skeletal muscle, can explain why the contractile function of these organs is reduced wherever the arterial PO_2 in the blood perfusing those tissues is reduced.

RELEVANCE OF MODEL TO THE TEACHING OF MODERN CARDIOLOGY

Factors limiting maximum exercise performance. This new model proposed here predicts that the maximum cardiac output is only the indirect determinant of the maximum exercise capacity, at least at sea-level. Rather, this theory postulates that it is the maximum capacity for oxygen delivery to the myocardium that determines the mass of skeletal muscle that can be activated and hence the peak workrate that can be achieved, during maximum exercise of short duration. The actual cardiac output that will be achieved at this limiting myocardial oxygen delivery will be determined by the contractility of the heart and its efficiency with respect to oxygen use. Similarly the actual external workrate (running speed or cycling velocity, for example) that is achieved will be determined by the contractility and efficiency of the mass of active skeletal muscles that receives the limiting, maximum oxygen delivery at the maximum cardiac output.

If this model is correct, it suggests that the peak coronary blood flow is the most important physiological variable measured during maximum exercise. It is interesting, for example, that the peak workload achieved during exercise is one of the most accurate predictors of further life expectancy in persons with myocardial dysfunction, secondary to coronary artery disease. Could this be because the peak workload achieved by this group of patients is determined directly by the extent of their coronary vascular disease?

Similarly this model predicts that the subjects with the highest VO_2 max values should have the greatest capacity for coronary blood flow as well as superior cardiac and skeletal muscle contractility and efficiency. If coronary blood flow is such an important determinant of ultimate athletic ability, the question that arises is whether this is a genetic attribute, fixed at birth, or whether heavy athletic training, early in life, might increase the coronary capacity and hence determine the ultimate athletic ability. This might explain why young swimmers, especially, train so intensively from a young age, a training for which, otherwise, there appears to be little physiological logic,

In addition, if this model is correct, it could help explain one of the most interesting phenomena in exercise physiology. Which is that during very high intensity exercise of short duration, the work output falls within the first few seconds and well before metabolite accumulation could begin to limit exercise. This model would predict that the governor can anticipate that the maintenance of such a high workrate would rapidly induce damage, either to the heart or skeletal muscle. As a result, the (subconscious) decision is taken to reduce the excessively high workrate, well before any such damage could occur.

Similarly, the traditional argument that the exercise intensity that can be sustained falls after 1–2 minutes because of an inability to generate ATP sufficiently rapidly, may simply reflect the action of the governor to reduce muscle activation specifically to ensure that myocardial ischaemia does not develop.

Prevention of myocardial ischaemia during maximum exercise in patients with coronary artery disease. It is perhaps surprising that patients with coronary artery disease develop myocardial ischaemia relatively infrequently. It is surprising because their muscles are presumably healthy and hence potentially able to generate a large power output, greater than that with which their damaged hearts can cope. The presence of the governor would ensure that maintained muscle function would not risk overtaxing the capacity of the damaged heart in patients with an impaired coronary blood flow.

Causes of fatigue in skeletal muscle disorders, including McArdle's syndrome. Patients with McArdle's syndrome are unable to produce lactate during exercise because of the absence of one or more of the glycogenolytic/glycolytic enzymes. Yet the exercise tolerance of these patients is profoundly impaired. This is inexplicable according to the traditional model. Furthermore, despite a reduced capacity to generate ATP, patients with this condition do not develop skeletal muscle rigor during maximum exercise.

The "governor" theory adequately explains why a reduced muscle recruitment in response to afferent sensory information resulting from the abnormal skeletal muscle metabo-

lism would terminate exercise before the onset of skeletal muscle rigor.

SUMMARY

In summary, this chapter provides circumstantial evidence for the existence of the "governors" proposed by A.V. Hill and his colleagues. Such governors act to "constrain" exercise via central, neural mechanisms in order to prevent the development of myocardial ischaemia during those forms of exercise that elicit a maximum cardiac output. In contrast, the paradoxically low muscle and blood lactate concentrations together with an absence of acidosis, during maximal exercise at extreme altitude or during exhausting exercise in patients with chronic cardiorespiratory diseases, indicates that the traditional Hill (Cardiovascular/Anaerobic) model cannot explain what constrains exercise under these conditions. Rather it is likely that the same "governor" must be active, perhaps responding also to a reduced PO_2 in the cerebral circulation.

Thus, perhaps the most remarkable feature of the enduring 75-year influence that A.V. Hill and his colleagues have exerted on cardiology and exercise physiology,[3-7,9-13,16] has been their immortalisation for that which they neither taught nor believed and which may be incorrect.[9-12] But their truly innovative ideas were that (a) it is the heart, not skeletal muscle, that is at greatest risk of anaerobiosis or ischemia during maximal exercise at sea level so that (b) a governor must exist to limit (their model) or prevent (the model presented here Figure 7-9) myocardial ischemia during maximum exercise.[9-12]

It is a theory ripe for investigation.

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Evidence that a central governor regulates exercise performance during acute hypoxia and hyperoxia

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Summary

An enduring hypothesis in exercise physiology holds that a limiting cardiorespiratory function determines maximal exercise performance as a result of specific metabolic changes in the exercising skeletal muscle, so-called peripheral fatigue. The origins of this classical hypothesis can be traced to work undertaken by Nobel Laureate A. V. Hill and his colleagues in London between 1923 and 1925. According to their classical model, peripheral fatigue occurs only after the onset of heart fatigue or failure. Thus, correctly interpreted, the Hill hypothesis predicts that it is the heart, not the skeletal muscle, that is at risk of anaerobiosis or ischaemia during maximal exercise. To prevent myocardial damage during maximal exercise, Hill proposed the existence of a 'governor' in either the heart or brain to limit heart work when myocardial ischaemia developed. Cardiorespiratory function during maximal exercise at different altitudes or at different oxygen fractions of inspired air provides a definitive test for the presence of a governor and its function. If skeletal muscle anaerobiosis is the protected variable then, under conditions in which arterial oxygen content is reduced, maximal exercise should terminate with peak cardiovascular function to ensure maximum delivery of oxygen to the active muscle. In contrast, if the function of the heart or some other oxygen-sensitive organ is to be protected, then peak cardiovascular function will be higher during hyperoxia and reduced during hypoxia compared with normoxia. This paper reviews the evidence that peak cardiovascular function is reduced during maximal exercise in both acute and chronic hypoxia with no evidence for any primary alterations in myocardial function. Since peak skeletal muscle electromyographic activity is also reduced during hypoxia, these data support a model in which a central, neural governor constrains the cardiac output by regulating the mass of skeletal muscle that can be activated during maximal exercise in both acute and chronic hypoxia.

Key words: central governor, altitude, cardiac output, hypoxia, hyperoxia, maximal rate of oxygen uptake, muscle recruitment.

Introduction

The maximum rate of oxygen uptake ($\dot{V}_{O_2max}$) is a measure of the fastest rate at which oxygen (O_2) can be utilized by the body during severe exercise. $\dot{V}_{O_2max}$ is usually considered to be an index of cardiorespiratory, circulatory and muscular fitness. A lively debate of the definition and limiting factors for $\dot{V}_{O_2max}$ has enriched the recent literature (Bassett and Howley, 1997; Noakes, 1997; Noakes, 1998; Bassett and Howley, 2000; Noakes, 2000; Wagner, 2000a). The classical theory (Mitchell and Blomqvist, 1971) proposes that exercise is limited only after oxygen delivery to the exercising skeletal muscles becomes inadequate, inducing anaerobiosis (Bassett and Howley, 1997; Bassett and Howley, 2000). Both cardiorespiratory O_2 delivery and tissue diffusion limitation are believed to limit $\dot{V}_{O_2max}$ in normal humans during maximal exercise (Roca et al., 1989). The studies of Richardson and colleagues (Richardson et al., 1999) demonstrated reduced cytoplasmic partial pressure of O_2 (P_{O_2}) at peak $\dot{V}_{O_2}$ during single-legged exercise even when cardiac output was submaximal. These results are consistent with a supply limitation to $\dot{V}_{O_2max}$ in trained skeletal muscle, even during hyperoxia. Their data also revealed a disproportionate increase in intracellular P_{O_2} during hyperoxia, which could mean that the mitochondrial limits determining peak muscle $\dot{V}_{O_2}$ are approached even at relatively high P_{O_2} in trained skeletal muscle. Additional theories analyzing the links between O_2 delivery and utilization have also received significant attention in the recent literature (Roca et al., 1989; di Prampero and Ferretti, 1990; Wagner, 1991; Wagner, 1992; Wagner, 1995a; Wagner, 1995b; Wagner, 2000a).

An alternative theory postulates that a 'central governor', which regulates the mass of skeletal muscle that is recruited during exercise, acts to protect the heart from developing myocardial ischaemia during maximal exercise (Noakes, 1997;

Noakes, 1998; Noakes, 2000; Noakes, 2001). Thus, a logical starting point in the search for a central governor are those studies of cardiorespiratory function during acute hypoxia, since the possibility that myocardial ischaemia will develop is increased during maximal exercise in hypoxia. Studies of cardiorespiratory function during chronic hypoxia are potentially complicated by additional adaptations or maladaptations that might occur in response to sustained hypoxic stress.

Numerous studies have shown that $\dot{V}_{O_2max}$ can be modified acutely by altering one or more of the variables considered to limit this measurement. These acute changes occur before structural adaptations, normally requiring several weeks to develop, can occur. Examples of acute modifications in $\dot{V}_{O_2max}$ are its increase in response to acute increases in the partial pressure of inspired oxygen ($P_{I_{O_2}}$) and, conversely, its impairment with decreasing $P_{I_{O_2}}$. Altering arterial oxygen content (Ca_{O_2}), either by ascending to altitude or by descending in a deep mine to below sea level, or modifying $P_{I_{O_2}}$, either in a hypobaric chamber or by breathing gas mixtures with varying oxygen fractions ($F_{I_{O_2}}$), have all been reported to affect $\dot{V}_{O_2max}$ in a predictable and reproducible manner (Fagraeus et al., 1973; Welch et al., 1974; Wyndham et al., 1970). Also, $\dot{V}_{O_2max}$ increases with acute red blood cell transfusion (Gledhill, 1982; Gledhill, 1985; Spriet et al., 1986; Gledhill et al., 1999) and decreases with sympathetic blockade (Hughson and MacFarlane, 1981; Tesch, 1985; Hughson and Kowalchuk, 1991). Over a longer (chronic) period, $\dot{V}_{O_2max}$ increases with endurance training but decreases with detraining (Saltin et al., 1968a) or with prolonged exposure to high altitude (Cymerman et al., 1989; di Prampero and Ferretti, 1990; Ferretti et al., 1990; Green et al., 2000). Structural as well as functional changes in cardiorespiratory and neuromuscular function are more likely to explain these chronic changes.

The purpose of the present review is to present the evidence for the possible existence of a central governor and to discuss the possible mechanisms by which this governor might limit $\dot{V}_{O_2max}$ and, hence, maximal exercise performance, certainly during hypoxia and also, perhaps, during maximal exercise at sea level.

Origin of the central governor hypothesis

Whilst preparing a rebuttal to the criticisms by Bassett and Howley (Bassett and Howle, 1997) of his previous manuscript (Noakes, 1997), Noakes (Noakes, 1998; Noakes, 2000; Noakes, 2001) rediscovered the long-forgotten central governor hypothesis as originally proposed by Hill, Long and Lupton in the 1920s (Hill et al., 1924a;. Hill et al., 1924b) In 1924, that group of classical physiologists, which included the Nobel Laureate, A. V. Hill, wrote: 'Apparently, however, the limit to which the muscles may be driven, while breathing air, is set, not so much by the exhaustion of the muscles themselves as by the distress (cardiac and cerebral) resulting from either the rise of hydrogen-ion concentration of the blood, or its imperfect saturation with oxygen while passing rapidly through the lungs" (Hill et al., 1924b). The authors continued: "It would seem probable, and although we have no direct evidence, the indirect evidence which we are adducing makes it very probable indeed, that the heart is able to regulate its output, to some extent, in accordance with the degree of saturation of the arterial blood, either of that which reaches it through the coronary vessels or by some reflex in other organs produced by a deficient oxygen supply. From the point of view of a well coordinated mechanism, some such arrangement is eminently desirable; it would clearly be useless for the heart to make an excessive effort if by so doing it merely produced a far lower degree of saturation of the arterial blood; and we suggest that, in the body (either in the heart muscle itself or in the nervous system), there is some mechanism which causes a slowing of the circulation as soon as a serious degree of unsaturation occurs, and *vice versa*. This mechanism would tend, to some degree, to act as a 'governor', maintaining a reasonably high degree of saturation of the blood: the breathing of a gas mixture rich in oxygen would produce a greater degree of saturation of the blood and so allow the output to increase until the 'governor' stopped it again" (Hill et al., 1924b). They were also amongst the first to test this hypothesis by conducting experiments in which human athletes exercised whilst inhaling hyperoxic oxygen mixtures. They summarized the results of these experiments thus: "The use of gas mixtures containing a high pressure of oxygen enables a considerably higher oxygen intake to be attained. The increase is often so large that it cannot be due simply to more complete saturation of the blood in its passage through the lungs. It is suggested that a 'governor' mechanism exist, either in the heart muscle itself, or elsewhere, which tends to coordinate the output of the heart with the degree of saturation of the blood leaving it" (Hill et al., 1924b). Just as Hill and his colleagues used modified oxygen fractions in the inspired air as a tool to probe the mechanisms that regulate $\dot{V}_{O_2max}$ and exercise capacity, so in this review we choose also to concentrate on those studies of acute (immediate, 1–2 days) hypoxia and hyperoxia which, in our opinion, add support to the original hypothesis of Hill and his colleagues.

Studies of exercise under conditions of modified oxygen partial pressure ($P_{I_{O_2}}$)

Numerous studies show that $\dot{V}_{O_2}$ and cardiac output ($\dot{Q}$) alter in response to alterations in $P_{I_{O_2}}$. During acute hypoxia, the only generally accepted finding is that $\dot{V}_{O_2max}$ is reduced whereas $\dot{V}_{O_2}$ is unaltered during submaximal exercise (Stenberg et al., 1966; Hughes et al., 1968; Hartley et al., 1973; Ekblom et al., 1975; Fulco et al., 1988; Peltonen et al., 2001). Acute hypoxia increases $\dot{Q}$, heart rate (f_H) (Asmussen and Nielsen, 1955; Stenberg et al., 1966; Wagner et al., 1986; Peltonen et al., 2001) and skeletal muscle blood flow (Calbet, 2000) at a given submaximal $\dot{V}_{O_2}$ or workload.

There is a lesser consensus of the responses of $\dot{V}_{O_2}$ to acute hyperoxia. Some studies indicate a significant increase in $\dot{V}_{O_2max}$ during hyperoxia compared with normoxia (Welch et

al., 1974; Ekblom et al., 1975; Welch, 1982; Peltonen et al., 2001), whereas others failed to measure any such increase (Hughes et al., 1968; Adams and Welch, 1980). Similarly, some studies reported a similar submaximal $\dot{V}_{O_2}$ during hyperoxia and during normoxia (Asmussen and Nielsen, 1955; Hughes et al., 1968), whereas others (Welch et al., 1974; Ekblom et al., 1975; Peltonen et al., 2001) found that the submaximal $\dot{V}_{O_2}$ was significantly higher during hyperoxia than during normoxia.

Compared with normoxia, $\dot{Q}$ is either the same (Asmussen and Nielsen, 1955; Davies and Sargeant, 1974; Peltonen et al., 2001) or reduced (Nakazono and Miyamoto, 1987) during submaximal exercise in hyperoxia. Skeletal muscle blood flow is reduced during submaximal (Welch et al., 1977) but unaltered during maximal (Knight et al., 1993) exercise in hyperoxia.

Skeletal muscle is not the only organ to which the blood flow is altered by changes in Ca_{O_2}: blood flow to the heart (Hilton and Eichholtz, 1925; Baron et al., 1990; Kaijser et al., 1990; Grubbstrom et al., 1991) and brain (Jones et al., 1981) also shows considerable adaptation in response to changes in Ca_{O_2}, increasing during hypoxia and falling during hyperoxia.

There is a general consensus that O_2 transport to muscle is the principal determinant limiting $\dot{V}_{O_2max}$ (Secher et al., 1977; di Prampero, 1985; Rowell, 1986; di Prampero and Ferretti, 1990; Rowell, 1993). Indeed, it is even more likely that O_2 transport is the factor limiting the $\dot{V}_{O_2max}$ of endurance-trained athletes than of normally active or sedentary subjects (Wagner, 2000a). However, as P_{IO_2} decreases, the role of the lungs in limiting $\dot{V}_{O_2max}$ increases, whereas the importance of the cardiovascular system diminishes (Ferretti and di Prampero, 1995).

Maximal cardiac function is reduced during chronic hypobaric hypoxia, with a reduction in both maximal heart rate (f_{Hmax}) and maximal stroke volume (V_{Smax}) (Vogel et al., 1974; Reeves et al., 1987). The classic explanation for the reduced $\dot{Q}_{max}$ during chronic hypoxia includes (i) increased blood viscosity from erythrocytosis causing an increased haematocrit; (ii) reduced cardiac filling pressures from reduced plasma volume; (iii) autonomic changes (either increased parasympathetic or reduced sympathetic activity); (iv) hypoxic myocardial dysfunction and (v) the possibility that hypoxia directly impairs skeletal muscle function, reducing exercise capacity so that $\dot{Q}_{max}$ is reduced in proportion to the reduced work output (Wagner, 2000b).

However, cardiac catheterization studies performed during Operation Everest II (Groves et al., 1987; Reeves et al., 1987) indicated that, although V_{Smax} decreased at altitude, the decrement was proportional to the decrease in atrial filling pressure, indicating that myocardial contractility was preserved. Reeves and colleagues (Reeves et al., 1987) concluded that a reduced maximum ventricular filling resulting from tachycardia or a reduction in plasma and blood volume or both was one possible cause of the reduced V_S. However, the point is that the proportional reduction in stroke volume and atrial filling pressure indicates that the heart was not ischaemic and that any increase in filling pressure should have produced an increase in the stroke volume and cardiac output.

Suarez et al. (Suarez et al., 1987) have concluded that: "Left ventricular systolic function is not a limiting factor in compromising the exercise capacity of normal humans on ascent to high altitude, even to the peak of Mount Everest". Similarly, Reeves et al. (Reeves et al., 1987) have concluded that "cardiac rate, cardiac output, and myocardial contractile function were preserved at extreme altitude... reduced heart rates and cardiac outputs at maximum effort were the result rather than the cause of the reduced maximal O_2 uptake".

However, it is important to stress that any reduction in $\dot{Q}_{max}$ during either acute or chronic hypoxia is paradoxical according to the classical model, which holds that the heart is simply the slave to the exercising muscles, with the unrequiting task of maximizing O_2 delivery to the exercising muscle under all conditions. Hence, for the classical model to be correct, cardiac output must always be maximal at maximal exercise regardless of P_{IO_2}, F_{IO_2} or Ca_{O_2}. Hence, any intervention such as anaemia or hypoxia that reduces Ca_{O_2}, thereby threatening oxygen delivery to the exercising muscles, must be countered by acute changes, the principal aim of which must be to maintain oxygen delivery to the exercising muscles. Clearly, the exact opposite holds during chronic hypobaric hypoxia. It is also of interest that the skeletal muscle blood flow is unaltered at maximal exercise during acute anaemia, even though cardiac output is submaximal (Koskolou et al., 1997).

Furthermore, the changes in left ventricular filling that are thought to cause the reduced V_{Smax} and f_{Hmax} during chronic hypoxia cannot explain why both f_{Hmax} and $\dot{Q}_{max}$ are reduced during acute hypoxia since the duration of the hypoxia is too short to alter atrial filling pressures consequent to a theoretical increase in ventilatory and urinary fluid losses.

As a result, the prevailing hypothesis is that $\dot{Q}_{max}$ should be the same during acute and chronic hypoxia so that any reduction in $\dot{V}_{O_2max}$ during acute hypoxia is due to the narrowing of the arterio-venous oxygen difference $[(a-v)_{O_2}]$ (Stenberg et al., 1966). Fig. 1 explains the basis for this belief whilst introducing another interpretation that has been overlooked.

Fig. 1 shows that any reduction in arterial P_{O_2} (Pa_{O_2}) will threaten oxygen delivery to all organs in the body including the heart and brain, and not just the skeletal muscles as is the usual interpretation.

Rather, according to this model, the reduced Pa_{O_2} during hypoxia will reduce potential oxygen delivery to both the skeletal muscles and the heart. Furthermore, if the heart is merely the slave to the skeletal muscles, then $\dot{Q}_{max}$ should be the same during maximal exercise in both hypoxia and normoxia since the heart's sole function is to maximize oxygen delivery to the hypoxic skeletal muscles. But if myocardial hypoxia must be prevented, then $\dot{Q}_{max}$ will fall in proportion to the reduction in Pa_{O_2}.

A large body of evidence shows that the determinants of $\dot{Q}_{max}$ (f_{Hmax} and V_{Smax}) are both altered during maximal exercise in hypoxia. Thus, several studies found that acute

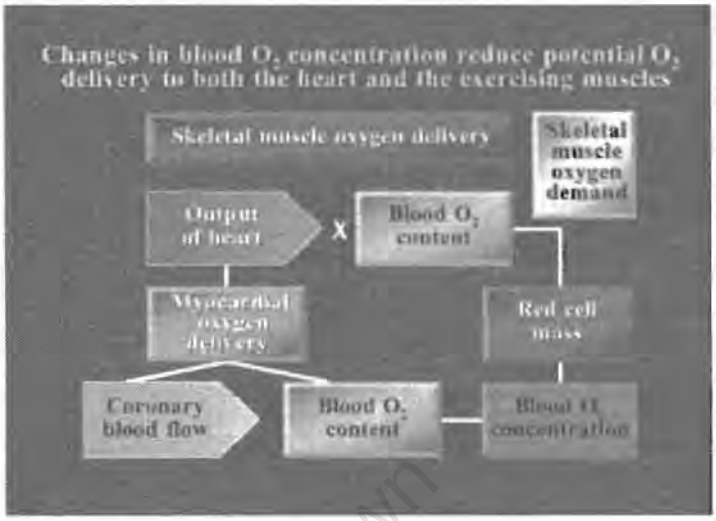

Fig. 1. Changes in blood oxygen concentration reduce the arterial oxygen supply to both the skeletal muscles and the heart. If the heart is the slave to the muscles, as predicted by the classical theory, then the output of the heart must increase during hypoxia to ensure that oxygen delivery to the skeletal muscles is maintained. In contrast, the central governor theory predicts that cardiac output will fall during hypoxia in proportion to the reduction in oxygen delivery to the heart, specifically to prevent hypoxic damage to the heart or other vital organs including, perhaps, the brain and respiratory muscles.

hypoxia decreases $f_{H_{max}}$ in both athletic and normally active men and women (Drinkwater et al., 1979; Andersen et al., 1985; Fulco et al., 1988; Lundby et al., 2001; Lundby and Olsen, 2001; Peltonen et al., 2001). Whilst these studies might indicate that the reduced $f_{H_{max}}$ is probably associated with a reduced $\dot{Q}_{max}$ during acute hypoxia, only two studies have measured a reduced $\dot{Q}_{max}$ during acute hypoxia.

Ekblom and colleagues (Ekblom et al., 1975) reported a decreased $\dot{Q}_{max}$ during carbon monoxide-induced hypoxia (Ca_{O_2} was on average 5.1% lower than during normoxia, $P<0.05$). The effect was due mainly to a decreased V_S. More recently, Peltonen et al. (Peltonen et al., 2001) demonstrated a reduced $\dot{Q}_{max}$ during acute hypoxia under physiological conditions (arterial desaturation caused by decreasing $F_{I_{O_2}}$, not by carbon monoxide inhalation) in endurance athletes (Table 1).

Perhaps even more interestingly, compared with findings during normoxia, peak muscle blood flow, a surrogate of $\dot{Q}_{max}$, is reduced in single-legged exercise during hypoxia and higher during hyperoxia, even though peak blood flows are well below $\dot{Q}_{max}$ in this model (Richardson et al., 1999) (Table 2).

Maximal heart rates follow a similar pattern and are submaximal at exhaustion (Table 2). Furthermore, leg blood flow per heart beat, an indirect indicator of the stroke volume, rises progressively from hypoxia to normoxia to hyperoxia (Table 2). The finding that leg blood flow is not increased during single-legged exercise during hypoxia, even though the cardiac output is submaximal, parallels the finding in acute anaemia (Koskolou et al., 1997).

Clearly, in this particular exercise model, which has become a standard for studying oxygen transport limitations during exercise, fatigue develops during both normoxia and hypoxia even though there is cardiac reserve shown as submaximal $\dot{Q}$ and f_H. Even hyperoxia does not overcome some mechanism that constrains $\dot{Q}$ and f_H preventing the highest possible oxygen transport to muscle. Since neither $\dot{Q}$ nor f_H is ever maximal in that model, it is clear that something other than a limiting cardiovascular function determines the limitation in O_2 delivery that obviously limits peak muscle $\dot{V}_{O_2}$ and, hence, $\dot{V}_{O_2max}$ in single-legged exercise. Rather, the alternative conclusion must be the low $\dot{Q}_{max}$ in single-legged exercise, even during hyperoxia, is the result not the cause of the low

Table 1. *Cardiac output during maximal whole-body exercise in hypoxia*

	% Inspired O_2		
	15	21	32
$\dot{V}_{O_2max}$ (l min^{-1})	3.58±0.41*†	4.55±0.32	5.17±0.34*
Maximum cardiac output (l min^{-1})	25.99±3.37*†	28.51±2.36	30.13±2.06
Maximum heart rate (breaths min^{-1})	177±15	181±11	186±10
Maximum stroke volume (ml)	147±19†	158±13	163±16

*Significantly different from normoxia ($P<0.05$).
†Significantly different from hyperoxia ($P<0.05$).
From the data of Peltonen et al. (Peltonen et al., 2001).
Values are means ± S.D. ($N=6$).

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Table 2. *The paradox of low cardiac output during single-legged exercise in hypoxia*

	% Inspired O_2		
	12	21	100
Quadriceps $\dot{V}_{O_2}$ ($l\,min^{-1}$)	0.86±0.1*	1.08±0.2	1.28±0.2*
Quadriceps blood flow ($l\,min^{-1}$)	6.3±0.6*	7.3±0.9	7.6±1.0
Heart rate (beats min^{-1})	145±3	140±4	136±2
Quadriceps blood flow per heart beat ($ml\,beat^{-1}$)	43	52	56

*Significantly different from normoxia ($P<0.05$).
From the data of Richardson et al. (Richardson et al., 1999).
Values are means ± S.E.M. ($N=5$).

work rate achieved and that both are the result of the small muscle mass that is activated in single-legged exercise.

Maximum heart rate is reduced, in a dose-dependant manner, in response to increasingly acute hypoxia, whereas maximal plasma norepinephrine and lactate concentrations are unchanged during acute hypoxia. Moreover, Lundby and Olsen (Lundby and Olsen, 2001) and Lundby et al. (Lundby et al., 2001) found that acutely changing the F_{IO_2} by breathing oxygen during experimentally induced acute hypoxia increased f_{Hmax} to sea-level values. A similar result has been reported during chronic hypoxia (Kayser et al., 1994; Savard et al., 1995), in which oxygen inhalation increased peak heart rate at exhaustion, although f_{Hmax} was still lower than during normoxia. To explain their findings, Lundby and Olsen (Lundby and Olsen, 2001) and Lundby et al. (Lundby et al., 2001) reported that blockade with domperidone demonstrated that hypoxic exercise in humans activates dopamine D2-receptors, which cause a reduction in circulating levels of norepinephrine. However, this mechanism does not play a major role in the hypoxia-induced reduction of f_{Hmax}. The authors suggest that postganglionergic desensitization and not downregulation of cardiac adrenoreceptors is responsible for the early decrease in f_{Hmax} during hypoxia.

The reduction in f_{Hmax} and $\dot{Q}_{max}$ during acute hypoxia favours the previous theories (Hill et al., 1924a; Hill et al., 1924b; Ferretti and di Prampero, 1995; Wagner, 2000a) that, without parallel upward adjustments in both pulmonary and muscle O_2 diffusive transport conductance, a very high cardiac output would cause substantial arterial desaturation and also impair muscle O_2 extraction. Although the reduced $\dot{Q}_{max}$ during acute hypoxia would be physiologically beneficial, the response remains paradoxical according to the classical model, which holds that the heart's function is to maximize oxygen delivery to muscle rather than to protect P_{aO_2}. Hence, the question that demands an answer is: What are the mechanisms that constrain the normal increases in $\dot{Q}$, V_S and f_H during severe exercise in acute hypoxia? As argued previously, the classical model proposed two separate mechanisms for fatigue during maximal exercise.

First was the development of myocardial hypoxia causing a progressive cardiac failure. Hence: "The enormous output of the heart of an able-bodied man, maintained for considerable periods, requires a large contemporary supply of oxygen to meet the demands for energy. When the oxygen supply becomes inadequate it is probable that the heart rapidly diminishes its output, so avoiding exhaustion" (Hill et al., 1924a; p. 443). The function of Hill's postulated governor was to reduce the work of the heart when myocardial hypoxia developed, thereby sparing the heart from damage. This concept that myocardial failure antedated the development of fatigue was included in Bainbridge's textbook, edited by the North American exercise physiologists David Dill and Arlie Bock: "The blood supply to the heart, in many men, may be the weak link in the chain of circulatory adjustments during muscular exercise, and as the intensity of muscular exertion increases, a point is probably reached in most individuals at which the supply of oxygen to the heart falls short of its demands, and the continued performance of work becomes difficult or impossible" (Bainbridge, 1931; p. 15). As a result: "The heart, as a rule, reaches the limit of its powers earlier than the skeletal muscles, and determines a man's capabilities for exertion" (Bainbridge, 1931).

Second, as a result, blood flow to the exercising muscles was reduced, inducing anaerobiosis with the production of 'lactic acid', the rising intramuscular concentrations of which ultimately caused the cessation of exercise (Hill, 1926).

Clearly, this model cannot explain the fatigue of chronic hypobaric hypoxia, including the profound muscle weakness at altitude described by Pugh (Pugh, 1958), or the inability of Peter Habeler and Reinhold Messner to walk upright to the summit of Mount Everest during their oxygen-less ascent, since (i) myocardial ischaemia does not occur during maximal exercise at extreme altitude (Reeves et al., 1987; Suarez et al., 1987) and (ii) maximum blood lactate concentrations fall in proportion to the elevation above sea level (Christensen and Forbes, 1937; West, 1986; Green et al., 1989), the so-called 'lactate paradox'. As a result "above an altitude of 7500 m, no blood lactate is predicted even for maximal exercise. If this extrapolation held good, a well-acclimatized climber who reached the summit of Mount Everest without supplementary oxygen would have no blood lactate. This is a paradox indeed, because such a climber is apparently more hypoxic during maximal exercise than in any other known situation" (West, 1986).

However the 'lactate paradox' is only paradoxical according to the classical model, which predicts that the extreme fatigue at altitude must result from abnormally elevated blood lactate concentrations despite the very low $\dot{V}_{O_2}$ and work rates when climbing at extreme altitude.

Clearly some other mechanism(s) must be operative, at least during chronic hypoxia.

Cardiovascular limitations

Although the natural temptation, according to the classical model, is to propose that myocardial hypoxaemia explains the reduced $f_{H\max}$, $V_{S\max}$ and $\dot{Q}_{\max}$ during hypoxia, the study of Blomqvist and Stenberg (Blomqvist and Stenberg, 1965) failed to reveal any electrocardiographic evidence of myocardial ischaemia during maximal exercise in acute hypoxia, as also shown during exercise in chronic hypoxia. That myocardial ischaemia does not develop even during severe exercise in either hypoxia or normoxia (Raskoff et al., 1976) is compatible with the theory of a central governor, which prevents the recruitment of so large a muscle mass that a plateau in cardiac output is reached, leading to the myocardial ischaemia predicted by the classical model (Noakes, 1998; Noakes, 2000; Noakes, 2001).

To maintain myocardial oxygen consumption during hypoxia, a more complete extraction of O_2 from the coronary blood flow compensates for the reduced Ca_{O_2} compared with sea-level values. During maximal exercise, the additional compensatory mechanism of increased coronary blood flow is activated, indicating that the normal heart has a 'coronary flow reserve' that is activated only during maximal exercise in hypoxia (Kaijser et al., 1990; Grubbstrom et al., 1991). This again supports the theory that a constrainer exists specifically to terminate the exercise before myocardial ischaemia can develop.

A possible reason why stroke volume falls during hypoxia, even when only a single leg is active (Richardson et al., 1999), could be the increase in coronary flow during hypoxia since this is accompanied by an increase in coronary arterial pressure and stiffness (Templeton et al., 1972). Any increase in left ventricular stiffness would shift the end-diastolic pressure/end-diastolic volume (P_{ED}/V_{ED}) curve to the left (Janicki et al., 1996), reducing V_{ED} at the same P_{ED}, and leading to a smaller V_{ED} with a similar P_{ED} and, thus, a smaller V_S according to the Frank–Starling mechanism. However, this theoretical mechanism does not occur even during chronic hypoxia since the relationship between V_S and V_{ED} is the same during exercise at altitude and at sea level (Reeves et al., 1987). It is difficult to believe that this mechanism exists only during acute hypoxia.

Alternatively, ventricular interdependence could explain the reduced V_S during hypoxia. Acute hypoxia raises pulmonary arterial pressure (Cudkowicz, 1970) and right ventricular pressure, causing bulging of the interventricular septum towards the left ventricular cavity (Ritter et al., 1993). This, together with a decreased pulmonary capillary wedge pressure, indicating a lowered left atrial pressure and, hence, a reduced preload, lowers the driving pressure across the mitral valve and, consequently, reduces diastolic filling during the rapid phase in early diastole (Ritter et al., 1993). However, as already argued, the unaltered relationship between V_S and V_{ED} during exercise in chronic hypoxia indicates that this mechanism is not the principal factor explaining the reduced maximum cardiovascular function during chronic hypoxia.

A third explanation would be simply that the reduced peak workload during hypoxia (Peltonen et al., 2001) reduces the action of the muscle pump, thereby reducing venous return (Rowell, 1993), so that the measured cardiovascular changes are the result and not the cause of the reduced workload during hypoxia.

It has also been argued that, since pericardiectomy increases $\dot{Q}_{\max}$ in dogs (Stray-Gundersen et al., 1986), diastolic filling therefore limits maximal cardiac output in humans during maximal exercise in the upright position. Yet this logic does not follow since dogs exercise on all four legs, in which position most of their blood volume is at the level of the heart (Rowell, 1986; Rowell, 1993) such that diastolic filling pressures are optimized.

Hence, the model of exercise studied by Stray-Gundersen et al. (Stray-Gundersen et al., 1986) is the equivalent of humans exercising in the supine position in which position diastolic filling pressures are higher at $\dot{V}_{O_2\max}$ than when humans exercise in the upright position (Rowell, 1993). Thus, the conclusion must be that, during maximal exercise in the upright position in humans, the heart is not at the limit of its capacity for diastolic filling. Rather, any limitation to diastolic filling must exist 'before' the heart, as may also occur during maximal exercise in hypoxia.

Finally, an increased afterload cannot explain the reduced V_S during acute hypoxia since peripheral vascular resistance (Vogel et al., 1974) and mean arterial pressure (Wolfel et al., 1991) are unaffected during acute hypoxia (Rowell and Blackmon, 1987) and elevated only during chronic hypoxia.

Furthermore, the finding that the peak exercise heart rate is higher in silent ischaemia than in symptomatic ischaemia (Visser et al., 1990) can be interpreted as evidence that the response to the sensory signals that cause exercise to terminate with submaximal heart rates during acute hypoxia, as in ischaemia, may arise from outside the myocardium itself, possibly in the central nervous system.

In summary, direct cardiovascular factors, including myocardial dysfunction secondary to hypoxia or ischaemia, altered left ventricular diastolic function secondary to an increased coronary blood flow or an increased pulmonary arterial pressure, are unable to explain the reduced $\dot{Q}_{\max}$ during hypoxia. Nor is the reduction in $\dot{Q}_{\max}$ during hypoxia compatible with the classical model, which holds that the heart is the slave of the exercising muscles and must therefore maintain the same $\dot{Q}_{\max}$, especially when oxygen delivery to the exercising muscles is threatened by any factor that reduces Ca_{O_2}.

Central nervous system limitation

The elevated $\dot{Q}$ and f_H during acute hypoxia at a given submaximal $\dot{V}_{O_2}$ suggest an augmented sympathetic activity (Suarez et al., 1987) with increased circulating catecholamine concentrations (Cunningham et al., 1965; Manchanda et al., 1975; Escourrou et al., 1984). However, the close relationships between blood norepinephrine concentrations, heart rate and percentage $\dot{V}_{O_2\max}$ are essentially unaffected by hypoxaemia; that is, they are all changed in the same relative proportions

Uncorrected Proof

(Rowell, 1986). Therefore, it is interesting that $\dot{Q}_{max}$, f_{Hmax}, V_{Smax} and peak workrate (P_{max}) are each reduced during acute hypoxia, in a situation in which maximal sympathetic activity would be expected.

One possible explanation for the reduced $\dot{Q}_{max}$ and P_{max} during hypoxia is that the limitation originates centrally in the brain. If the level of sympathetic activity at a given heart rate is the same under normoxic and hypoxic conditions (Rowell, 1986), then the lower f_{Hmax} values during hypoxia could indicate a lesser sympathetic stimulation.

However, the finding that plasma norepinephrine and lactate concentrations were similar to normoxic values after maximal exercise during acute hypoxia, despite a lower f_{Hmax} with increasing altitude (Lundby et al., 2001), suggests that sympathetic activity *per se* was not reduced but that the response of the heart to sympathetic stimulation was blunted.

These authors (Lundby et al., 2001) concluded that postganglionic desensitization and not a reduction in cardiac adrenoreceptor numbers is responsible for the early decrease in f_{Hmax} during maximal exercise in hypoxia. In accordance with this interpretation, Manchanda et al. (Manchanda et al., 1975) reported that acute hypoxia reduced the stimulatory effects of catecholamines on cardiac function even during submaximal exercise. They found that, although cardiac performance increased in proportion to the rise in plasma catecholamine concentrations during normoxia, the response was blunted during acute hypoxia even though plasma catecholamine concentrations were elevated. They postulated that the depressant effect of increased hypoxaemia and acidosis during moderately heavy exercise in acute hypoxia may override the cardiostimulatory effects of elevated circulating catecholamine concentrations.

There are, however, studies to indicate that the central nervous system itself may act as a 'central governor' during maximal exercise in hypoxia. First, the typical signs of peripheral neuromuscular fatigue, i.e. an increase in the integrated electromyogram signal (IEMG) are absent during chronic (Kayser et al., 1994) and acute (Peltonen et al., 1997) hypoxia. Rather, IEMG activity is reduced at peak exercise but increases with oxygen administration at altitude (Kayser et al., 1994). Hence, Kayser et al. (1994) conclude that: "during chronic hypobaric hypoxia, the central nervous system may play a primary role in limiting exhaustive exercise and maximum accumulation of lactate in blood". Second, blunting of afferent sensory signals from the working muscles does not diminish the hypoxia-induced cardiovascular adaptations to acute hypoxia, suggesting that the limitations in exercise performance are of central origin (Kjaer et al., 1999). Third, vasomotor depression on exposure to acute hypoxia is induced by central hypoxia in non-acclimatized subjects (Koller et al., 1991). Fourth, the animal experiments of Jones et al. (Jones et al., 1981) have shown that, as Ca_{O_2} falls, regardless of whether this is due to a reduction in P_{O_2} or in haematocrit or both, there is a reciprocal increase in cerebral blood flow such that cerebral O_2 delivery remains constant. This indicates that the brain has the ability to sense acute hypoxia and to increase blood flow in response. The finding that the extent of the cerebral microvasculature increases with chronic exposure to hypoxia (Harik et al., 1996) further indicates the capacity of the central nervous system to sense, and to respond to, hypoxia. Moreover, hypoxia has a tendency to increase both overall and respiratory perceptions of effort for a given absolute $\dot{V}_{O_2}$ (Shephard et al., 1992).

All these findings, but most especially those of Kayser et al. (Kayser et al., 1994), support the original central governor hypothesis of Hill and colleagues (Hill et al., 1924a; Hill et al., 1924b), as modified by Noakes (Noakes, 1998; Noakes, 2000; Noakes, 2001), that skeletal muscle recruitment during severe exercise is regulated by a central governor specifically to prevent the development of progressive arterial desaturation leading to myocardial ischaemia or cerebral hypoxia. Thus, reduced $\dot{Q}_{max}$ and $\dot{V}_{O_2max}$ during acute hypoxia might be the result rather than the cause of the reduced skeletal muscle recruitment (Peltonen et al., 2001). The postulated pathways for this effect are presented in Fig. 2.

Further evidence for the existence of a central governor is provided by an analysis of the theories of the relationship between $\dot{V}_{O_2max}$ and exercise performance and how these predict the responses of both to either hypoxia or hyperoxia. Two different interpretations exist: one favours the belief that $\dot{V}_{O_2max}$ directly determines the maximal workload that can be achieved; the other that $\dot{V}_{O_2max}$ is the effect rather than the cause of the measured exercise performance. If $\dot{V}_{O_2max}$ determines maximal exercise performance, then $\dot{V}_{O_2max}$ and exercise performance should change in direct and equal proportion during acute hypoxia and hyperoxia compared with values measured during normoxia. However, this is not the case: all the earlier and modern studies show a greater change in $\dot{V}_{O_2max}$ than in maximal performance both during hypoxia and hyperoxia (Saltin et al., 1968b; Drinkwater et al., 1979; Maresh et al., 1983; Fulco et al., 1988; Roca et al., 1989; Knight et al., 1993; Peltonen et al., 1995; Gore et al., 1997; Nielsen et al., 1998; Peltonen et al., 2001). Furthermore, the change in exercise duration at a constant workload during either hypoxia or hyperoxia exceeds the measured changes in $\dot{V}_{O_2max}$ under those conditions (Fagraeus et al., 1973; Adams and Welch, 1980).

Although exercise performance and $\dot{V}_{O_2max}$ do not change equally with changes in F_{IO_2}, an interesting finding is the strongly positive correlation between changes in maximal workload and $\dot{Q}_{max}$ during both hypoxia and hyperoxia (Peltonen et al., 2001), supporting the theoretical existence of a central governor linking cardiac function and exercise performance (Fig. 2).

Finally, it is of interest to speculate about the site of the oxygen sensor that appears to link cardiovascular function and exercise performance during hypoxia and hyperoxia. Noakes' original suggestion was that the oxygen tension in the coronary vascular bed would be the monitored variable to prevent the development of a progressive myocardial ischaemia (Noakes, 1998; Noakes, 2000; Noakes, 2001; Fig. 2).

Alternatively, other studies suggesting that a central governor limits exercise during hypoxia or at altitude (Koller

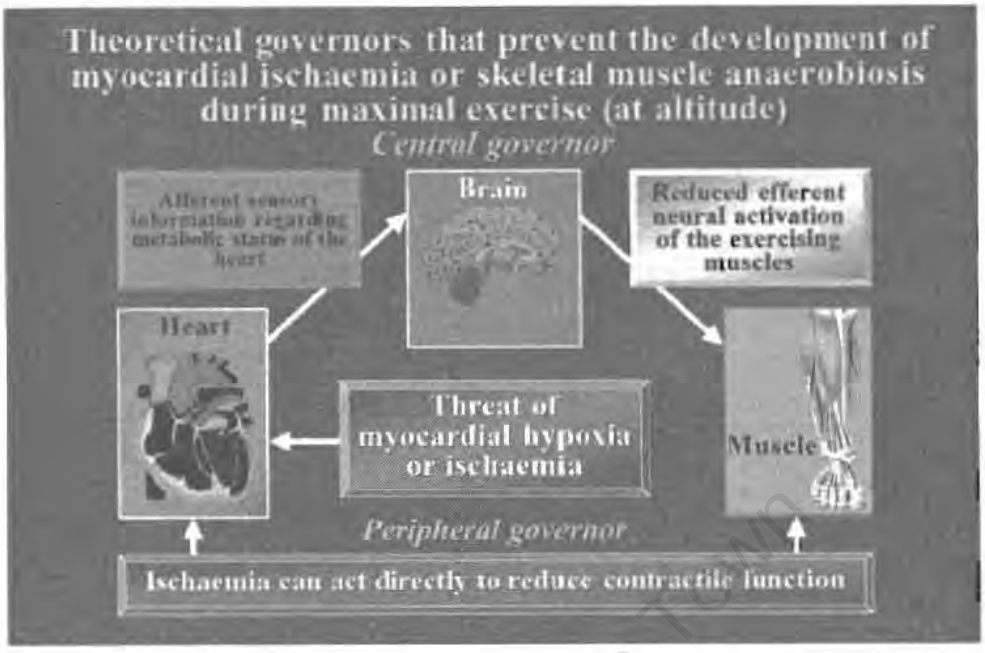

Fig. 2. The central governor theory proposes that afferent sensory information from the heart, but also perhaps from the brain and respiratory muscles, informs the brain of any threat that hypoxia or ischaemia may develop in those organs. In response, the central governor acts via the motor cortex to reduce the efferent neural activation of the exercising muscles, thereby reducing the mass of muscle that can be recruited and, hence, reducing the exercise intensity that can be sustained. The existence of peripheral governors in skeletal muscle and heart is proved by the rapidly deleterious effects of ischaemia on contractile function of both the heart and skeletal muscles and the existence of the condition of myocardial hibernation (Noakes, 2001).

et al., 1991; Kayser et al., 1994; Harik et al., 1996; Peltonen et al., 1997; Kjaer et al., 1999) can be interpreted to show that the efferent information to the central governor (Fig. 2), and which terminates exercise at a lower fH_{max}, V_{Smax} and $\dot{Q}_{max}$, may arise not in the coronary vessels or myocardium but possibly in the central nervous system itself.

For example, the evidence presented here can be interpreted as indicating that skeletal muscle has the potential to increase its blood flow and oxygen utilization up to the point at which a short mean capillary transit time causes a peripheral oxygen diffusion limitation to develop. However, if a similar diffusion limitation exists in the central nervous system, this would also offer a possible explanation for the observed reductions in $\dot{Q}$, fH, exercise performance and electromyographic activity during acute hypoxia since all would slow the transit time in the cerebral capillaries, thereby preventing the development of cerebral hypoxia. However, the same model would also explain how the central governor would prevent the development of myocardial ischaemia.

Concluding remarks

The arguments presented in this review are compatible with the theory that the reduced fH_{max}, V_{Smax} and $\dot{Q}_{max}$ during acute and chronic hypoxia are due to central regulation, the goal of which is to prevent the development of hypoxia in one or more of the vital organs including the brain, heart or perhaps the respiratory muscles. The action of this central governor is to regulate the mass of muscle that can be recruited during exercise under conditions in which the oxygen delivery to these vital organs is threatened. By limiting the muscle mass that can be activated, the central governor limits the peripheral peak $\dot{V}_O$, to a level that will not induce hypoxia in any of the vital organs.

If this model is correct, it suggests that a search for the possible factors limiting maximal exercise performance should include studies of the central nervous system, since such studies might uncover the possible existence and mode of action of the proposed central governor.

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Reduced neuromuscular activity and force generation during prolonged cycling

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St Clair Gibson, A., E. J. Schabort, and T. D. Noakes. Reduced neuromuscular activity and force generation during prolonged cycling. *Am J Physiol Regulatory Integrative Comp Physiol* 281: R187–R196, 2001.—We examined neuromuscular activity during stochastic (variable intensity) 100-km cycling time trials (TT) and the effect of dietary carbohydrate manipulation. Seven endurance-trained cyclists performed two 100-km TT that included five 1-km and four 4-km high-intensity epochs (HIE) during which power output, electromyogram (EMG), and muscle glycogen data were analyzed. The mean power output of the 4-km HIE decreased significantly throughout the trial from 319 ± 48 W for the first 4-km HIE to 278 ± 39 W for the last 4-km HIE ($P < 0.01$). The mean integrated EMG (IEMG) activity during the first 4-km HIE was 16.4 ± 9.8% of the value attained during the pretrial maximal voluntary contraction (MVC). IEMG decreased significantly throughout the trial, reaching 11.1 ± 5.6% during the last 4-km HIE ($P < 0.01$). The study establishes that neuromuscular activity in peripheral skeletal muscle falls parallel with reduction in power output during bouts of high-intensity exercise. These changes occurred when <20% of available muscle was recruited and suggest the presence of a central neural governor that reduces the active muscle recruited during prolonged exercise.

electromyogram; muscle; power output; carbohydrate; glycogen

PREVIOUS STUDIES OF THE FATIGUE process during endurance cycling exercise have examined the ability of fuel substrates such as carbohydrate (CHO) or fat to attenuate these fatigue processes (5, 11). These studies have used either an open-loop design in which there is no fixed endpoint so that subjects terminate exercise of their own volition or a closed-loop design in which either the distance or duration of exercise is predetermined. They have shown that the ingestion of CHO before or during the trial increases the time to fatigue during the open-loop design or decreases the time required to complete the trial during closed-loop design experiments (7, 8, 23, 24, 48).

The mechanisms for this enhancement are unknown but are generally assumed to result from changes in skeletal muscle metabolism (30), which delay the onset of muscle glycogen depletion, or as a result of the prevention or reversal of hypoglycemia (10). But it remains unclear why altered skeletal muscle metabolism induced by muscle glycogen depletion should induce fatigue. Thus Fitts (15) concludes that muscle glycogen depletion has not been identified as the exclusive cause of fatigue during prolonged exercise. Similarly, using an intermittent closed-loop sprint model, Bangsbo et al. (2) showed that decrements in skeletal muscle power output were not tightly correlated with any measured metabolic changes. They suggested that other factors, in particular neural control mechanisms, could cause fatigue during prolonged closed-loop exercise.

Yet there are relatively few studies of the contribution of neural factors to fatigue during prolonged, submaximal exercise. Rather, research investigating any possible neural basis for fatigue has used surface or invasive electromyographic (EMG) techniques during submaximal or maximal isometric or isokinetic contractions.

It is usually found that during submaximal isometric or isokinetic contractions, the subject is able to increase the motor command to counteract the reduction of force output thought to be due to metabolic changes in the recruited but fatiguing muscle fibers (12, 19, 21). Peripheral fatigue of this type is thus defined as a decrease in the force-generating capacity of the skeletal muscle due to altered crossbridge cycle activity, to excitation/contraction coupling failure, or to failure of the action potential propagation in the presence of unchanged or increasing neural drive (43).

Thus, if exercise-induced metabolic factors, in particular muscle glycogen depletion, cause peripheral fatigue during prolonged exercise, there may be a progressive increase in neural efferent drive to the active skeletal muscles. Increased neural efferent drive would initiate the recruitment of additional muscle fibers to offset any decrement in force production by the substrate-depleted, fatiguing muscle fibers.

In contrast, central fatigue is defined as a reduction in efferent motor command to the active muscles resulting in a decline in force or tension development (13). Although some studies have shown that maximal

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voluntary contraction (MVC) and integrated EMG (IEMG) are decreased by ~30% after a 42-km marathon foot race (33), no study has examined the changes in central neural efferent drive during exhaustive endurance exercise or the effect of CHO manipulation on this central command.

The aim of this study was therefore to examine neuromuscular activity and force output in the active skeletal muscle and the effect of CHO manipulation on this neuromuscular activity during prolonged cycling involving a stochastic closed-loop exercise design that mimicked normal racing conditions. In addition, the study was adequately placebo controlled and evaluated endurance-trained individuals performing at their own volition and subjective maximal capacity.

METHODS

Aspects of this study have been published in a companion paper that evaluated metabolic changes and performance during these trials (9).

Subjects. Seven endurance-trained male cyclists, accustomed to riding for prolonged periods (3–4 h), participated in this study. At the time of the investigation, each subject was riding between 250 and 500 km/wk. Before commencement of the trial, all subjects were informed that the purpose of the investigation was to test two different sports supplements designed for race preparation. The study was approved by the Ethics and Research Committee of the University of Cape Town Faculty of Health Sciences. Subjects gave written informed consent in accordance with the guidelines outlined by the American College of Sports Medicine (1). The subject characteristics are shown in Table 1.

Preliminary testing. On their first visit to the laboratory, subjects were tested for peak oxygen uptake ($V_{O_{2peak}}$) and peak sustained power output (PPO) on their own bicycles, which were mounted on the Kingcycle ergometer (described below). After a 5- to 10-min warm-up at a self-selected intensity, the test commenced at a workload of 200 W; the load was then increased by 20 W/min until the subject could no longer maintain the required power output. The subject's PPO was taken as the highest average power produced during any 60-s period of the exercise test. During these incremental tests to exhaustion, subjects were requested to remain in a seated position to prevent whole limb recruitment pattern changes initiated by changing from a seated to a standing cycling position.

Throughout the maximal test, subjects wore a face mask attached to an Oxygen Alpha automated gas analyzer (Jaguar, The Netherlands). Before each test, the gas analyzer was calibrated using a Hans Rudolf 5530 3-liter syringe and a 5% $C0_2$-95% N_2 gas mixture. Analyzer outputs were processed by an IBM computer that calculated minute ventilation, oxygen consumption, and rates of carbon dioxide production using conventional equations. Each subject's $V_{O_{2peak}}$ was taken as the highest oxygen uptake measured during any 60-s period of the test.

Table 1. *Subject characteristics*

	Mean ± SD	Range
Age, yr	28 ± 4.5	22–37
Mass, kg	72.1 ± 6.7	62–81
$V_{O_{2peak}}$		
$ml \cdot kg^{-1} \cdot min^{-1}$	63.9 ± 4.7	58.0–70.2
l/min	4.6 ± 0.6	3.5–5.2
Peak power output, W	411 ± 52	313–464
P:W, W/kg	5.7 ± 0.5	5.1–6.2

$V_{O_{2peak}}$, peak oxygen uptake; P:W, power-to-weight ratio (n = 7).

After completing the maximal test, subjects performed a familiarization ride on the Kingcycle (Kingcycle, High Wycombe, UK) ergometry system, which allows cyclists to ride on their own racing bicycles in the laboratory. After removing the front wheel, the subject's bicycle is attached to the ergometer by the front fork and supported by an adjustable pillar under the bottom bracket. The bottom bracket support is used to position the rolling resistance of the rear wheel correctly on the air-braked flywheel. The ergometer was calibrated as previously reported in detail (35). The familiarization ride consisted of the first 25 km of the 100-km time trial (TT; described below). Subjects were requested to "ride as fast as possible" and were not given any feedback other than their elapsed distance. Before the trial, all subjects were told that the subject with the fastest time in either trial would receive a financial reward at the end of the trial. This was done to motivate subjects to complete the trial in the fastest time possible.

Dietary intervention. Individual food plans were constructed for each subject based on body mass (BM) and food preferences. Each subject was supplied with his food intake for the 72-h period before each trial. Menu plans were provided in written form, and the food assigned to each meal was individually prepared and packaged so that the need for further preparation by subjects was minimized. Subjects were required to record their actual food and fluid intake in dietary logs to account for any portion of meals left unconsumed or any additional intake. Although some food items differed between subjects, each cyclist received identical breakfast, lunch, and dinner menus for both of his trials, with the CHO intake of these meals designed to provide 6 $g \cdot kg\ BM^{-1} \cdot day^{-1}$. Snacks were then provided for each day to provide the dietary source of differentiation between TT. For the CHO-loading diet, subjects received 1,200 ml of water each day and a number of sports bars (Gijima, Sasko, Paarl, South Africa) calculated to provide an additional 3 g $CHO \cdot kg^{-1} \cdot BM^{-1}$. Each sports bar had a composition of 27 g CHO, 6.5 g fat, and 2.7 g protein. For the placebo trial, daily snacks were provided in the form of 1,200 ml of an artificially sweetened, low-calorie drink that was described to the subjects as a "CHO-loading" drink. Total energy (4,149 ± 315 vs. 2,726 ± 202 kcal; $P < 0.05$), protein (110 ± 7 vs. 88 ± 6 g; $P < 0.05$), and fat (126 ± 9 vs. 79 ± 7 g; $P < 0.05$) intake were significantly higher during CHO compared with placebo trials.

Experimental trials. Each subject completed a random crossover design of two experimental TT separated by 7 days. Subjects performed their TT at the same time of day under standard laboratory conditions (~20°C, 55% relative humidity). Subjects were requested to perform the same type of training for the duration of the experimental period and to refrain from heavy physical exercise on the day preceding a TT. Training diaries were kept to assess compliance to this condition. On the morning of an experiment, subjects reported to the laboratory between 0700 and 0800, 12–14 h after an overnight fast. At this time, the Kingcycle ergometer was calibrated, after which subjects consumed a standard breakfast providing 2 g of CHO/kg BM. After resting quietly for 105 min, a preexercise muscle biopsy sample was taken from the vastus lateralis of the right leg according to the technique of Bergstrom (4) as modified by Evans et al. (14). After this procedure, the subject mounted his bicycle and began a 5-min self-paced warm-up.

Exactly 2 h after the subjects had consumed breakfast, they commenced the 100-km TT. To mimic the stochastic nature (variable nature) of cycle road races (36), the TT included a series of high-intensity epochs (HIE): five 1-km HIE after 10, 32, 52, 72, and 99 km, as well as four 4-km HIE after 20, 40, 60, and 80 km. Just before commencement of these sprints, an investigator gave a distance countdown and instructed the cyclist to complete the sprint in the fastest time possible as soon as he reached the specific distance at which the sprint started. Subjects viewed a diagram of the "course profile," which graphically illustrated where the 1- and 4-km HIE occurred before and during each ride. Instantaneous power output was recorded at each 500-m split of both the 1- and 4-km HIE to provide an estimate of the average power output for that HIE. Subjects were instructed to complete the total distance as well as the HIE, in "the fastest time possible." The only feedback given to subjects during TT was their elapsed distance and heart rate (HR). Subjects were not informed of their total time or their times for the HIE until completion of the experiment. Throughout each TT, power output, speed, and elapsed time were monitored continuously and stored for later analysis. HR was recorded using a SportTester HR monitor (Polar Electro, Kempele, Finland). We previously reported that the between-test correlation for the time taken by eight well-trained cyclists and triathletes to complete this protocol was 0.93 [95% confidence interval (CI), 0.79–0.98], and the within-cyclist coefficient of variation was 1.7% (95% CI, 1.1–2.5%) (39).

During the 100-km ride, subjects ingested a 7 g/100 ml glucose polymer solution at a rate of 15 $ml \cdot kgBM^{-1} \cdot h^{-1}$. This drinking regimen was intended to replace ~80% of sweat loss (32) while providing CHO at ~ 1 $g \cdot kg\ BM^{-1} \cdot min^{-1}$, the maximum rate at which muscle can oxidize exogenous glucose (22). A fan was positioned to cool the subjects during their TT. The average sweat loss was estimated as the average fluid intake plus weight change over the trial of all seven subjects. Immediately on completion of the TT, a second biopsy was taken from the same leg at a distance 4 cm distal to the first incision. No metabolic measurements were taken during the trials, as the TT were performance trials and it was felt that interfering with the athletes during the trials would impair their performance by distracting their concentration.

Isometric testing. Before the start of each cyclist's TT, his quadriceps muscle strength was tested on a Kin-Com isokinetic dynamometer (Chattanooga Group). The knee extensors were tested isometrically at a knee angle of 60°, with the reference point being full knee extension. Each subject performed four submaximal familiarization 5-s isometric knee extensions at ~50% of maximal effort, two 5-s isometric knee extensions at ~70% of maximal effort, and two 5-s isometric knee extensions at ~90% of maximal effort. Subsequent to this familiarization and warm-up protocol, subjects performed four maximal 5-s second isometric contractions. The MVC attained in these four trials was used for subsequent analysis. Subjects were directed to begin maximal effort immediately and not "save" effort for the final seconds of the test. Subjects were verbally encouraged during the test to exert maximum effort.

EMG testing. Before maximal isometric strength testing on the Kin-Com isokinetic dynamometer, EMG electrodes with a bandwidth of 20–500 Hz and sensitivity of <0.08 μV were attached to the "belly" of the rectus femoris muscle. The skin overlying the vastus lateralis muscle was carefully prepared. Hair was removed by shaving, the outer layer of epidermal cells were abraded, and oil and dirt were removed from the skin with an alcohol swab. Triode electrodes (Thought Technology Triode, MIEP01–00, Montreal, Canada) were placed on the muscle site as described above and linked via a fiber-optic cable to the Flexcomp/DSP EMG apparatus (Thought Technology) and host computer. A 50-Hz line filter was applied to the EMG data to prevent interference from electrical sources. Each test was sampled at 1,984 Hz for the duration of the two TT and isometric tests, thus yielding raw signals.

Five seconds of raw data were collected at the midpoint of each 1-km HIE (10.5, 32.5, 52.5, 72.5, and 99.5 km), 4-km HIE (22, 42, 62, and 82 km), and at three nonsprint distances (5, 55, and 95 km) during each TT.

The raw EMG signals were full-wave rectified, the movement artifact was removed using a high-pass second-order Butterworth filter with a cut-off frequency of 15 Hz, then smoothed with a low-pass second-order Butterworth filter with a cut-off frequency of 5 Hz. This was performed using MATLAB gait-analysis software. This IEMG data was used for subsequent analysis.

The frequency spectrum of each HIE of the raw EMG data was analyzed using a fast Fourier transformation algorithm. The frequency spectrum analysis was restricted to frequencies in the range 5–500 Hz, as the EMG signal content outside of this range consists mostly of noise. The frequency spectrum from each epoch of data was compared with that derived from the MVC, and the amount of spectral compression was estimated. This was performed using the technique described by Lowery et al. (28) as a modification of the work of Lo Conte and Merletti (27) and Merletti and Lo Conte (31). The spectrum of the raw signal of each epoch was obtained, and the normalized cumulative power at each frequency was calculated. The shift in each percentile frequency (i.e., at 0, 50, 100% of the total cumulative data) was examined. The percentile shift was then estimated by calculating the mean shift in all percentile frequencies throughout the midfrequency range (i.e., 5–500 Hz). This method has been suggested as a more accurate estimate of spectral compression than median frequency analysis, which uses the value of a single (50th) percentile frequency only (27, 28, 31). This change in mean percentile frequency shift (MPFS) data was used for subsequent analysis.

All EMG data were normalized by dividing the value at each time point during the cycle trial by the EMG value obtained during the MVC performed before the start of each TT. IEMG and MPFS data were therefore expressed as a percentage of this MVC data.

Analytic techniques. Muscle samples were subsequently freeze-dried; dissected free of blood, connective tissue, and fat; and weighed. Muscle glycogen content was determined after acid hydrolysis by a hexokinase method (25). The coefficient of variation for this assay in this laboratory is <5% for duplicate glycogen assays of a single piece of muscle and <7% for assays of the glycogen content of separate pieces of the same muscle biopsy sample (22).

Statistical analyses. Data from both TT were first combined and analyzed, and, subsequent to this, data were also analyzed to assess differences between the CHO and placebo trials. The EMG and force data are also expressed as normalized data, as described above. Differences in the HIE times and HIE power outputs, IEMG and MPFS data, and glycogen concentrations were examined using repeated-measures ANOVA, whereas glycogen use and total 100-km time and total power output were compared using Student's *t*-tests. All data are reported as means ± SD, and all calculations were performed using Statistica for Windows (Version 6, Statsoft, Tulsa, OK).

RESULTS

The mean $V_{O_{2peak}}$ value for the subjects was 63.9 ± 4.7 ml·kg^{-1}·min^{-1}, and PPO was 411 ± 52 W (Table 1). Their maximal force output during the pretest MVC was 703 ± 119 N. The mean power output during the 100-km TT and the time taken for completion were 256 ± 39 W and 148.27 ± 10.11 min, respectively.

The mean power output, IEMG, time taken, and MPFS for the five 1-km HIE for the group are shown in Fig. 1. The mean power output for the first 1-km HIE decreased significantly throughout the trial from 379 ± 52 to 300 ± 63 W for the last 1-km HIE ($P < 0.01$). The mean IEMG activity during the first 1-km HIE was 19.6 ± 12.8% of the value attained during the pretrial MVC. IEMG decreased significantly from this initial value throughout the trial to 11.34 ± 5.62% attained during the last HIE ($P < 0.05$). Time taken for each 1-km HIE increased significantly from 1.22 ± 0.07 for the first HIE to 1.36 ± 0.11 min for the last HIE ($P < 0.01$). MPFS for the first 1-km HIE compared with the pretest MVC was 84.8 ± 9.3%. MPFS increased significantly throughout the test and the value for the last HIE was 98.0 ± 14.4% ($P < 0.01$).

The mean power output, IEMG, time taken, and MPFS for the four 4-km HIE for the group are shown in Fig. 2. The mean power output decreased significantly throughout the trial from 319 ± 48 W for the first 4-km HIE to 278 ± 39 W for the last HIE ($P < 0.01$). The mean IEMG activity during the first 4-km HIE was 16.4 ± 9.8% of the value attained during the pretrial MVC. IEMG decreased significantly from this initial value throughout the trial to 11.1 ± 5.6% during the last HIE ($P < 0.01$). Time taken for each 4-km HIE increased significantly from 5.37 ± 0.32 for the first 4-km HIE to 5.67 ± 0.11 min for the last HIE ($P < 0.01$). MPFS for the first 4-km HIE compared with the pretest MVC was 91.3 ± 9.3%. Although MPFS increased throughout the TT, with the value for the last HIE being 95.7 ± 14.7%, this increase was not significant.

The HR changes during the three self-paced, five 1-km HIE, and four 4-km HIE for both TT are shown in Fig. 3. The HR during self-paced cycling increased significantly from 152 ± 11 beats/min after 5 km to 164 ± 12 beats/min after 95 km ($P < 0.01$). The HR during the 4-km HIE was maintained at 175 ± 8 beats/min for the first 4-km HIE to 175 ± 9 beats/min for the last 4-km HIE. The HR during the 1-km HIE increased from 172 ± 10 beats/min after the first 1-km HIE to 175 ± 9 beats/min after the last 1-km HIE. None of these differences was statistically significant.

With regard to the effects of CHO manipulation, there were no significant differences in the force output generated during the pretest MVC between CHO (720 ± 158 N) and placebo (684 ± 72 N) trials. Nor were there significant differences in the decrease in power output and IEMG between CHO and placebo trials during either the 1-km HIE (Fig. 4) or 4-km HIE (Fig. 5). There were no significant differences in the increase in time taken and PFS between CHO and placebo trials during either the 1- or 4-km HIE. There were also no significant differences in HR changes between CHO and placebo groups during either the self-paced trial, 1-km HIE, or 4-km HIE.

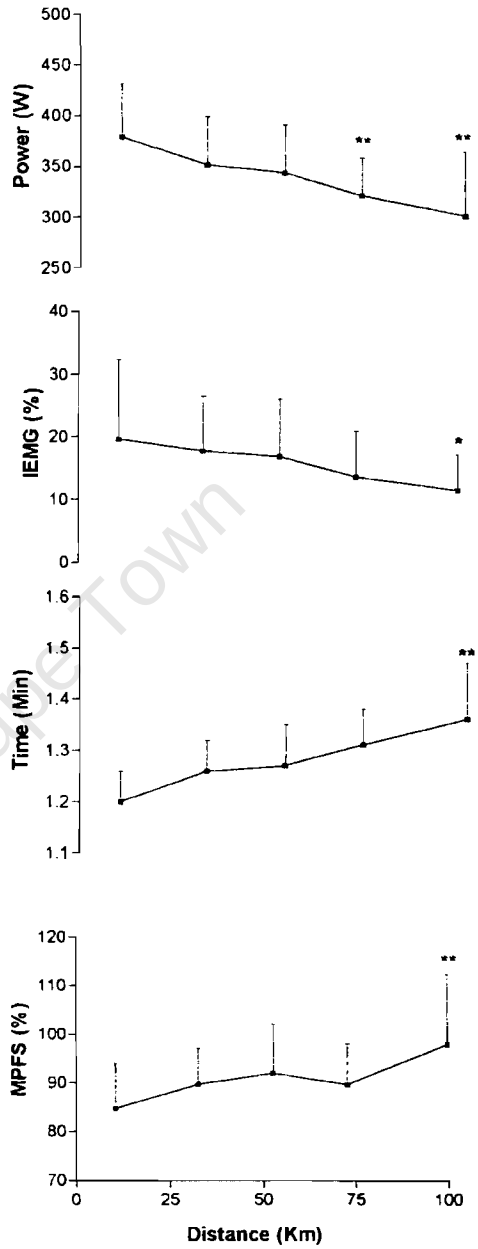

Fig. 1. Power output (W), integrated electromyogram (IEMG; %), time (min), and mean percentile frequency shift (MPFS; %) changes for the entire group during the 1-km high-intensity epoch (HIE). *$P < 0.05$, time *point 1* vs. time *point 5* IEMG; **$P < 0.01$, time *point 1* vs. time *points 4* and *5*; time, power, and MPFS.

As reported previously (8), the dietary CHO intake was significantly higher when subjects were CHO

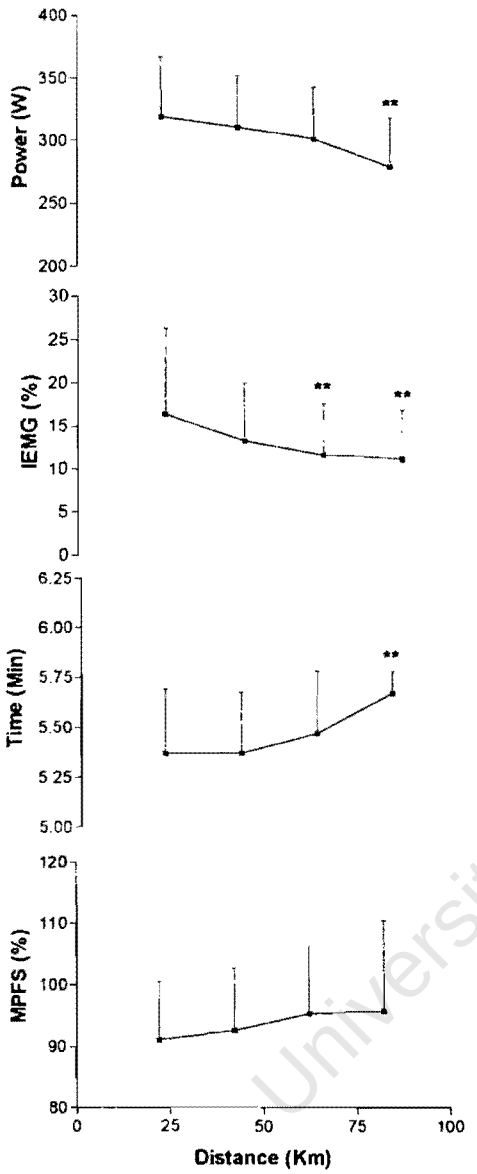

Fig. 2. Power output (W), IEMG (%), time (min), and MPFS (%) changes for the entire group during the 4-km HIE. **$P < 0.01$ time *points 1* vs. *3* and *4*; IEMG, power, MPFS.

loaded (9.0 ± 0.3 g/kg BM) compared with the placebo diet (5.8 ± 0.2 g/kg BM; $P < 0.05$). The preexercise muscle glycogen concentrations were significantly higher in the CHO trial (572 ± 107 mmol/kg dry wt) compared with the placebo trial (485 ± 128 mmol/kg dry wt; $P < 0.05$). There were also no significant differences in postexercise muscle glycogen values between CHO (96 ± 63 mmol/kg dry wt) and placebo (55 ± 28 mmol/kg dry wt) trials (Fig. 6). There were no significant differences in glycogen use during the TT between CHO (476 ± 66.5 mmol/kg dry wt) and placebo (431 ± 116 mmol/kg dry wt) trials, as previously reported (8).

A representative illustration of normalized IEMG activity of rectus femoris activity during 1-km HIE for one subject is shown in Fig. 7. No obvious EMG pattern changes were detected during cycling activity during either TT as subjects fatigued.

DISCUSSION

In this study, we report two unexpected findings. First, we found that IEMG activity declined parallel with decreases in power output and increases in the time taken to complete repeat 1- and 4-km high-intensity exercise bouts during a 100-km cycling TT. Second, we found that these changes occurred although only ~20% or less of the available muscle activated during an MVC was recruited at any time during the cycling TT.

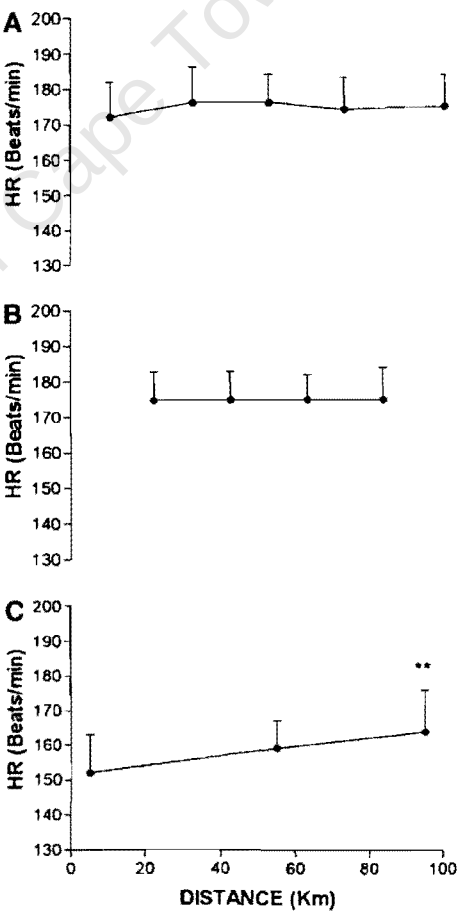

Fig. 3. Heart rate (HR) changes for the entire group for 1 (*top*)- and 4 (*middle*)-km HIE and self-paced (*bottom*) cycling during the 100-km time trial (TT; **$P < 0.01$ self-paced 5 vs. 95 km).

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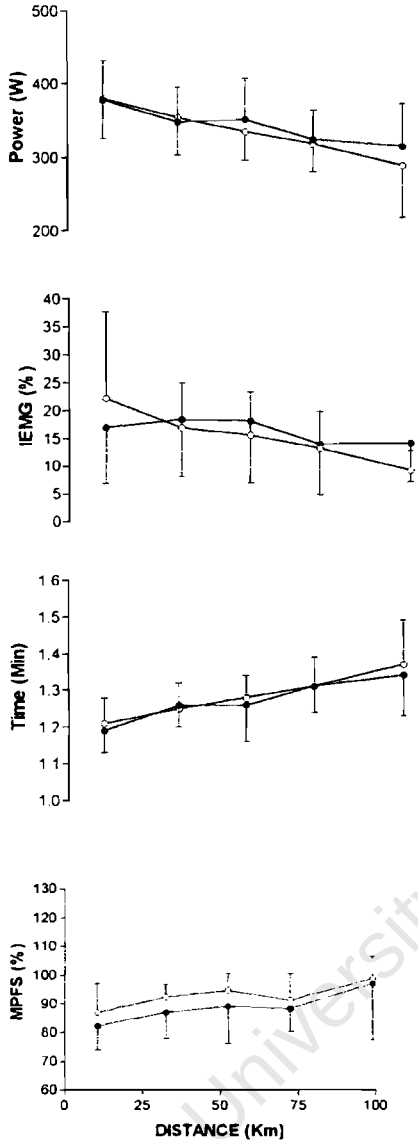

Fig. 4. Power output (W), IEMG (%), time (min), and MPFS (%) changes for the carbohydrate (CHO; ●) and placebo (○) groups during the 1-km HIE.

The first finding of decreased IEMG activity associated with decreased power output was unexpected, as previous studies have described that IEMG activity increases during prolonged submaximal exercise (12, 19, 21). As described previously, increasing IEMG activity generally indicates the recruitment of a greater number of motor units controlled by the development of a peripherally located fatigue due either to skeletal muscle mechanical damage or metabolic substrate perturbations (21). However, some other studies have reported decreased IEMG activity after prolonged submaximal exercise. For example, Nicol et al. (33) found that MVC and IEMG decreased by ~30% in subjects studied after a 42-km marathon foot race. They speculated that this was caused either by insufficient conscious effort or altered central recruitment strategies.

The findings of this study therefore show, for the first time, that neuromuscular activity starts to decline early in the exercise activity despite the conscious efforts of the subjects to maintain maximal power output. Others have shown that during isometric contractions these changes effect not only the active muscles (18) but also synergistic muscles uninvolved in the exercise (38).

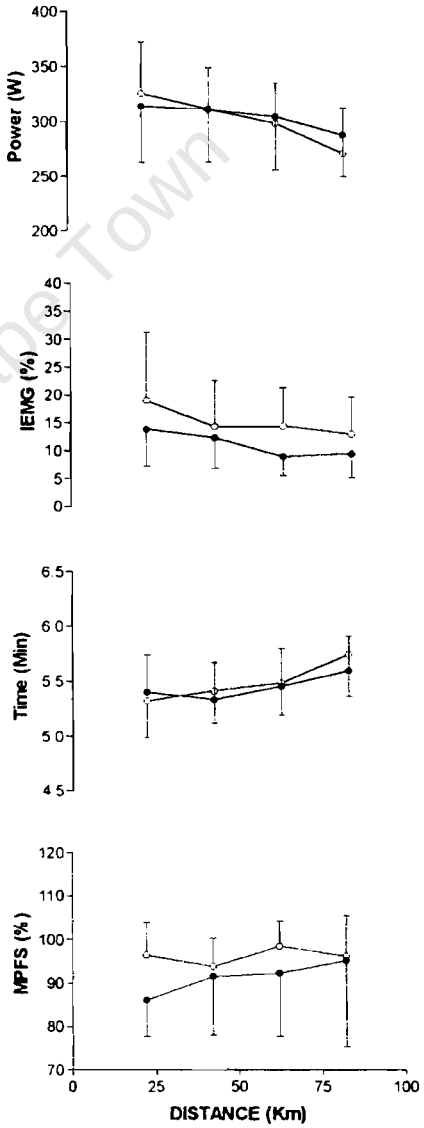

Fig. 5. Power output (W), IEMG (%), time (min), and MPFS (%) changes for the CHO (●) and placebo (○) groups during the 4-km HIE.

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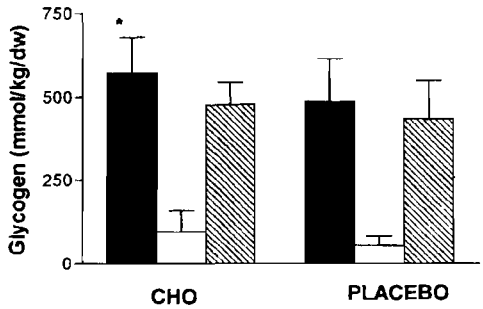

Fig. 6. Muscle glycogen content before (solid bars) and after (open bars) the 100-km TT and muscle glycogen (hatched bars) use during the 100-km TT for CHO and placebo groups (*$P < 0.05$ preexercise muscle glycogen in CHO compared with placebo trial). dw, Dry wt.

These findings could be due to fatigue originating in the motor cortex or to decreased efferent output from the motor cortex secondary to inhibitory influences arising from elsewhere in the body or to reflex muscle recruitment changes arising directly from groups III and IV metaboreceptor afferent input from the peripheral muscles at the spinal cord level (37). Previous studies that examined cortical and efferent output changes during isometric contractions (16, 17, 44) found that fatigue of the motor cortex was not responsible for decreased efferent command. Rather, the changes in motor command were regulated by changes "upstream" from the motor cortex, either excitatory or inhibitory changes in other brain structures, or as a result of failure to recruit corticospinal neurons due to decreased afferent input from group III and IV afferents in the exercising muscles. Changes in neuromuscular activity in our study could therefore be due to commands generated in the higher cortical structures or in response to afferent input from metabolic changes in the peripheral organs or both.

The protocol in this study was of a closed-loop design so that subjects knew the length of the trial and the number of sprints to be performed during the trial. Ulmer (45) speculated that efferent command signals to skeletal muscles regulate not only the spatial and temporal pattern of motion but also control the metabolic rate by adjustment of power output. He speculates that a central "programmer" would consider the time necessary to complete both the sprints and the total activity and the metabolic changes in the different body systems involved during exercise. The programmer would then regulate those systems so that the individual would complete the activity without bodily damage or premature fatigue. This regulatory system is described as teleoanticipation. In our study, the decrease in neuromuscular activity during the sprint activity may represent teleoanticipation, in which the power output was subconsciously decreased despite external encouragement and each subject's maximal conscious effort.

A limitation of our study was that the efferent neural command was measured only in the rectus femoris muscle. Other lower limb muscles might have received either excitatory or inhibitory commands different to those measured in that muscle. Other studies have shown that muscle recruitment patterns change during fatiguing activity (2, 33, 34). For example, Takaishi

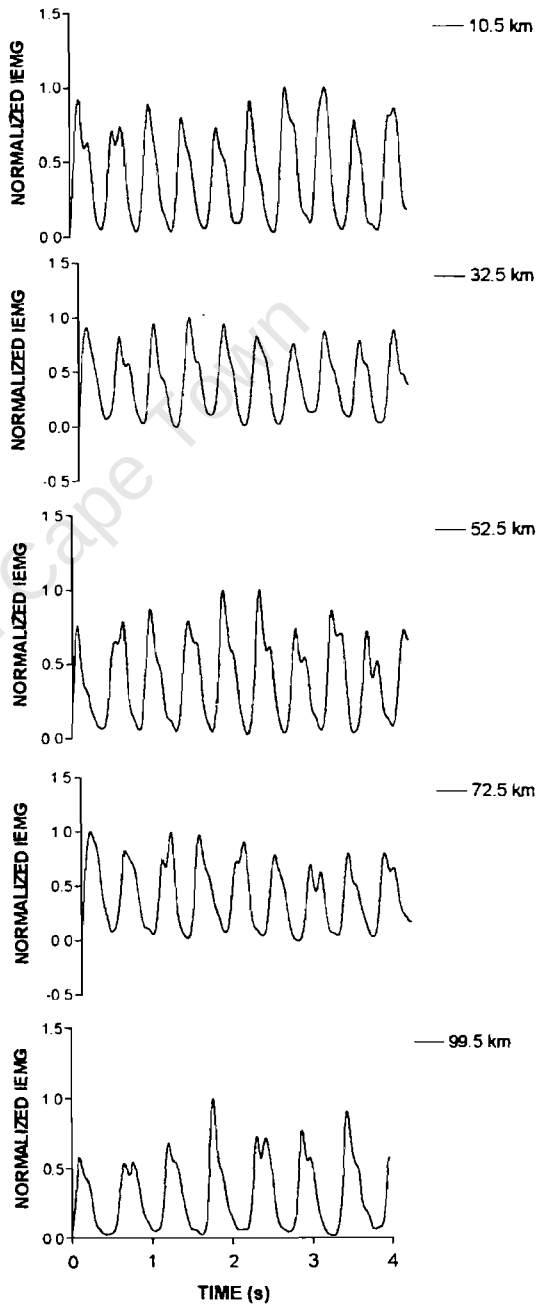

Fig. 7. Representative normalized IEMG data during the 1-km HIE in 1 subject.

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et al. (42) showed that recruitment pattern changes during cycling were cadence dependent so that different muscles were used at different cadences. Thus it is possible in this study that the recruitment strategies of the lower limb were altered as the cyclists became fatigued during the TT, with other muscles being recruited to different levels compared with the changes measured in the rectus femoris muscle. The decrement in power output was ~21%, whereas the decrement in IEMG activity was ~42% during the 1-km high-intensity bouts. Similar differences were found during the 4-km high-intensity bouts. These findings suggest that recruitment strategies of different muscles involved in cycling activity must vary, as either a relative increase in force is provided by the remaining rectus femorus muscles not tested or other muscles are recruited to a greater extent compared with the rectus femoris during the high-intensity cycling activity. However, the study of Sacco et al. (38) found that reduced recruitment of one fatigued muscle was associated with reduced recruitment of synergistic muscles and there was a decline in both the overall IEMG and power output during the cycling trial.

It is also unlikely that these findings can be explained by the biomechanics of cycling preventing greater levels of muscle recruitment. Studies in our (unpublished observations) and other laboratories (29, 46) have shown that during open-loop exercise testing, including progressive exercise to exhaustion for measurement of $\dot{V}O_{2max}$, IEMG activity increases with increasing work rate in a repeatable manner (29). Indeed, further studies in our laboratory (26) have shown that in stochastic exercise of short duration (1 h), power output and IEMG activity decreased during the first sprints similar to the finding in this study. However, in contrast to the finding in Figs. 1 and 2, in that study both power output and IEMG activity increased in the final sprint, indicating that IEMG activity was tracking power output changes and that decrements in IEMG during the first few sprints could not be explained solely by temperature, conductivity, or electrode placement changes during the trial. Hence the decrements in IEMG activity and low percentage of muscle recruitment throughout this trial are not an artifact of the testing method used. These findings were reproduced on two separate occasions in the above study as part of a repeatability trial (26).

It was previously suggested that alterations in excitation/contraction coupling or in the contractile apparatus (2, 20) may be responsible for the decrement in power output during fatigue. Although no obvious cycling EMG pattern changes occurred (Fig. 7) during the HIE bouts, excitation/contraction coupling impairments may also be a cause of the reduced neuromuscular activity and force output decrements.

The decreases in power output during the 1 (Fig. 4)- and 4-km (Fig. 5) HIE bouts occurred similarly in both trials despite different starting muscle glycogen concentrations induced by the different dietary practices. Hence the progressive reduction in power output and neuromuscular activity was not related to differences in preexercise muscle glycogen concentrations.

The second important finding was that these decreases in power output occurred despite the recruitment of ~20% or less of the muscle mass during the cycling TTs compared with during the MVC. Previous studies have also shown the recruitment of an equally small muscle mass during cycling activity (40). Metabolic studies have shown that all available muscle fibers are never completely activated during maximal treadmill running (41), with ~41–90% of muscle fibers being recruited in different subjects during horizontal treadmill running and ~40–80% during uphill running.

Despite the low percentage of muscle fiber recruited at any instance in this study, severe muscle glycogen depletion occurred at the end of the trial coincident with marked subjective fatigue in both CHO and placebo groups. Such low muscle glycogen concentrations could not have occurred if only the same 20% or less of all muscle fibers were recruited during the entire TT.

Therefore, we conclude that the decreased neuromuscular activity was part of a strategy in which the recruitment patterns of either the entire lower limb or individual muscle fibers in the same muscle were altered during the fatiguing process. Thus different muscle fibers must have been recruited at different times so that previously quiescent muscle fibers were recruited to replace fatiguing fibers at the same time that overall efferent neural command was decreasing.

Indeed, Enoka and Stuart (13) suggested that recruitment of motor units in the same muscle alternate during fatiguing activity to attenuate fatigue during submaximal activity. Recently, Westgaard and De Luca (47) confirmed that motor unit substitution and alternation occurs during submaximal isometric contractions. They speculated that efferent neural command patterns must have knowledge of the previous activation history and temporal variation in recruitment activity and that this substitution phenomenon protected motor units from excessive fatigue during sustained submaximal isometric contractions. Further studies examining the relationship between glycogen, glycogen phosphorylase, and succinyl dehydrogenase histochemical changes in type I and II fibers during this protocol and IEMG and power output from the agonist and antagonist muscles are needed to confirm the findings of this study.

The percentile frequency shift increased significantly during the 1- and 4-km HIE exercise bouts after showing a leftward spectral compression in the first HIE relative to that during MVC. The initial leftward spectral compression may be related to the dynamic nature of cycling. A rising core temperature increases spectral density toward the higher frequencies (6). Although not measured, it is likely that rectal temperature rose progressively during this trial and might have explained this effect. It is also possible that these changes were related to a recruitment strategy in which larger, fatigue-sensitive type II fibers were selectively recruited later in the trial (3).

Surprisingly, decreases in IEMG and power output were not associated with any significant changes in HR during either the 1- or 4-km HIE (Fig. 3). Furthermore, heart rate rose significantly during the self-paced cycling (Fig. 3). These findings indicate that the subjects performed to their own maximal volitional capacity and support the conclusion that the neuromuscular activity changes were subconsciously generated. In contrast, reduced conscious effort would have been shown by reduced HR during both the HIE bouts and the steady-state exercise. Subjects also indicated verbally that they were working at maximal effort during all the HIE bouts and subjectively appeared completely exhausted at the completion of the trial. Indeed, the terminal glycogen concentrations were amongst the lowest ever recorded in this laboratory, indicating an exhaustive conscious effort.

Finally, we note that the first HIE bouts were performed at an intensity of ~90% of that achieved during their $\dot{V}O_{2peak}$ protocols and at ~70% of their $\dot{V}O_{2peak}$ intensity in the last HIE bout. Therefore, at no stage did subjects perform at power outputs higher than those reached during their $\dot{V}O_{2max}$ test.

In conclusion, the main findings of this study were that during 1- and 4-km HIE cycling bouts, IEMG declined parallel to decreases in power output and increases in time taken to complete these HIE. These changes occurred despite only ~20% or less of the available muscle fibers being recruited at any time during the time trial. Decreases in power output and IEMG activity were not associated with a reduction in HR during either 1- or 4-km HIE despite significant increases in HR during self-paced cycling. Although preexercise CHO loading significantly increases pretrial muscle glycogen concentrations, this did not influence any of the variables measured during the trial.

On the basis of these findings, we postulate that the progressive reduction in neuromuscular activity may be the cause of fatigue in this trial as an anticipatory mechanism occurring at a subconscious level. Further work examining multiple physiological systems, including afferent input and central command generation during dynamic endurance cycling activity, is needed to verify these findings.

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ORIGINAL ARTICLE

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Evidence for neuromuscular fatigue during high-intensity cycling in warm, humid conditions

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Abstract The purpose of this study was to examine and describe the neuromuscular changes associated with fatigue using a self-paced cycling protocol of 60-min duration, under warm, humid conditions. Eleven subjects [mean (SE) age 21.8 (0.8) years; height 174.9 (3.0) cm; body mass 74.8 (2.7) kg; maximum oxygen consumption 50.3 (1.8) ml · kg · min^{-1}] performed one 60-min self-paced cycling time trial punctuated with six 1-min "all out" sprints at 10-min intervals, while 4 subjects repeated the trial for the purpose of determining reproducibility. Power output, integrated electromyographic signal (IEMG), and mean percentile frequency shifts (MPFS) were recorded at the mid-point of each sprint. There were no differences between trials for EMG variables, distance cycled, mean heart rate, and subjective rating of perceived exertion for the subjects who repeated the trial ($n = 4$). The results from the repeated trials suggest that neuromuscular responses to self-paced cycling are reproducible between trials. The mean heart rate for the 11 subjects was 163.6 (0.71) beats · min^{-1}. Values for power output and IEMG expressed as a percentage of that recorded for the initial sprint decreased during sprints 2–5, with normalised values being 94%, 91%, 87% and 87%, respectively, and 71%, 71%, 73%, and 77%, respectively. However, during the final sprint normalised power output and IEMG increased to 94% and 90% of initial values, respectively. MPFS displayed an increase with time; however, this was not significant ($P = 0.06$). The main finding of this investigation is the ability of subjects to return power output to near initial values during the final of six maximal effort sprints that were included as part of a self-paced cycling protocol. This appears to be due to a combination of changes in neuromuscular recruitment, central or peripheral control systems, or the EMG signal itself. Further investigations in which changes in multiple physiological systems are assessed systematically are required so that the underlying mechanisms related to the development of fatigue during normal dynamic movements such as cycling can be more clearly delineated.

Key words Integrated electromyographic signal · Fatigue · Temperature · Self-paced cycling · Power

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Introduction

The ease with which trained athletes perform masks the complex interactions between the physiological systems involved. Successful performance relies on the maintenance of neuromuscular function; however, factors such as temperature may interfere with such control systems and their function (Montgomery and MacDonald 1990). The most notable modification to the neuromuscular system during exercise is the development of fatigue. Although a common experience, a century of investigation has been unable to completely elucidate a common physiological basis for this phenomenon, as the complexity of the neuromuscular system does not facilitate the evaluation of all of the events that occur during fatigue development. Electromyography (EMG) allows for one aspect of the neuromuscular system to be assessed, that of motor unit pool activation patterns (Viitasalo and Komi 1977). While the measurement of myoelectric activity is a classical approach to investigating the motor control of human movement, multiple factors other than fatigue may induce changes in this variable (Oska et al. 1996).

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Central to the study of fatigue is the definition that is employed. In general, fatigue is viewed as an unavoidable and negative consequence of physical activity, since the outcome almost exclusively results in reduced performance and function (Kirkendall 1990). However, such a view limits the understanding of this phenomenon. It may be more appropriate to view fatigue as a safety mechanism, modulated by either central or peripheral input, preventing metabolic crisis and preserving the integrity of the muscle fibre (Sargeant 1994), thus preventing the development of injury or death by forcing a reduction in the intensity or cessation of activity (Noakes 1998; Wagenmakers 1992). As suggested previously (Kay and Marino 2000), fatigue should be viewed as a continuous process that transforms the functional state, with exhaustion being the point at which exercise is terminated.

Traditionally, submaximal endurance exercise has been used to assess and infer a level of "fatigue". Such protocols do not facilitate the systematic study of muscle fatigue, since no provision is made for the periodic assessment of muscle force/power output, permitting only a "snapshot" of the physiological events associated with muscular exhaustion (Lewis and Fulco 1998). Alternatively, it may be possible to quantify muscle fatigue following dynamic movements such as running and cycling by performing static contractions at the completion of exercise. However, this may not allow for adequate crossover between the musculature used to develop the fatigue and those used to assess it. Moreover, the inevitable delay in assessment would result in a partial recovery of force production capacity (Lewis and Fulco 1998). Furthermore, the results of previous investigations suggest that fatigue development is activity and contraction-type specific (Enoka and Stuart 1992; Kay et al. 2000; Tesch et al. 1990). Studies by Nielsen et al. (1993) and Gonzalez-Alonso et al. (1999) indicate that a potential limiting factor for human performance is the capacity to store heat. The conditions of elevated temperature and humidity reduce the capacity of the body to dissipate heat to the environment, thus increasing the internal thermal load. According to the model presented by these authors, environmental thermal stress would increase heat storage, thus prematurely developing fatigue during exercise.

With such specificity in the factors associated with the onset of fatigue it seems appropriate, if not essential, that data describing the development of fatigue be obtained from the performance of specific activities. It is recommended that the investigation of muscle function take place during normal movements where numerous factors combine to complicate the application and interpretation of the resultant neuromuscular patterns (Sargeant 1987). In response to the paucity of data describing the development of fatigue under dynamic conditions, this study was undertaken to examine and describe the neuromuscular events associated with fatigue using a self-paced cycling protocol of 60-min duration, under elevated environmental conditions.

Methods

Subjects and experimental design

Eleven subjects (8 men, 3 women) were recruited for the study. All were physically active, and were familiar with cycling exercise and the performance of intense physical activity for extended periods. The mean physical characteristics of the subjects are given in Table 1. The study was conducted with the approval of the Ethics in Human Research Committee of the University, and each subject signed a letter of informed consent. Initially all subjects completed an incremental test to exhaustion. This was followed by a familiarisation session 7 days later, which incorporated the self-paced cycling protocol to be undertaken in the experimental trials under similar experimental and environmental conditions.

Seven to 14 days after all subjects had completed the incremental test and familiarisation session, all subjects completed at least one experimental trial. In order to assess the reproducibility of neuromuscular responses to exercise of this nature, 4 of the 11 subjects repeated the trial at least 5 days following the initial experimental trial.

Peak power determination

During this session of the study, descriptive data were collected and all subjects underwent a progressive incremental test to exhaustion for the determination of peak power output and peak oxygen consumption ($\dot{V}O_{2peak}$). Subjects performed this test using his or her own bicycle, which was mounted onto an electromagnetic trainer (Tacx, Technische Industrie Tacx, Wassenaar, The Netherlands). Following a brief warm-up at a self-selected intensity, the test commenced at a workload of 100 W. The load was then increased by 10 W at 30-s intervals until the required power output could no longer be maintained. At all times throughout the test subjects were required to remain in a seated position.

During the maximal test, subjects breathed through a two-way non-rebreathing valve (series 2700 large, Hans Rudolph, St. Louis, Mo., USA), using respiratory tubing of 2.74 m length and 3.5 cm diameter (Hans Rudolph). Expired air passed via the respiratory

Table 1 Data are given as the means, standard error of the mean (SE) and range for physical characteristics and peak physiological variables for 11 subjects (8 males, 3 females). (ΣSF Sum of skinfolds, f_{cmax} maximum heart rate achieved during incremental power tests, $\dot{V}O_{2peak}$ peak oxygen consumption)

Parameter	Age (years)	Height (cm)	Mass (kg)	ΣSF (mm)	$\dot{V}O_{2peak}$ (ml · kg · min^{-1})	f_{cmax} (beats · min^{-1})	Peak power (W)	Mean power output (W)	Total distance cycled (km)
Mean	21.8	174.9	74.8	109.0	50.3	186.2	285.6	215.1	29.06
Range	18–26	164–197	57.2–86.0	62.0–211.0	37.7–58.3	169–202	220–310	131–297	20.1–36.0
SE	0.8	3.0	2.7	17.2	1.8	2.8	11.3	14.8	1.5

tubing to an automated gas analyser (Quinton Instrument Company, Bothell, Wash, USA). The pneumotach (Hans Rudolph) and gas analysers were calibrated prior to analysis, using a 3-l syringe and gasses of known concentration. Expired air passed through a mixing chamber of 5.5-l volume and subsequently sampled at 30-s intervals.

Performance trial

The performance trial required participants to undertake a 60-min self-paced cycling time trial, with the primary goal to complete the greatest distance possible within the allotted time. Throughout the trials the average temperature and humidity was 33 ± 0.3 °C and 64 ± 0.2%, respectively. Trials were performed with subjects using their own bicycle, which was mounted onto the electromagnetic cycle trainer that was used in the peak power tests. During the trial subjects were allowed to alter the gear ratio and pedalling cadence as required. In an attempt to represent the stochastic nature of cycle racing and to provide an additional measure of performance, six 1-min "all out" sprints were included in the performance trial. Sprints were scheduled during the 10th, 20th, 30th, 40th, 50th, and 60th min of the trial. Subjects were encouraged to perform a maximal effort for the entire duration of the sprint. Throughout all sprint intervals subjects were required to remain in a seated position to prevent alterations in muscle fibre recruitment patterns that result from changes in posture. The intra-class correlation for distance cycled for this protocol has been previously determined to be 0.93. Furthermore, the within-cyclist coefficient of variation (CV) following the completion of at least one familiarisation trial for this protocol is 1.34% (Marino et al., unpublished observations).

Participants were instructed to complete the greatest distance possible in the allowed time, taking into consideration the sprints. Prior to each sprint the investigator gave subjects a time count leading up to the commencement of the sprint. During the trial subjects viewed a course profile indicating where sprints occurred, and were permitted to monitor elapsed time and heart rate (f_c). Power output (W) and distance (km) were monitored throughout each experiment and were recorded at 5-min intervals. During all trials, a fan providing a constant wind speed of 3 $m \cdot s^{-1}$ was placed directly in front of the subject and positioned so that the airflow was directed towards the head and torso when in a normal cycling position. Throughout the cycling trials fluid (water) was available to the participants ad libitum to a maximum of 200 ml.

Subjects were requested to perform the same type of physical activity for the duration of the study and to refrain from heavy physical exercise on the day prior to the time trial. Participants were requested to standardise their fluid and food intake for the day preceding the trial, as well as for the day of the time trial. In addition, subjects were required to abstain from the ingestion of alcohol, caffeine, and tobacco for 24 h prior to each trial.

Neuromuscular measurements

Prior to exercise, EMG electrodes with a bandwidth of 20–450 Hz were attached to the "belly" of the rectus femoris muscle. The skin overlying these muscles was carefully prepared. Hair was shaved off, the outer layer of epidermal cells abraded, and oil and dirt were removed from the skin with an alcohol swab. Differential surface electrodes (Delsys, Boston, Mass., USA) were placed on the muscle site as described above, and linked via insulated cable to the signal acquisition apparatus (Bagnoli 4, Delsys) and host computer, which was equipped with data acquisition software (Delsys). EMG data were sampled at 1024 Hz during all tests, thus yielding raw signals; no notch filter was applied. The EMG electrodes consisted of a parallel bar configuration with an inter-electrode distance of 10 mm. The reference electrode consisted of a gel adhesive electrode. The site for the reference electrode was prepared as described above and positioned over an electrically neutral and mechanically stable site.

Raw EMG signals were full-wave rectified. The movement artefact was removed using a high-pass second order Butterworth filter with a cut-off frequency of 15 Hz, then the signal was smoothed with a low-pass second-order Butterworth filter with a cut-off frequency of 5 Hz. This was performed using MATLAB gait analysis software. Commencing at the midpoint of each of the six sprints, 5 s of EMG data were obtained. The mean EMG activity for each 5-s interval was then calculated. The data collected during the initial sprint is described as 100% EMG activity; while all subsequent data were normalised by using this value as the denominator in Eq. 1:

$$\text{Sprint } (x) \text{ value} = \text{absolute value } x \text{ (Volts)/sprint 1 value} \times 100 \quad (1)$$

where x represents sprints 2–6 to be compared with the values from sprint 1. All subsequent sprints were normalised with respect to time against the value obtained in the initial sprint. Corresponding data for power output was normalised with respect to time using the above procedure.

The frequency spectrum of each epoch of the raw EMG data was analysed using a fast Fourier transformation algorithm. The frequency spectrum analysis was restricted to frequencies in the range 5–500 Hz, as the EMG signal content outside of this range consists mostly of noise. The frequency spectrum from each epoch of data was compared with that from the first epoch, and the amount of spectral compression was estimated. This was performed using the technique described by Lowery et al. (1998), as a modification of the work of Lo Conte and Merletti (1996) and Merletti and Lo Conte (1997). The spectrum of the raw signal of each epoch was obtained and the normalised cumulative power at each frequency was calculated. The shift in each percentile frequency (i.e. at 0%...50%...100% of the total cumulative) was examined. The frequency shift was then estimated by calculating the mean shift in all percentile frequencies (MPFS) throughout the mid-frequency range (i.e. 5–500 Hz). It has been suggested that this method is a more accurate estimate of spectral compression than median frequency analysis, which uses the value of a single (50th) percentile frequency only (Lo Conte and Merletti 1996; Lowery et al. 1998; Merletti and Lo Conte 1997).

f_c and rating of perceived exertion

f_c was recorded during all sessions using an f_c monitor and transmitter strap (Vantage NV, Polar Electro Oy, Kempele, Finland). Maximal f_c was determined as the maximum f_c recorded during the peak power test. f_c data were recorded at 15-s intervals and transferred to computer for subsequent analysis. Subjective ratings of perceived exertion (RPE; Borg 1982) were also recorded at 5-min intervals during each trial.

Body temperatures and sweating

Nude body mass was measured to the nearest 10 g prior to and following each cycling trial, using an electronic precision balance (HW-100KAI, GEC, Avery, Australia). The difference in body mass was then used to determine total body sweating ($l \cdot h^{-1}$) after correcting for fluid ingestion. For the four subjects who repeated the experimental trials, the changes in core temperature were monitored using a tympanic thermometer (IRT 1020, Thermoscan, San Diego, Calif., USA) for ethical and safety reasons and as an indicator of thermal strain between trials. It was thought that a more invasive procedure such as oesophageal or rectal probe might have interfered with the performance of subjects. However, after assessing the responses to these trials and determining that there were no significant physiological differences between trials, the remaining seven subjects had core temperature monitored via a rectal thermistor (Mono-a-therm, Mallinckrodt Medical, St. Louis, Mo., USA), which was inserted 10 cm beyond the anal sphincter and connected to a telethermometer (Zencor, Australia).

Statistics

Descriptive statistics were generated for all data. The data for the repeated trials ($n = 4$) were analysed by repeated-measures (trial × time) analysis of variance (ANOVA), and no statistical differences were detected. Therefore, a within-subject one-way repeated-measures ANOVA for time was used to analyse the data for the entire group ($n = 11$). To avoid violation of the homogeneity of variance assumption, the Huynh-Feldt correction factor was used to adjust the degrees of freedom associated with each of the separate repeated-measures analysis. Once the main effects were identified, individual differences between means were located using Tukey's HSD post hoc procedure. The CV was determined from the mean value of individual calculations. Paired samples t-tests were used where appropriate. Significance was accepted at $P < 0.05$. All data are presented as the means (SE).

Results

The mean values for $\dot{V}O_{2peak}$, peak power output, power output and distance cycled during the 60-min trial are given in Table 1. The four subjects who repeated the trials showed no differences between trials for total distance cycled [26.63 (2.25) km vs 28.80 (2.25) km; $P = 0.28$]. Similarly, there were no differences between trials for f_c ($P = 0.66$) and RPE ($P = 0.93$), with mean values being 170 (1) and 170 (1) beats · min^{-1}, and 14 (2) and 13 (1), respectively, for trials 1 and 2, respectively. For both trials, the starting tympanic temperature was ≅36.4 °C, and this had increased to ≅37.9 °C (Δ1.4 °C; $P < 0.05$) by the end of exercise. There were no differences between trials for normalised power output ($P = 0.71$), integrated EMG (IEMG; $P = 0.35$), and MPFS ($P = 0.90$) during any of the sprint intervals (Fig. 1). During both trials, normalised IEMG values were significantly decreased for all sprint intervals following the initial sprint ($P < 0.05$). For each of the repeated trials normalised power output displayed a similar pattern in tracking normalised IEMG responses (Fig. 1). The CV for IEMG, power output, and MPFS for the repeated trials were 16.1%, 4.3%, and 1.9%, respectively. Previous studies reporting the test-retest reliability of EMG variables have described similar results (Taylor and Bronks 1995).

f_c and RPE for the eleven subjects are shown in Fig. 2. The mean f_c for the entire trial was 163.6 (0.71) beats · min^{-1}, with mean values attained during sprints 1–6 being 171 (4.3), 177 (4.2), 178 (5.0), 179 (4.3), 182 (3.8), and 183 (4.2) beats · min^{-1}, respectively. The starting rectal temperature was 37.5 (0.1) °C, and this had increased to 38.9 (0.2) °C ($P < 0.05$; Δ1.4 °C; $n = 7$) by the end of exercise. The mean total body sweat rate was 1.49 (0.15) l · h^{-1}. Subjective ratings of RPE over time are presented in Fig. 2, with the mean RPE for the trial being 13.6 (1.0).

Normalised power output, IEMG, and MPFS for all eleven subjects are shown in Fig. 3. Values for power output expressed as a percentage of initial sprint power decreased with respect to time, reaching significance during sprints 4 and 5 ($P = 0.05$). Values for power output expressed as a percentage of initial sprint decreased during sprints 2–5, with normalised values being 94%, 91%, 87% and 87%, respectively. Similarly, normalised IEMG values for the same sprints were 71%, 71%, 73%, and 77% of initial values, respectively. However, during the final sprint, normalised power output and IEMG recovered to 94% and 90% of initial values, respectively. MPFS increased with time; however, this increase was not significant ($P = 0.06$). A representative sample of IEMG data obtained from one subject during each sprint interval is presented in Fig. 4.

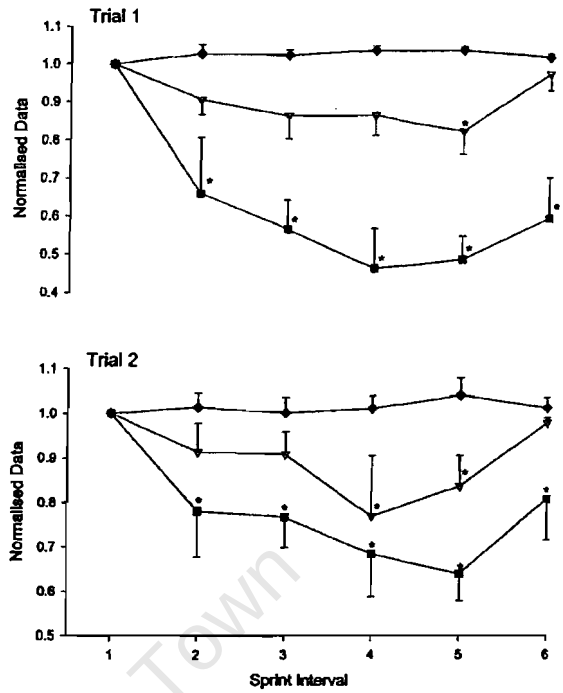


Fig. 1 Time-normalised data for power output (*open triangles*), integrated electromyogram (IEMG; *closed squares*), and frequency spectrum (*closed diamonds*) during trials 1 and 2, collected at the mid-point of each of the sprints during a 60-min cycling trial conducted under warm, humid conditions. Data are presented as the means ± SE ($n = 4$). *$P < 0.05$, significant compared with first time point

Discussion

This study describes the efferent neural output of the rectus femoris muscle during high-intensity sprints that were included in a 60-min self-paced cycling protocol. The results of the present study demonstrate a reduction in efferent drive and power output commencing in the early stages of exercise. However, this initial reduction in efferent drive, observable in sprints 2–4, was accompanied by an increasing efferent output to the

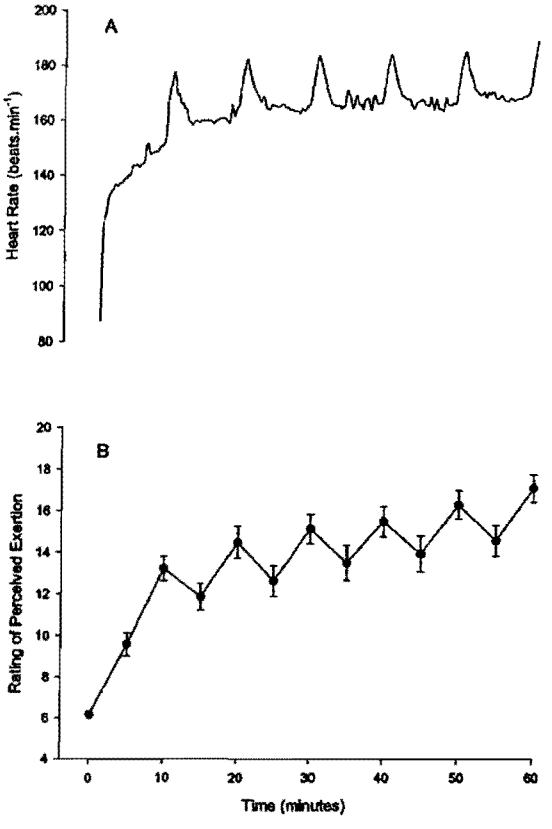
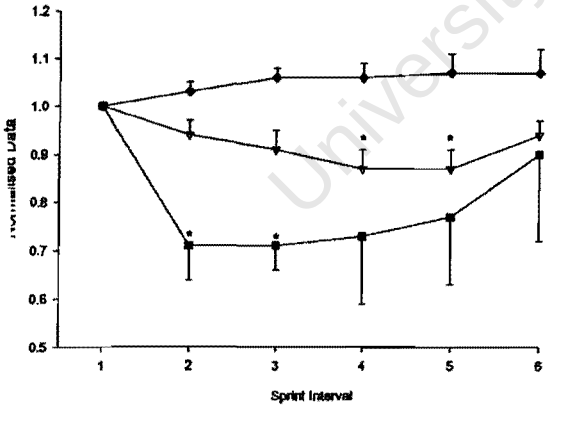


Fig. 2 Mean heart rate at 15-s intervals A and rating of perceived exertion B during the 60-min self-paced cycling time trial. Data are presented as the means ± SE ($n = 11$)



ig. 3 Time normalised data for power output (*open triangles*), EMG (*closed squares*), and frequency spectrum (*closed diamonds*) ollected at the mid-point of each of the sprints during a 60-min ycling trial conducted under warm, humid conditions. Data are resented as the means ± SE ($n = 11$). *$P < 0.05$, significant ompared with first time point

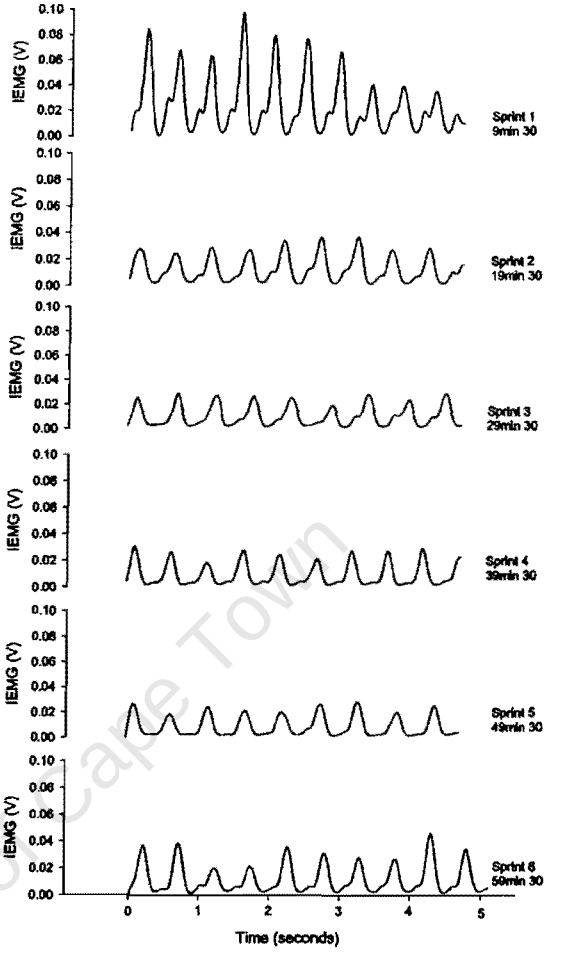


Fig. 4 Representative IEMG data for one subject. Data were collected at the mid-point of each of the sprints during a 60-min cycling trial conducted under warm, humid conditions

active muscle during the concluding stages of exercise (sprint 6), resulting in a concomitant increase in power output. This suggests the existence of a subconscious muscle reserve during the initial five sprints, despite a conscious effort by all subjects, as evidenced by the similar f_c and RPE response prior to and following each sprint. A secondary finding of the present investigation is that this neuromuscular response pattern to stochastic self-paced exercise is reproducible between trials (Fig. 3).

The results of the present study show that during the final minute of a 60-min self-paced cycling protocol where subjects were required to produce a maximal effort, it was possible to restore power output to near initial values. This restoration of power output during the final sprint was accompanied by a similar increase in

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the IEMG signal of the rectus femoris muscle (Fig. 3). Subjects were clearly able to increase the neural drive to the muscle in conjunction with an increasing power output during the final sprint, suggesting not only maintenance of the ability to activate the muscle, but the presence of a neuromuscular reserve during self-paced exercise. This occurred despite subjects being required to perform a maximal effort for the entire duration of each sprint interval.

Migration of motor unit activity to synergist muscles may have allowed for the maintenance of force output relative to the observed IEMG of the rectus femoris (Komi and Tesch 1979). However, we were unable to determine the degree with which the activation of synergist muscles contributed to the power output during this study. Previous investigations have shown recruitment patterns to be altered with fatiguing activity (Bangsbo et al. 1992; Nicol et al. 1991; Nummela et al. 1992). It remains possible that lower limb inter-muscular recruitment strategies were altered as subjects fatigued, with other muscles being recruited at different levels to the single muscle measured in this study. However, investigation by Sacco et al. (1997) suggests that fatigue of one muscle is closely associated with fatigue of synergistic muscles. The finding that the reduction in IEMG activity was mirrored by power output suggests that the synergistic muscles involved in cycling activity display a similar pattern to that of the rectus femoris and were not recruited to compensate for the falling power output or reduced efferent drive to this muscle.

It has been suggested that alterations in excitation/contraction coupling or the contractile apparatus (Bangsbo et al. 1992; Häkkinen and Komi 1983) are the factors that are responsible for the reduction in power output observed during fatiguing activity. However, throughout all sprints a regular cycling EMG pattern was maintained (Fig. 4), indicating that impairment of the excitation/coupling mechanism is unlikely to be the cause of the attenuated efferent signal observed in the present study. If this mechanism was responsible it would result in the cessation of cycling exercise. In addition to the progressive reduction in amplitude, a feature of Fig. 4 is the double peak that occurs prominently during muscle activation throughout the initial sprint. This is a result of the rectus femoris muscle being active in conjunction with the extensor muscles, assisting with flexion of the hip during the recovery phase of the pedalling motion (Burke 1995). Activation of the rectus femoris during the recovery phase is clearly distinguishable from the propulsive phase during the initial sprint. However, by the fifth sprint this component of the pedal cycle can no longer be observed. During the final sprint, although distinguishable, this component of the pedal cycle remains irregular compared to that observed during the initial sprint. Although qualitative, these data indicate an alteration in the coordination pattern of the cycling movement in conjunction with the development of fatigue.

Rectal temperature increased progressively during the cycling trial, resulting in terminal values of ≅38.9 °C. The relationship between the core temperature and muscle temperature (T_m) response during physical activity appears to be proportional (Kozlowski et al. 1985). Since all neural processes are temperature sensitive (Montgomery and MacDonald 1990), changes in T_m induced either by environmental conditions or physical activity have the potential to alter the contractile and metabolic properties of muscle fibres, in turn impacting on the capacity to sustain work output (Sargeant 1994).

Increases in T_m have been associated with increases in peak muscle force (Davies and Young 1983; Sargeant 1987), due to temperature-induced alterations in neuromuscular recruitment patterns (Holewijn and Heus 1992), increased conduction velocity and contractile speed (Bell 1993; Davies and Young 1983; Sargeant 1987; Zhou et al. 1998), and the earlier and more pronounced development of muscle fatigue (Holewijn and Heus 1992), suggesting failure of the fatigue-susceptible fast-twitch fibres. However, since we did not measure T_m, it is not possible to fully relate EMG responses to changes in this variable. Furthermore, the EMG signal may be influenced by alteration in the fluid content of the muscle (Winkle and Jørgensen 1991) and the additional perspiration generated by prolonged activity (Bell 1993), particularly under conditions of elevated temperature.

The data from the present study indicate that during 60 min of continuous cycling activity under elevated environmental conditions, power output was tracking IEMG activity (Figs. 1, 3). This finding suggests that the observed attenuation in IEMG activity during the initial stages of the trial may not be a function of changes in temperature, conductivity, or electrode placement. With the continuation of exercise and the development of fatigue, progressive decreases in the frequency content of the active muscle could be expected (Viitasalo and Komi 1977). In contrast, the present results demonstrate the maintenance of MPFS during exercise. It is possible that this resulted from either increasing core temperature and T_m, or changes in recruitment strategy, with the selective recruitment of type II fibres occurring towards the end of the trial (Basmajian and DeLuca 1985).

Finally, the protocol utilised in the present study was self-paced; thus subjects were aware of the duration of the trial and the number of sprints to be performed. Ulmer (1996) suggested that efferent command signals to muscles not only regulate the spatial and temporal pattern of motion, but also act to control metabolic rate. This suggestion includes the presence of a central control that acts to balance the requirements of the activity with metabolic changes within the body. This system would act to allow the individual to most efficiently complete the activity without the development of physiological damage or premature fatigue. The present results give support to the existence of such a mechanism through the decreasing power output and efferent command to the active muscle during the initial sprint intervals, despite a similar physiological effort during the trial, as

evidenced by f_c and RPE values prior to and immediately following the sprints.

In summary, this investigation has described the neuromuscular and performance changes that occur during self-paced cycling. Further investigations in which the changes in multiple physiological systems are assessed systematically are required so that the underlying mechanisms responsible for the development of fatigue during normal dynamic movements such as cycling can be more clearly described.

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Superior performance of African runners in warm humid but not in cool environmental conditions

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[1]*School of Human Movement Studies, Charles Sturt University, Bathurst NSW 2795, Australia; and* [2]*MRC/UCT Research Unit for Exercise Science and Sports Medicine, Department of Human Biology, Faculty of Health Sciences, University of Cape Town 7725, South Africa*

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Marino, Frank E., Mike I. Lambert, and Timothy D. Noakes. Superior performance of African runners in warm humid but not in cool environmental conditions. *J Appl Physiol* 96: 124–130, 2004. First published August 29, 2003; 10.1152/japplphysiol.00582.2003. – The purpose of this study was to examine the running performances and associated thermoregulatory responses of African and Caucasian runners in cool and warm conditions. On two separate occasions, 12 (n = 6 African, n = 6 Caucasian) well-trained men ran on a motorized treadmill at 70% of peak treadmill running velocity for 30 min followed by an 8-km self-paced performance run (PR) in cool (15°C) or warm (35°C) humid (60% relative humidity) conditions. Time to complete the PR in the cool condition was not different between groups (~27 min) but was significantly longer in warm conditions for Caucasian (33.0 ± 1.6 min) vs. African (29.7 ± 2.3 min, $P < 0.01$) runners. Rectal temperatures were not different between groups but were higher during warm compared with cool conditions. During the 8-km PR, sweat rates for Africans (25.3 ± 2.3 ml/min) were lower compared with Caucasians (32.2 ± 4.1 ml/min; $P < 0.01$). Relative rates of heat production were less for Africans than Caucasians in the heat. The finding that African runners ran faster only in the heat despite similar thermoregulatory responses as Caucasian runners suggests that the larger Caucasians reduce their running speed to ensure an optimal rate of heat storage without developing dangerous hyperthermia. According to this model, the superior running performance in the heat of these African runners can be partly attributed to their smaller size and hence their capacity to run faster in the heat while storing heat at the same rate as heavier Caucasian runners.

efficiency; ethnicity; fatigue; pacing; anticipation; thermoregulation

THERE IS EVIDENCE THAT ATHLETES of (East) African ancestry presently dominate international distance running events (10, 22). A number of studies have searched for a physiological explanation for this apparent superiority of African athletes.

Results from early studies suggested that Africans might enjoy a superior economy of movement (18, 26, 35). Indeed, a recent study confirms that African runners had a significantly lower maximum oxygen uptake ($\dot{V}O_{2\,max}$) than did Caucasian runners of matched ability but were more economical, at least over a 10-km race distance (33). In addition, African runners generally have a lower absolute $\dot{V}O_{2\,max}$ than do Caucasian runners of matched ability. However, these differences diminish when $\dot{V}O_{2\,max}$ is expressed relative to body mass (7, 32).

Bosch et al. (4) compared various physiological responses of (South) African and Caucasian runners during a 42-km treadmill marathon in cool conditions and concluded that the only discernable difference was the ability of African runners to run at a higher percentage of $\dot{V}O_{2\,max}$ during competition. Coetzer et al. (7) have also shown greater fatigue resistance in a group of elite African runners who were able to sustain a higher %$\dot{V}O_{2\,max}$ during races longer than 3 km. African athletes also had lower blood lactate concentrations for a given oxygen consumption. Furthermore, African athletes fatigued less rapidly during repetitive bouts of isometric testing of the quadriceps muscles. The physiological basis for this enhanced fatigue resistance was unclear because muscle fiber types were not different between groups, although the African athletes tended to have a lower percentage of type I muscle fibers. More recently, and in support of these previous findings, Weston et al. (32) showed that African runners took 21% longer to fatigue during an incremental running test. This superior resistance to fatigue was associated with higher skeletal muscle enzyme activity and a lower proportion of type I fibers compared with Caucasian athletes. A higher skeletal muscle oxidative capacity has also been found in nonathletic persons of (West) African ancestry (29).

A fundamental problem when comparing (East and South) African and Caucasian athletes is the inherent difference in body size between the two groups given that elite East and South African athletes are generally smaller than Caucasian athletes (7, 27, 33). It has also been shown that a small body size could be an advantage in distance running, particularly in the heat (8, 19), and that lean body mass may account for differences in running performance in the heat between individuals of different sizes (34). It has been hypothesized that, as ambient temperature rises from 25 to 35°C, larger and heavier runners must run slower because the accumulation of body heat would increase body temperature to levels commonly associated with fatigue (8, 12, 19, 21). Given the evidence that African athletes seem to be more economical, have higher fatigue resistance, and are generally smaller than their Caucasian counterparts, it seems feasible to postulate that smaller East and South African runners might have an advantage over Caucasian athletes during distance running in warmer environmental conditions. We are unaware of any studies that have specifically tested this hypothesis.

Therefore, the purpose of this study was to examine whether African distance runners enjoy any advantage over Caucasian runners when running in warmer ambient conditions because, as previously postulated (8, 19), their smaller size would allow a faster running speed with a similar or lesser thermoregulatory strain.

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METHODS

Subjects. Twelve (6 African, 6 Caucasian) well-trained male endurance runners were recruited for the study. Table 1 shows the mean physical characteristics of each group. Overall, the physical characteristics of the subjects indicate that the sample for each group was comprised of representative African and Caucasian runners as those reported in previous studies (e.g., African ~57 kg; Caucasian ~67 kg) (2, 4, 7, 17, 18, 27, 33). It was assumed that subjects were not naturally heat acclimatized because the experiments were conducted during the months of September and October, at which time the daily temperature ranged from 8 to 25°C. None of the subjects reported any international travel within the 3 mo before the experiments. All experimentation was carried out in a climate chamber. On average, the subjects maintained a training volume of 60–80 km/wk for at least 3 mo before the study. Subjects also competed in national and local running events on a regular basis. All participants were instructed to maintain a regular diet during the study period and were asked to refrain from alcohol and caffeine ingestion for at least 24 h before testing. The study was approved by the Research and Ethics Committee of the Faculty of Health Sciences of the University of Cape Town, and each subject signed a letter of consent after being informed of the risks associated with the experiment.

Descriptive measurements. Stature (cm) and body mass (kg) were determined by use of a precision stadiometer and balance (model 770, Seca, Bonn, Germany). All measurements were recorded with the subject fully instrumented and wearing light running shorts. Nine skinfold sites (biceps, triceps, subscapular, pectoral, midaxilla, midabdominal, suprailiac, midthigh, and medial calf) were measured in duplicate with skinfold calipers (Holtain, Crymych, UK) to the nearest millimeter. Percent body fat was estimated as previously described (14), and body surface area (A_D) was calculated from mass and height as described by DuBois and DuBois (9).

Familiarization and incremental running tests. During a familiarization session, peak oxygen uptake ($\dot{V}O_{2\,peak}$) and peak treadmill running velocity (PTV) were determined in moderate environmental conditions in which the ambient temperature, relative humidity, and wind velocity were set at 21.0 ± 0.6°C, 50.0 ± 0.9%, and 5.0 ± 0.6 km/h, respectively. The individual $\dot{V}O_{2\,peak}$ and PTV were determined on a motorized treadmill (Powerjog EG30, Sports Engineering, Birmingham, UK) set at a 1% gradient. Subjects started running at 12 km/h with speed increments of 1 km/h every minute until they could no longer keep pace. The last increment in speed that could be maintained for at least 1 min was defined as the PTV. During the incremental tests, the subjects wore a nose clip and breathed through a mouthpiece connected to an automated gas analyzer (Oxycon Alpha, Jaeger). Before each test, the gas analyzer was calibrated with gases of known concentration and the ventilometer was calibrated with a 3-liter syringe (Hans Rudolph, Vacumed, Ventura, CA). Oxygen consumption, CO_2 production, minute ventilation, and respiratory exchange ratio were calculated for each breath. $\dot{V}O_{2\,peak}$ (ml·kg^{-1}·min^{-1}) was the average of the highest values attained over the final minute of exercise. After the measurements of $\dot{V}O_{2\,peak}$ and PTV, the subjects rested for ~5–7 min and then performed a familiarization run on the treadmill to minimize a "learning effect" for the subsequent experimental trials. They began the familiarization trial by running at 70% of PTV for 1–2 min and then as far as possible in 10 min by adjusting their running speed with a touch pad on the side arm of the treadmill.

Table 1. *Characteristics of African and Caucasian runners*

	African	Caucasian
Height, cm	167.4 ± 4.4	183.4 ± 6.5*
Mass, kg	59.3 ± 4.4	76.6 ± 9.3*
A_D, m^2	1.66 ± 0.1	1.98 ± 0.2*
%BF	5.1 ± 0.2	5.3 ± 0.3
Skinfold, mm	49.1 ± 2.0	55.5 ± 3.2
$\dot{V}O_{2peak}$, ml·kg^{-1}·min^{-1}	62.6 ± 3.5	64.3 ± 3.0
PTV, km/h^{-1}	21.2 ± 0.8	20.8 ± 1.2

Values are means ± SD. A_D, body surface area; %BF, percent body fat; $\dot{V}O_{2peak}$, peak oxygen uptake; PTV, peak treadmill velocity. *$P < 0.01$ compared with African.

Experimental trials. Each trial was conducted at the same time of day so that the effect of circadian variation could be minimized. During each trial, relative humidity and wind velocity were kept constant at 60.3 ± 0.8% and 15.1 ± 0.6 km/h, respectively, while the ambient temperature was set at either 15 or 35°C.

Before the experimental trials, the subjects voided and inserted a rectal thermistor (Mon-a-therm, Mallinckrodt, OH) secured by a bead 10 cm beyond the anal sphincter. Four skin thermistors were then secured as previously described (25), and subjects were fitted with a heart rate monitor (Sport Tester, Polar Electro, Kempele, Finland).

The subject then entered the climate chamber and started a submaximal run for 30 min at 70% PTV (range 14.7–16.1 km/h). Thereafter, there was a 5-min interval during which the subject removed socks and shoes and was toweled dry, reweighed, and permitted to drink up to 300 ml of distilled water. The subject was then prepared for an 8-km performance run that was to be completed as fast as possible by adjusting the running speed. The running speed was noted at the end of each minute and at the end of exercise. A mean running speed was calculated at the end of each 5-min interval and when subjects completed the 8 km. An overall mean running speed was calculated for the time taken to complete the run. The changes in body mass were adjusted for fluid ingested and were used to calculate total body sweat rates (without correction for metabolic fuel utilization during the trial).

Throughout the submaximal and 8-km trials, rectal and skin temperatures at four sites (chest, arm, thigh, leg) were monitored continuously with a telethermometer (YSI model 4002, Yellow Springs, OH) and recorded at 5-min intervals. Mean skin temperature was calculated as previously described (25).

Heart rate and subjective measurements. Heart rate was monitored continuously and recorded at 5-min intervals with a Polar heart rate monitor (Sport Tester, Polar Electro). Rating of perceived exertion (RPE) was measured at 5-min intervals as previously described (3).

Heat production, storage, and dissipation. Although varying slightly with running economy, heat production in runners has been shown to amount to ~4 kJ·kg body mass^{-1}·km^{-1} (20). Therefore, rate of heat production (H) in watts (W) is equal to the product of the runner's body mass (in kg), the running speed (v, in m/s), and ~4 J produced per kilogram of body mass. The rate of heat storage (S) was estimated with the equation $S = (3.48 \cdot 10^3) \cdot (\text{body mass} \cdot \Delta \bar{T}_B / s) \cdot A_D^{-1}$, where ($3.48 \cdot 10^4$) is the specific heat of body tissue (in J·kg^{-1}·°C^{-1}), $\Delta \bar{T}_B$ is the change (Δ) in mean body temperature ($\bar{T}_B$) calculated from $\bar{T}_B = 0.87\ T_{re} + 0.13\ \bar{T}_{sk}$, where T_{re} is rectal temperature and $\bar{T}_{sk}$ is mean skin temperature, over the exercise period in seconds, and A_D is body surface area in square meters. Heat loss via potential evaporation (E_P) was calculated from the predicted sweat rates determined from changes in body mass and the 40.55 kJ·mol latent heat of evaporation of water and its 18 g·mol molecular weight. The evaporation of 1 liter of sweat per hour dissipates ~675 J/s or W, assuming that all the sweat is evaporated (8). Potential rates of heat loss via convection (C) and radiation (R) were estimated with the following equations (20)

$$C = (\bar{T}_{sk} - T_a) \cdot v^{0.5} \cdot A_D \cdot 8.3$$

$$R = (\bar{T}_{sk} - T_r) \cdot A_D \cdot 5.2$$

where ($\bar{T}_{sk} - T_a$) is the difference between mean skin temperature and the ambient air (in °C), $v^{0.5}$ is the square root of the velocity of air flow over the skin in (m/s), A_D is the body surface area (in m^2), 8.3 and 5.2 are heat transfer coefficients (in W·m^{-2}·°C^{-1}), and ($\bar{T}_{sk} - T_r$) is the difference between mean skin temperature and mean radiant

temperature of the walls of the climate chamber. The required evaporation (E_R) was estimated from the residual component from $H \pm S \pm C \pm R$.

Statistics. Separate ANOVAs for repeated measures on time and trials were applied to determine treatment effects during exercise. If a main effect was detected post hoc, comparisons were made with either Tukey's honestly significant difference test for pairwise comparisons or simple main effects for significant interactions. Significance was accepted at $P < 0.05$. All data are presented as means ± SD.

RESULTS

Performance run. The African runners completed the performance run in cool (15°C) conditions in 27.4 ± 1.0 min, which was not different from the 27.4 ± 0.4 min for Caucasian runners. African runners ran marginally slower (29.7 ± 2.3 min) in the heat (35°C), but this was not significant. In contrast, compared with their time in the cool condition, Caucasian runners ran slower in the heat (33.0 ± 1.6 min vs. 27.4 ± 0.4; $P < 0.05$).

Figure 1 shows the mean running speed at 5-min intervals for both groups during the submaximal and performance runs in each ambient condition. During the performance run in cool conditions, mean running speed for Caucasian runners was 17.5 ± 0.6 (range 17.0–17.7) km/h and was similar to the mean running speed of 17.4 ± 0.8 (range 16.8–18.4) km/h for the African runners. Conversely, during the performance run in the heat, Caucasian runners were only able to maintain a mean running speed of 14.5 ± 0.7 (range 13.8–16.6) km/h compared with the mean running speed of 16.0 ± 1.2 km/h ($P < 0.01$) (range 15.2–16.7 km/h) for the African runners. Thus running speed in the heat was significantly slower at all time points for Caucasian runners compared with their performance in the cool condition (Fig. 1). In contrast, the speed of the African runners was significantly reduced only at the last two time points compared with their performance in the cool conditions (Fig. 1).

Thermoregulatory responses, heat production, storage, and dissipation. During the submaximal and performance runs, mean skin temperatures were not different between African and Caucasian runners (Fig. 2). However, during cool conditions, the mean skin temperature ranged from 24.5 to 25.7°C compared with a range of 33.9–34.9°C during the warm condition. Mean skin temperatures at 5-min intervals were significantly different between ambient conditions for both groups (Fig. 2). Rectal temperature increased over time during the submaximal run from preexercise to ~37.8°C in cool conditions and ~38.4°C in warm conditions for both groups. However, the sole difference between groups became apparent in warm conditions during the remaining 10 min of the performance run, when Caucasian athletes reached higher rectal temperatures than when they ran in cool conditions (Fig. 2) despite the fact that they were running significantly slower. Rectal temperatures at the end of the performance run were 38.7 ± 0.4°C in cool and 39.2 ± 0.2°C ($P < 0.05$) in warm conditions for African runners and 38.6 ± 0.5°C in cool and 39.5 ± 0.5°C ($P < 0.05$) in warm conditions for Caucasian runners. The rate of increase in rectal temperature during the submaximal run was similar in cool and warm conditions but was 2.2°C/h for African runners and 3.2°C/h ($P < 0.05$) for Caucasian runners. This rate of increase was reduced for both groups during the performance run in warm conditions and was similar for African (1.6°C/h) and Caucasian (1.8°C/h) runners.

The total body sweat rates for the combined submaximal and performance runs in cool conditions were 13.1 ± 2.2 ml/min for African runners and 19.5 ± 5.0 ml/min for Caucasian runners, but these were not significantly different. Compared

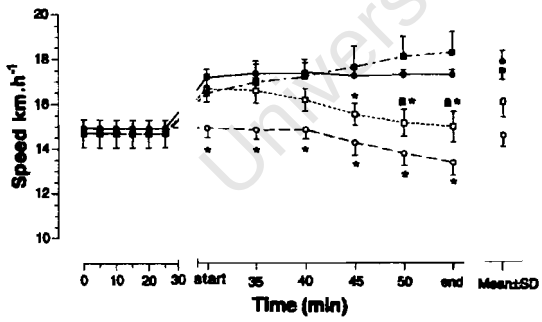

Fig. 1. Running speed during the submaximal run (0–30 min) at 70% peak treadmill velocity and during the 8-km performance run (start–end). Cool conditions: ■, Africans; ●, Caucasians. Warm conditions: □, Caucasians; □, Africans. *$P < 0.001$ compared with African and Caucasian in cool conditions; †$P < 0.01$ compared with Caucasians in warm conditions. Data at end of y-axis represent the mean ± SD running speed during the 8-km performance run.

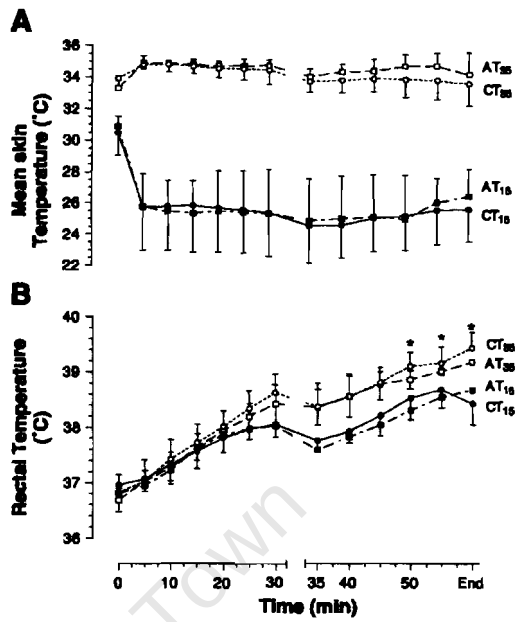

Fig. 2. Mean skin temperature (*A*) and rectal temperature (*B*) during the submaximal run (0–30 min) at 70% peak treadmill velocity and during the 8-km performance run (35 min–End). Cool conditions (T_{15}): ■, Africans (A); ●, Caucasians (C). Warm conditions (T_{35}): □, Caucasians; □, Africans. Mean skin temperatures in warm conditions were significantly different ($P < 0.001$) compared with cool conditions. *$P < 0.05$ compared with Caucasians in cool conditions (CT_{15}).

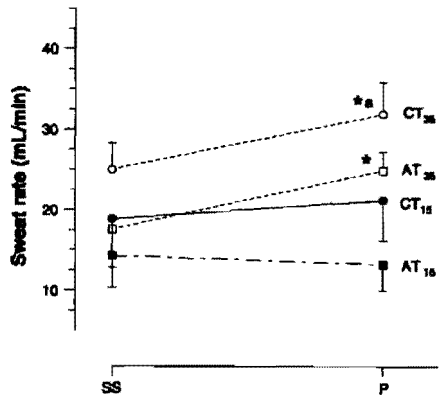

Fig. 3. Total body sweat rate during the submaximal run (SS) at 70% peak treadmill velocity and during the 8-km performance run (P). Cool conditions (T_{15}): ■, Africans (A); ●, Caucasians (C). Warm conditions (T_{35}): ▽, Caucasians; □, Africans. *$P < 0.01$ compared with cool conditions; *$P < 0.05$ compared with Africans.

with the cool conditions, the sweat rate increased during warm conditions to 22.1 ± 3.0 ml/min for Africans and 28.9 ± 4.1 ml/min ($P < 0.03$) for Caucasian runners. Figure 3 shows the separate total body sweat rates for submaximal and performance runs in both cool and warm conditions. The sweat rate for African runners was similar during submaximal (13.3 ± 2.8 ml/min) and performance (12.8 ± 2.5 ml/min) runs in cool conditions. In warm conditions, the sweat rate tended to increase in the African runners from the submaximal to performance runs (18.9 ± 6.0 ml/min vs. 25.3 ± 2.3 ml/min), but this was not significant. Caucasian runners tended to sweat more than Africans in the cool condition (20.1 ± 3.3 vs. 18.9 ± 6.0 ml/min), although this was not significant during either submaximal or the performance runs. During warm conditions in the performance run, the sweat rate was higher in Caucasian runners (32.2 ± 4.1 ml/min) compared with African runners (25.3 ± 2.3 ml/min; $P < 0.01$; Fig. 3).

Table 2 shows the separate heat-exchange values for submaximal and performance runs for each group in both ambient conditions. Heat production for submaximal and performance runs in the cool condition was significantly ($P < 0.05$) higher for Caucasian compared with African runners. This trend continued during the warm condition with heat production for Caucasians remaining significantly ($P < 0.05$) higher than Africans during submaximal and performance run. The S in the cool environment was higher ($P < 0.05$) for Caucasian than African runners in both submaximal and performance runs. However, in warm conditions, S increased significantly ($P < 0.05$) compared with the cooler condition for both groups with this difference also significant between groups (Table 2). Heat loss via $C + R$ was similar between groups in the cool condition and between submaximal and performance runs. However, both groups gained heat via $C + R$ during the warm compared with the cool condition (Table 2). Sweat rates from the submaximal and performance runs indicate that E_P was increased in warmer conditions compared with the cooler condition for both groups. During the cool condition, the E_R was similar for both groups, although the African runners had a significantly lower E_R during the submaximal run. In the warm condition, E_R increased significantly ($P < 0.05$) compared with the cool condition for both African and Caucasian runners with a tendency for E_R to be greater than or equal to E_P for both groups. The E_R for Caucasian runners was significantly ($P < 0.01$) greater than the African runners.

Heart rate and RPE responses. The heart rate was significantly lower for African runners at each 5-min interval during the submaximal run in cool conditions from 10 to 30 min (Fig. 4). During the submaximal run in the cool condition, the average heart rate for the African runners was 149 ± 10 beats/min compared with 160 ± 7 beats/min ($P < 0.01$) for Caucasian runners. The heart rate was significantly higher during the submaximal run for Caucasian runners at each 5-min interval from 10 to 30 min in the warm condition. The mean heart rate for the Caucasian runners was 179 ± 5 beats/min compared with 160 ± 8 beats/min ($P < 0.01$) for Africans during the submaximal run in warm conditions (Fig. 4).

During the performance run in cool conditions, the mean heart rate was 171 ± 4 beats/min for the African runners compared with 176 ± 6 beats/min for Caucasians, which was not significantly different. The African runners commenced the

Table 2. *Heat exchange values for African and Caucasian runners in each submaximal and 8-km performance runs in cool (15 °C) and warm (35 °C) humid conditions*

	H, W	S, W/m²	$C + R$, W/m²	E_P, W	E_R, W
African 15 °C					
Submax	967 ± 67	21 ± 1	−755 ± 93	−538 ± 113	−232 ± 40*†
8-km PR	1,126 ± 97	29 ± 1	−620 ± 159	−475 ± 92	−535 ± 135
Caucasian 15 °C					
Submax	1,271 ± 170‡	71 ± 4‡	−759 ± 184	−769 ± 93‡	−583 ± 157
8-km PR	1,458 ± 178‡	81 ± 4‡	−742 ± 180	−777 ± 94‡	−797 ± 103
African 35 °C					
Submax	967 ± 67	123 ± 4*†‡	26 ± 12*	−765 ± 143†	−1,116 ± 63*
8-km PR	1,062 ± 143	73 ± 2*	45 ± 19*	−1,014 ± 92*	−1,180 ± 149*
Caucasian 35 °C					
Submax	1,271 ± 170‡	106 ± 5*†	19 ± 12*†	−1,012 ± 133*†‡	−1,397 ± 175*‡
8-km PR	1,244 ± 169*‡	44 ± 2*	78 ± 33*	−1,435 ± 182*	−1,367 ± 106*‡

Values are means ± SD. H, heat production; S, rate of heat storage; $C + R$, heat loss via convection (C) and radiation (R); E_P, potential evaporation; E_R, required evaporation. Submax, 30-min submaximal treadmill run; 8-km PR, 8-km performance run. *Different between ambient conditions ($P < 0.05$); †different between submaximal and performance runs ($P < 0.05$); ‡different between groups ($P < 0.05$).

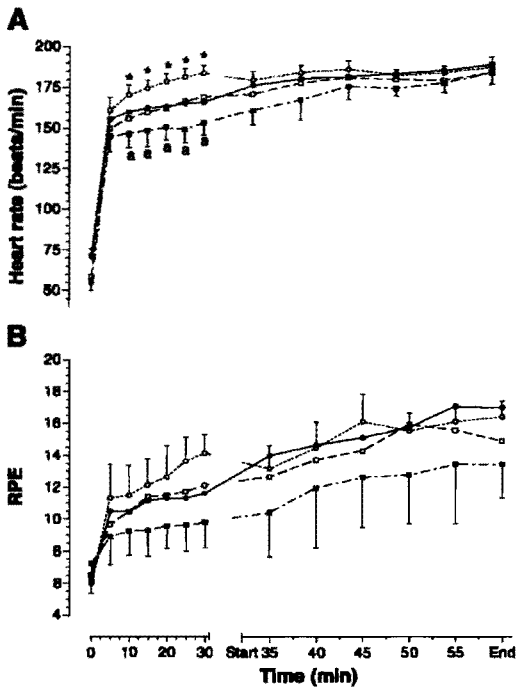

Fig. 4. Heart rate (*A*) and ratings of perceived exertion (RPE; *B*) during the submaximal run (0–30 min) at 70% peak treadmill velocity and during the 8-km performance run (35 min–End). Cool conditions: ■, Africans; ●, Caucasians. Warm conditions: □, Caucasians; ○, Africans. $^{*}P < 0.001$ compared with Africans and Caucasians in cool conditions; $^{a}P < 0.05$ compared with Caucasians in cool conditions.

performance run in cool conditions with a lower heart rate (35–40 min) than Caucasians, but this difference was not evident for the remainder of the run (Fig. 4). The mean heart rate during the performance run in warm conditions was 185 ± 7 beats/min for Caucasians and 182 ± 6 beats/min for Africans. However, there were no differences in heart rates at any time between Africans and Caucasians during the performance run in warm conditions (Fig. 4). Heart rates at the end of the performance run in the cool condition were 191 ± 6 and 186 ± 7 beats/min for Caucasians and Africans, respectively, and in warm conditions terminal heart rates were 189 ± 6 and 186 ± 9 beats/min for Caucasians and Africans, respectively.

RPE during the submaximal run in the cool condition tended to be lower for African (9 ± 1 units) compared with Caucasian runners (11 ± 1 units), but this difference was not significant (Fig. 4). In warm conditions during the submaximal run, Caucasian runners also tended to report higher RPE responses (12 ± 2 units), but again these were not significant. There were no discernable differences in RPE during the performance runs in any condition other than the generally lower RPE of the African runners (12 ± 3 units) in the cool condition (Fig. 4). RPE during the performance runs in warm conditions were ~15 units for both groups.

DISCUSSION

Previous studies have shown that anthropometric characteristics such as mass, surface area-to-mass ratio, adiposity, and muscularity are key factors in determining individual heat strain levels during exercise (1, 13). In particular, runners with a low body mass have a distinct thermal advantage when running in conditions in which heat-dissipation mechanisms are at their limit (8, 19, 34). Specifically, as the ambient temperature rises from 25 to 35°C with a relative humidity >60%, larger heavier runners are unable to maintain a similar running pace compared with their smaller counterparts because this entails faster rates of heat accumulation and hence the more rapid onset of a limiting hyperthermia (8, 19). Although the difference in size between the African and Caucasian runners in the present study was significant, the physical characteristics of the African runners are not dissimilar to those reported in previous studies comparing physiological responses and performances of elite African and Caucasian athletes (2, 4, 7, 17, 18, 33). The present findings in addition to the observation that African athletes are generally smaller than their Caucasian counterparts suggest that the body size of the Africans provides an advantage during distance running, particularly in the heat. Conversely, for the Caucasian runners, their larger size presents a disadvantage during distance running in the heat, whereby it seems that these athletes adopt an anticipatory reduction in running speed and hence the rate of heat production, such that a limiting hyperthermia is not reached before the successful completion of the exercise bout.

In the present study, African and Caucasian subjects had similar percent body fat, but Caucasian runners were ~17 kg heavier than the African runners. Thus, when running at the same pace, African runners produced less heat than did the Caucasian runners and had lower rates of heat storage and lower potential evaporation in cool conditions, in which the environment does not limit rates of heat loss (8). The rate of increase in rectal temperature during the submaximal run was similar for Caucasians and Africans, with the end submaximal rectal temperature reaching identical levels for each group for almost identical running speeds (14.8 vs. 14.6 km/h). This confirms that under cool conditions the larger Caucasians are able to thermoregulate as effectively as smaller African runners and can finish the submaximal run with identical rectal temperatures as these smaller African runners. However, this was not achieved without some cost, because Caucasian runners had higher, but not significant, sweat rates (Fig. 3) and significantly higher heart rates (Fig. 4) even under these cool conditions in which their pacing strategy was imposed and not self-selected.

Similarly, during the performance run in the cool conditions, African and Caucasian runners self-selected the same pacing strategy so that their overall performance was similar (Fig. 1). However, there was a trend for African runners to progressively increase their speeds throughout the performance trial with some evidence for an "end-spurt" from 45 min to the end of the trial (Fig. 1). In contrast, in the heat, the Caucasian runners ran significantly slower from the initiation of the trial, compared with their performance in the cool condition. Furthermore, in both African and Caucasian runners, running speeds fell progressively after 40 min and were significantly

lower in Caucasian than in African runners in the final two time points in the trial (Fig. 1).

Presently it is thought that exercise in the heat is limited by an elevated and limiting critical body temperature such that subjects will continue to exercise until a limiting core body temperature is reached at which point exercise terminates (21, 24). It is also thought that a critical limiting temperature acts directly on the central nervous system by reducing the drive or motivation for further exercise (5, 21, 23). However, this interpretation comes from studies in which the work rate is fixed and externally imposed so that the athlete is unable to alter their rate of heat production in response to the prevailing environmental conditions. In contrast, the findings of the present study indicate that performance in the heat is not limited solely by the attainment of a critical terminal rectal temperature per se but rather is regulated by the rate of increase in rectal temperature and hence the rate of heat storage based on the anticipated duration of the exercise bout. This ensures that the critical (limiting) core body temperature is not reached before the anticipated completion of the specific exercise bout. Interestingly, the rate of increase in rectal temperature during the performance trial was similar between African and Caucasian runners, with identical terminal rectal temperatures for both groups in cool (38.7 vs. 38.6°C) and warm (39.2 vs. 39.5°C) conditions even though the Caucasian runners took ~3.22 min longer to complete the performance run.

It has been previously suggested that athletes must arrange the energy consumption per unit time with respect to the finishing point (31). In the present example, both groups of athletes would need to draw on previous experience and arrange the required energy consumption relative to the anticipated rate of heat production and storage. The evidence for this anticipatory regulation of exercise performance in the present study is the following: First, the rate of increase in core temperature was similar for African and Caucasian runners in both warm and cool conditions. Second, running speed was significantly slower in Caucasian runners when they ran in the heat than in the cool, suggesting that they ran slower specifically to ensure that their rate of heat accumulation was similar to that in cool conditions, thereby ensuring that a limiting hyperpyrexia did not occur before the anticipated termination of the exercise bout. Third, Caucasian runners ran slower immediately from the onset of the performance trial in the heat (Fig. 1) when their rectal temperatures were 38.2°C (Fig. 2) and identical to values measured in African runners who were running substantially faster at that time. This indicates the action of an anticipatory process that reduced the running speed of Caucasian runners in the heat long before they developed a significant hyperpyrexia. Hence, the slower running speed of the Caucasian runners in the heat could not be explained by the attainment and maintenance of higher rectal temperatures for the duration of the performance trial. Fourth, both groups progressively reduced their running speeds during the latter half of the time trial in the heat but maintained (Caucasian) or increased (African) their speed when running in cool conditions. Despite, or more likely because of, these changes in running speed and hence in metabolic rate, the rate of heating was similar in all conditions.

Indeed, we are not the first to suggest that humans pace themselves during exercise in the heat specifically to prevent an excessive rate of heat production for the anticipated duration of the exercise bout (15). Tatterson et al. (30) found that the core temperature response of elite cyclists performing a 30-min time trial in moderate and warm humid conditions was similar, with terminal core temperature values for each condition reaching 39.0 and 39.2°C, respectively. Despite the similar core temperature response, mean power output was 6.5% lower in the warm humid conditions, essentially similar to the present findings. These authors concluded that, during self-paced exercise, cyclists select a power output that allows them to maintain a body temperature below a critical limit during exercise.

Thus the fact that the African runners were able to run at ~1.5 km/h faster than the Caucasian runners during the performance run with identical terminal rectal temperatures and a lower rate of heat storage suggests that these African runners were much more efficient in either heat production or heat dissipation when forced to run in limiting environmental conditions. The possibility that heat dissipation might have been more efficient for Africans than Caucasians can be discounted on the basis of the high humidity in the present trial (20). However, heat production was higher for Caucasians in both cool and warm conditions even though African runners ran at higher speeds. This can be explained by the higher body mass of the Caucasians, although this was partly offset by their lower running speed. Another possibility is that African runners were more economical at higher gait speeds. Generally, efficiency of skeletal muscle is improved from 45% at 8 km/h to 80% at 32 km/h (6). However, Weston et al. (33) have shown that at 16 km/h African athletes were at least 5% more efficient than Caucasian runners, with this difference increasing to 8% when corrected for differences in body mass. It is noteworthy that in the present study the mean running speed in the heat for African runners was 16 km/h.

Another possibility explaining the different performances of African and Caucasian runners was the heart rate response. It was evident that Caucasian runners had a significantly higher cardiovascular strain during the submaximal run in the heat compared with the African runners (Fig. 4). This difference disappeared in both cool and warm conditions during the 8-km performance run. The fact that the Caucasians ran slower during the performance run in the heat but at similar heart rates as those measured in cool conditions and comparable to that measured in the African runners suggests that the cardiovascular strain was similar in all conditions. However, it has been shown that heat stress reduces $\dot{V}O_{2\,max}$ by 8% despite heart rate and core temperature reaching similar peak values as in the control condition (11). These authors also showed that, in trained humans, severe heat stress reduces $\dot{V}O_{2\,max}$ by accelerating the decline in cardiac output and mean arterial pressure, leading to decrements in exercising muscle blood flow, oxygen delivery, and uptake. If this is the case, then African runners must be able to maintain a higher cardiac output or alternatively a higher oxygen extraction from the working muscles for any given running speed because the $\dot{V}O_{2\,max}$ values for both groups were similar. This supports previous findings that suggest that African runners are able to maintain a higher $\%\dot{V}O_{2\,max}$ during a treadmill marathon (4) and at 10- and 21.1-km distances (7). It is also noteworthy that all runners finished the performance run with identical heart rates irrespective of ambient conditions. Although it remains unclear why these athletes would finish the self-paced run with identical heart rates,

it is possible that terminal heart rate is yet another means by which the body self-regulates pacing during prolonged exercise.

In summary, this study shows that African and Caucasian runners of equivalent running ability in cool conditions and with similar maximal physiological characteristics, but with marked differences in body size and mass but not in body fat content, perform quite differently during an 8-km time trial in the heat. In particular, African runners were able to run ~1.5 km/h faster than Caucasian runners. Because this difference in running speed was apparent from the onset of the time trial, when rectal temperatures were the same in African and Caucasian runners and were only modestly elevated (~38°C), the slower running speed of the Caucasian runners was not caused by their reaching a higher limiting core temperature earlier in exercise than did the African runners. Rather, these findings implicate an anticipatory exercise response, the goal of which is to ensure an increase in core body temperature that does not produce a critical limiting temperature before the anticipated termination of the exercise bout. This anticipatory response would control the exercise work rate by regulating the number of motor units that are recruited or derecruited during prolonged exercise in the heat (16, 28).

In conclusion, the superior running performance of African runners in the heat in this study would likely be explained by physiological adaptations, in particular their smaller body mass and perhaps a greater capacity for heat loss in hot environmental conditions, both of which allow African runners to self-regulate pacing during exercise and attenuate the physiological stress signals to the central nervous system so that physiological limits are not prematurely reached.

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EXERCISE, TEMPERATURE REGULATION

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Impaired exercise performance in the heat is associated with an anticipatory reduction in skeletal muscle recruitment

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Abstract Exercise in the heat causes "central fatigue", associated with reduced skeletal muscle recruitment during sustained isometric contractions. A similar mechanism may cause fatigue during prolonged dynamic exercise in the heat. The aim of this study was to determine whether centrally regulated skeletal muscle recruitment was altered during dynamic exercise in hot (35 °C) compared with cool (15 °C) environments. Ten male subjects performed two self-paced, 20-km cycling time-trials, one at 35 °C (HOT condition) and one at 15 °C (COOL condition). Rectal temperature rose significantly in both conditions, reaching maximum values at 20 km of 39.2±0.2 °C in HOT and 38.8±0.1 °C in COOL (P<0.005 HOT vs. COOL). Core temperatures at all other distances were not different between conditions. Power output and integrated electromyographic activity (iEMG) of the quadriceps muscle began to decrease early in the HOT trial, when core temperatures, heart rates and ratings of perceived exertion (RPE) were similar in both conditions. iEMG was significantly lower in HOT than in COOL at 10 and 20 km, while power output was significantly reduced in the period from 80% to 100% of the trial duration in the HOT compared with COOL condition. Thus, reduced power output and iEMG activity during self-paced exercise in the heat occurs before there is any abnormal increase in rectal temperature, heart rate or perception of effort. This adaptation appears to form part of an anticipatory response which adjusts muscle recruitment and power output to reduce heat production, thereby ensuring that thermal homeostasis is maintained during exercise in the heat.

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Introduction

Exercise performance is impaired during both self-paced [16, 35] and externally regulated [5, 7, 25, 26] exercise in the heat. The biological mechanisms explaining this impairment are, however, poorly understood. Originally it was believed that an increase in the oxygen-independent contribution to energy production [3], resulting from a reduction in skeletal muscle blood flow [6, 30] secondary to reduced stroke volume and cardiac output [30], explained this phenomenon.

It is now known, however, that fatigue during exercise in the heat is not caused by reductions in cardiac output or exercising muscle blood flow, or by impaired substrate availability or utilization, or by the accumulation of lactate or K^+ [8, 19, 20, 32]. Such fatigue has been observed to occur at a core temperature of approximately 40 °C [7, 24], irrespective of the rate of heat storage, the pre-exercise core temperature [8] or the extent of prior heat acclimatization [20, 21]. It has thus been proposed that fatigue during exercise in the heat is associated with a "critical core temperature limiting exercise performance" [8], in which a high body temperature directly affects central nervous functions [19, 24].

Recently, Nybo and Nielsen [24] have shown that force production and voluntary activation percentage in the exercised muscle groups (knee extensors) are lower during a sustained isometric maximal voluntary contraction (MVC) following cycle exercise in hot (40 °C, sufficient to raise body temperature to 40 °C) than in temperate (18 °C, final core temperature 38 °C) conditions. Significantly, the overall force produced when electrical stimulation is superimposed upon voluntary contraction is unchanged from values measured during the temperate trial. This indicates that the force-generating capacity of the exercised muscle is unaffected by the elevated core and

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muscle temperatures after exercise in the heat. It was concluded that exercised-induced hyperthermia causes a form of "central fatigue", in which elevated body temperature (>40 °C) causes reduced central activation in the exercised muscles leading to a lower force production. The authors speculated that a similar mechanism exists during dynamic exercise in the heat. To our knowledge, this possibility has yet to be tested.

Accordingly, the aim of this study was to investigate whether centrally-regulated recruitment of skeletal muscle motor units is altered during dynamic exercise in hot (35 °C, HOT) compared with cool (15 °C, COOL) environments. To evaluate this effect during, as opposed to after the completion of exercise, we studied cyclists during a self-paced, 20-km, laboratory cycling time-trial in which they received no verbal or visual feedback other than the distance covered (every kilometre). We have shown previously that this form of testing produces pacing strategies during exercise that are highly reproducible when the testing conditions are identical [33]. We hypothesized that to prevent core temperatures from reaching harmful levels during exercise, subjects would subconsciously select a lower power output soon after the start of the time-trial in the HOT compared with the COOL environment, when core temperatures were still significantly lower than levels shown previously to be associated with bodily harm or diminished central drive [8, 19]. Furthermore, it was hypothesized that integrated electromyographic (iEMG) activity in the exercising muscle would be lower in the HOT than in the COOL condition. It has been shown that within an individual, iEMG activity is roughly proportional to the number and diameter of active muscle fibres [1, 9], and iEMG measurements during exercise therefore allow insight into the degree of muscle recruitment and muscle recruitment patterns. A reduction in iEMG activity and power output early on in the HOT condition, before rectal temperatures increase to potentially harmful levels would indicate that skeletal muscle recruitment and power output are down-regulated in advance of thermoregulatory failure. This contrasts with the prevailing hypothesis of fatigue in the heat, which predicts that "central fatigue" develops only after the homeostatic regulation of body temperature has failed and a critical level of hyperthermia is reached.

Materials and methods

Subjects

Ten male cyclists were recruited for the study from local cycling clubs and gymnasia. All subjects were physically active and were fully informed of the risks associated with the study. Subjects signed an informed consent before commencing the study, and upon completion of the trials, were remunerated for their participation. The study was approved by the Research and Ethics Committee of the Faculty of Health Sciences of the University of Cape Town. The mean (±SD) age, height, mass and peak power output (PPO) of the subjects were 24.7±4.6 years, 176.2±6.5 cm, 72.4±8.6 kg and 376 ±47 W respectively.

Preliminary testing

Subjects reported to the laboratory for preliminary testing consisting of anthropometric measurements and to perform a PPO trial. Stature and body mass were recorded using a precision stadiometer and balance (Model 770, Seca, Bonn, Germany). Percentage body fat was calculated according to [4] from skinfold measurements taken at seven sites [29]. Lean thigh volume for each subject was calculated according to [13], based on the assumption that the thigh is a truncated cone.

PPO was determined on a Kingcycle ergometer (described later) using a modified protocol [10]. Subjects performed a self-paced warm-up for 10 min before beginning the test at a starting power output of 3 W/kg body weight. The workload was increased by 20 W/min until exhaustion. Subjects were required to match a continuously increasing power output displayed in analogue form on the computer monitor. The test was terminated when the subject was unable to match the required power output. PPO was recorded as the highest mean power output achieved over a period of 1 min during the test. Subjects were requested to remain in a seated position throughout the test.

Kingcycle ergometry system

All trials were conducted on an ergometer (Kingcycle, High Wycombe, U.K.) that allows the subjects to ride their own bicycles in the laboratory. After removing the front wheel, the bicycle was firmly secured to the ergometry system by the front fork and supported by an adjustable pillar under the bottom bracket. The bottom bracket support was used to position the rolling resistance of the rear wheel correctly on an air-braked flywheel. A photo-optic sensor monitored the velocity of the flywheel in revolutions per second (RPS), from which an IBM-compatible computer calculated the power output (W) that would be generated by a cyclist riding at that speed on level terrain, using the equation: $W=0.000136(\mathrm{RPS})^3+1.09(\mathrm{RPS})$.

The Kingcycle was calibrated before both the peak power output test and the 20-km time-trials. For the calibration, subjects were required to accelerate to a power output of 115 W while seated in their normal cycling position. Once they reached this power output, subjects were instructed to stop pedalling immediately and remain in their riding position. The bottom bracket support was then adjusted until the computer display indicated that the slowing of the flywheel matched a pre-determined reference power decay curve.

Familiarization trial

Within 1 week of the PPO determination, subjects reported to the laboratory for a familiarization trial, during which they became accustomed to the equipment and laboratory conditions for the remaining two trials. Subjects completed a familiarization 20-km time-trial at an ambient temperature of 20 °C, relative humidity of 60% and wind velocity of 10 km/h. Subjects were able to drink water ad libitum during the trial. All conditions and procedures were identical to those used in subsequent experimental trials.

Experimental protocol

Within 1 week, subjects reported to the laboratory for the experimental trials, which were conducted in an environmental chamber (Scientific Technology Corporation, Cape Town, South Africa). Each subject performed two experimental 20-km time-trials, one at 35 °C (HOT) and one at 15 °C (COOL). Relative humidity was 60% and wind speed 10 km/h for both conditions. Five subjects performed the HOT trial first while five performed the COOL trial first. For each subject, trials were conducted at the same time of day so that the effect of circadian variation could be minimized. Trials

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were separated by between 4–7 days in all subjects to allow sufficient recovery. It was also assumed that subjects were not naturally heat acclimatized as the experiments were conducted between July and October, at which time the outside air temperature was 12–25 °C. Subjects were requested not to modify their training for the duration of their involvement in the trial, and to refrain from heavy physical exercise the day before the trial. During trials, subjects were allowed to drink water ad libitum. The only feedback given to subjects during the trials was the elapsed distance at the completion of each kilometre.

Maximal voluntary contraction testing

Prior to each 20-km time-trial, subjects performed a maximal voluntary contraction (MVC) for normalization of the EMG signal obtained during the subsequent trial. The subject's right knee extensor strength was measured on an isokinetic dynamometer (Kin-Com, Chattanooga Group, USA), while the electromyographic (EMG) activity of the vastus lateralis muscle was recorded. Subjects sat on the dynamometer with their arms folded across their chest and their hips, thighs and upper bodies strapped firmly to the seat. In this position, the hip angle was 100° flexion. The right leg was then attached to the arm of the dynamometer at a level slightly above the lateral malleolus and the axis of rotation of the arm was aligned with the lateral femoral condyle. The arm was then set so that the knee was at a 60° angle from full leg extension. Each subject then performed four sub-maximal familiarization contractions prior to performing four 5-s maximal contractions, separated by 5-s recovery periods. Subjects were encouraged verbally to exert the maximal possible force during each contraction. The contraction producing the highest force was recorded and used for subsequent normalization of the EMG signal obtained during the 20-km time-trial.

EMG testing

During each MVC and subsequent 20-km time-trial, the EMG activity of the vastus lateralis muscle was recorded. Before placement of the electrode, the skin was shaved and cleaned with 95% ethanol, according to methods previously described [14, 34]. A triode electrode (Thought Technology, West Chazy, N.Y., USA) was placed over the muscle belly of the vastus lateralis and connected to a pre-amplifier. The electrode was firmly taped to the skin using micropore tape, and a bandage (Flexwrap) wrapped around the electrode to minimize sweat interference. Outputs from the pre-amplifier were relayed to a Flexcomp/DSP EMG apparatus (Thought Technology, USA) via a fibre-optic cable and stored by an online computer. EMG signals were captured at 1984 Hz during the MVC and the time-trials. EMG activity was captured for 5-s periods during the MVC. During the 20-km time-trials, EMG activity was measured at 1, 5, 10, 15 and 20 km. For analysis of the signal, 5 s of data were analysed because subjects selected their own cadence while cycling. The raw EMG signals were full-wave rectified, movement artefacts removed using a high-pass, second-order Butterworth filter with a cut-off frequency of 15 Hz, then smoothed with a low-pass, second-order Butterworth filter with a cut-off frequency of 5 Hz. This was performed using MATLAB gait analysis software. This iEMG was used for subsequent analysis. All EMG data were normalized by dividing the EMG value obtained at each measurement point during the time-trials by the EMG value obtained during the MVC performed before the start of each time-trial. iEMG data were therefore expressed as a percentage of this MVC data. We have previously shown that this method of EMG normalization is reliable and valid for use in cycling trials, [12] and that the neuromuscular responses (iEMG) during self-paced cycling in the heat are reproducible between trials using this methodology [14]. Because of technical problems with the EMG computer, a complete set of EMG measurements could not be obtained during two of the time-trials and so EMG data from two subjects were rejected and the EMG data reported here represents the results from eight subjects.

Following MVC testing, subjects reported to the environmental chamber and inserted a rectal thermometer (YSI409AC, Yellow Springs Instruments, Yellow Springs, Ohio, USA) 10 cm beyond their anal sphincter. The measurement of rectal temperature is as good an index of core temperature during cycling at high work rates as oesophageal temperature [31]. Four surface thermocouples (model 427, YSI) were taped securely to the sternum region, left mid-thigh, left calf and forehead for measurement of skin temperature. Three of these sites (sternum, mid-thigh and calf) are typically measured during temperature-related studies [27], as they measure skin temperature over the heart (sternum thermocouple) and the working skeletal muscle (thigh and calf thermocouples). The forehead site was selected since it was speculated that the temperature of the head may be important in monitoring temperature and regulating exercise intensity, according to the current hypothesis. Upon entering the chamber, the Kingcycle was calibrated as described, and subjects performed a self-paced, 2-min warm-up. The duration of the warm-up was restricted to 2 min to ensure that the initial values for heart rate, rating of perceived exertion (RPE) and core temperature were not different between HOT and COOL conditions. The initial values of skin temperature, rectal temperature and heart rate were obtained at the completion of the warm-up. Temperatures were recorded at 1, 5, 10, 15 and 20 km during the trial using a digital telethermometer, accurate to 0.1 °C (YSI 400 series).

Power output during the time-trials was recorded by the Kingcycle equipment. To allow comparisons to be made between power outputs during trials of different duration, the recorded power output was normalized by dividing the trial into intervals of 5% of the total trial duration. Power output is thus reported as the average power output over each of these intervals of 5% total trial duration.

Heart rate was recorded at the start of the trial, and at 1, 5, 10, 15 and 20 km using a Polar Accurex NV heart rate monitor (Polar Electro, Kempele, Finland).

RPE was recorded at the start of the trial and at 1, 5, 10, 15 and 20 km, using the Borg category ratio scale [2].

Subjects recorded their nude body mass before each trial, and again after completion of the trial after wiping off sweat with a towel. The volume of water ingested during each trial was also recorded. Rate of weight loss (in kilograms/hour) was estimated by the change in body mass adjusted for fluid consumption. This weight loss was considered a proxy for sweat rate, but was not corrected for other body weight losses caused by irreversible fuel oxidation, since it was assumed that such losses would be essentially similar in both trials.

Statistical analysis

Power outputs, EMG data, temperatures and heart rate data were analysed using a two-way ANOVA for repeated measures, to examine the interaction of temperature and time. Where a significant effect was detected, post-hoc comparisons were made using Tukey's "honestly significantly different" (HSD) test for pairwise comparisons. Performance times, average power output, pre and post body weights and fluid ingestion were analysed using a dependent t-test. For all analyses significance was accepted at $P<0.05$. Data are presented as means±SD.

Results

Time-trial performance and power outputs

The time taken to complete the 20-km trial was significantly greater in the HOT than in the COOL condition ($P<0.001$) (Table 1). The average power output

in HOT was correspondingly lower; 255±47 W compared with 272±45 W in COOL ($P<0.01$) (Table 1).

Figure 1 shows the normalized power output recorded during the time-trials, at intervals of 5% of the total duration of the time-trial. Power outputs were identical for the first 30% of the trial duration in both conditions. In HOT, power output declined progressively in the period from 30% to 80%, whereas in COOL, power output remained constant from 10% to 90% of the time-trial. The power output in HOT became significantly lower than in COOL at 80%, 90%, 95% and 100% of the total duration ($P<0.05$). In both HOT and COOL conditions, the power output in the final 5% interval was significantly greater than in the previous intervals ($P<0.05$). The highest power output over any 5% interval was recorded in the final 5% in both HOT and COOL conditions.

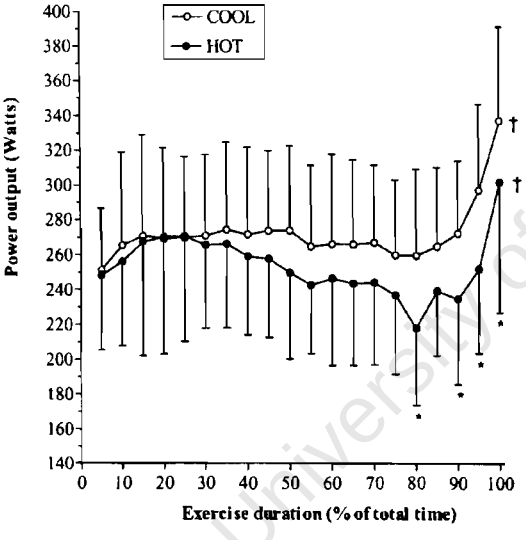

Fig. 1 Power output at intervals of 5% of the total duration of a self-paced, 20-km cycling time-trial at 35 °C (*HOT*) or 15 °C (*COOL*). Means±SD for ten subjects. *$P<0.05$ vs. COOL; †$P<0.05$ vs. preceding time intervals within the same environmental condition

Table 1 Time and average power output during self-paced, 20-km cycling time-trials in *HOT* (35 °C) and *COOL* (15 °C) conditions. Means±SD of ten subjects

	HOT	COOL
Time (min)	29.6±1.9	28.8±1.8*
Average power (W)	255±47	272±45†

*$P<0.001$, †$P<0.01$ vs. HOT

Thermoregulatory responses

Rectal temperature increased significantly over time ($P<0.001$) in both HOT and COOL conditions (Fig. 2). In HOT, the final rectal temperature was 39.2±0.6 °C, compared with 38.8±0.4 °C in COOL ($P<0.005$). At all other intervals, rectal temperatures were not significantly different between conditions.

Figure 3 shows the rate of increase in rectal temperature calculated at 2-km intervals. There were no significant differences in rate of increase in rectal temperature over any of the intervals. The average rate of rise in rectal temperature in HOT was 0.085±0.030 °C/km, compared with 0.070±0.017 °C/km in COOL. These were not significantly different.

All four skin temperatures (chest, thigh, calf, forehead) were significantly greater in HOT than in COOL conditions throughout the time-trials ($P<0.001$) (Fig. 4a–d).

iEMG amplitude

iEMG amplitude, expressed as a percentage of the iEMG amplitude during the MVC prior to each trial, is shown in Fig. 5. iEMG activity was lower in HOT than in COOL at 10 km and 20 km ($P<0.05$). At 15 km, there was a tendency for iEMG to be lower in HOT than in COOL, but this was not significant ($P=0.1$). iEMG did not change during the HOT trial, whereas iEMG in COOL at 20 km was significantly greater than at 1, 5, 10 or 15 km ($P<0.005$).

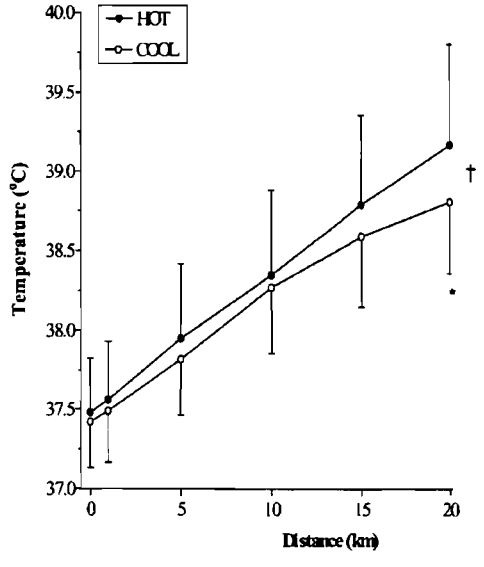

Fig. 2 Rectal temperatures at 0, 1, 5, 10, 15 and 20 km during trials in HOT (35 °C) and COOL (15 °C) conditions. Means±SD for ten subjects. †$P<0.001$ for time main effect; *$P<0.005$ vs. HOT

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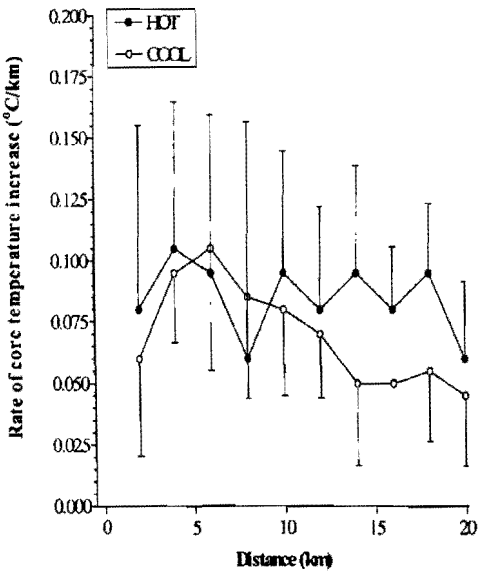


Fig. 3 Rate of increase in rectal temperature calculated at 2-km intervals during trials in HOT (35 °C) and COOL (15 °C) conditions. Means±SD for ten subjects

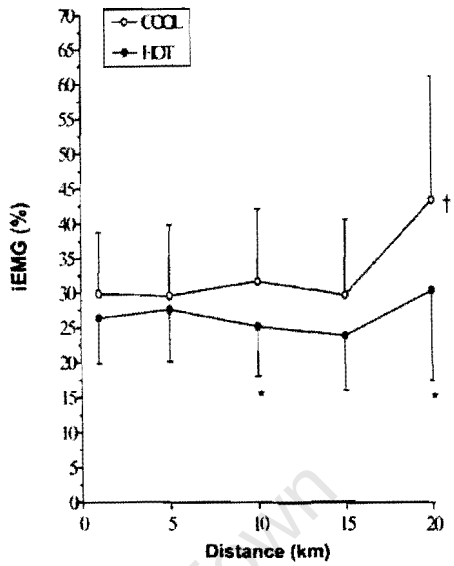
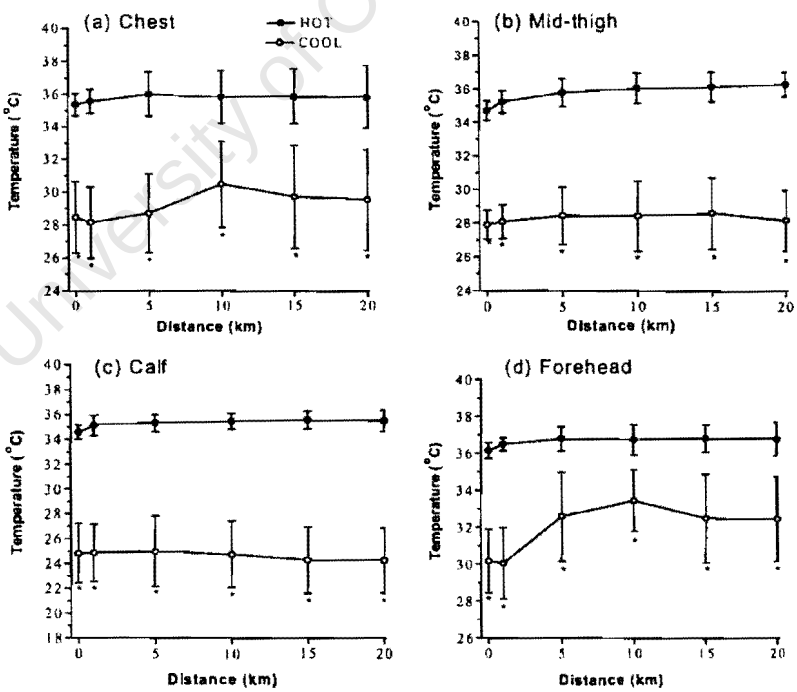


Fig. 5 Integrated electromyogram (*iEMG*) from the vastus lateralis muscle at 1, 5, 10, 15 and 20 km during trials in HOT (35 °C) and COOL (15 °C) conditions. Means±SD for eight subjects. **P*<0.05 vs. COOL; †*P*<0.05 vs. other points during COOL

Fig. 4 Skin temperatures over the (**a**) chest, (**b**) mid-thigh, (**c**) calf and (**d**) forehead at 0, 1, 5, 10, 15 and 20 km during trials in HOT (35 °C) and COOL (15 °C) conditions. Means±SD. **P*<0.001 vs. HOT



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Heart rates

Heart rate in both conditions increased similarly over time, and final heart rates were significantly greater than at rest ($P<0.0001$) (Fig. 6). Final heart rates in HOT and COOL were 184±8 and 181±10 bpm respectively. These were not significantly different.

Ratings of perceived exertion

RPE increased significantly over time in both trials (Fig. 7), but were not significantly different between HOT and COOL. The final RPE in HOT and COOL were 9.0±1.5 and 9.6±1.2 respectively.

Fluid intake and weight loss

Body weight changes during the trials, total fluid intakes and rates of weight loss are presented in Table 2. There were no significant differences in pre- and post-trial body weights between conditions, or in changes in body weight during the trials. Fluid intake in HOT was significantly greater than in COOL ($P<0.001$). Total weight losses and rates of weight loss were not significantly different between conditions.

Discussion

Current models of exercise-related fatigue attribute fatigue or exhaustion to homeostatic failure in one or more organ

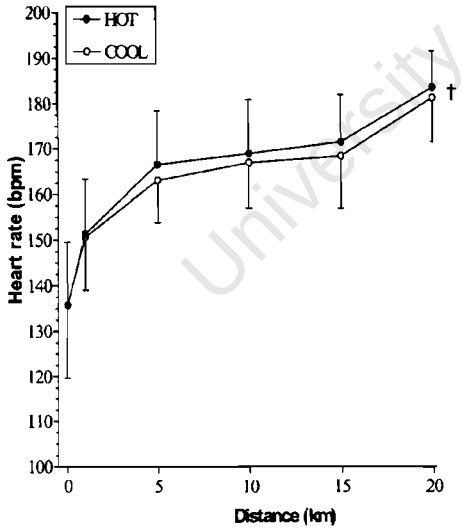

Fig. 6 Heart rate at 0, 1, 5, 10, 15 and 20 km during trials in HOT (35 °C) and COOL (15 °C) conditions. Means±SD for ten subjects. †$P<0.0001$ for time main effect

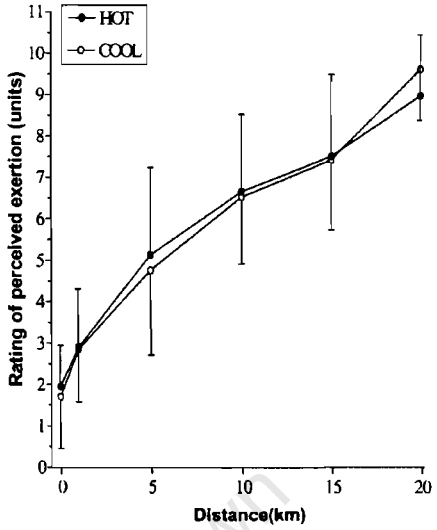

Fig. 7 Ratings of perceived exertion (*RPE*) at 0, 1, 5, 10, 15 and 20 km during trials in HOT (35 °C) and COOL (15 °C) conditions. Means±SD for ten subjects. †$P<0.0001$ for time main effect

Table 2 Body weight, fluid intakes and weight loss during trials in HOT (35 °C) and COOL (15 °C) conditions. Means±SD of ten subjects

	HOT	COOL
Pre-trial body mass (kg)	72.3±8.8	72.1±8.7
Post-trial body mass (kg)	71.8±8.8	71.5±8.7
Change in body mass (kg)	0.44±0.37	0.58±0.36
Fluid intake (ml)	581.1±171.2	243.6±177.0*
Rate of mass loss (kg/h)	2.06±0.58	1.73±0.77

*$P<0.001$ vs. HOT

systems that are crucial for sustained exercise performance [22]. Accordingly, it was originally proposed that fatigue during exercise in the heat developed after a limitation in blood supply, oxygen delivery or fuel utilization had developed. Recent, novel studies have shown, however, that such homeostatic failure does not occur, since skeletal muscle blood flow and metabolism do not reach limiting values in the heat [32]. It is now proposed that central [20] neural recruitment of skeletal muscle motor units is reduced when core body temperature rises to "critical" levels [19, 24]. Thus, according to this model, a failure of body temperature regulation causes critical brain and/or core temperatures to be reached. Central fatigue then occurs, as the "hot brain" is no longer able to recruit a sufficient number of motor units to sustain the previous or expected power output.

To our knowledge, we are the first to show that this general model does not explain accurately what actually happens during self-paced exercise in the heat. For we show that when self-paced exercise is performed in the

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heat, work output and skeletal muscle recruitment are down-regulated early during the trial, before body temperature is significantly elevated, with the result that thermal homeostasis is maintained similarly during exercise in both temperate and hot conditions. The critical findings that support this novel interpretation are the following.

First, despite marked differences in the environmental conditions in which the time-trials were performed, rectal temperatures were not different between HOT and COOL for the first 15 km of the 20 km time-trial (Fig. 2). Rectal temperatures were different at the end of the trials, but did not reach temperatures measured in heatstroke (>41 °C) in either condition. Hence, relative thermal homeostasis was maintained during exercise, and the exercise bout was completed without dangerous levels of hyperthermia being reached.

Second, power output began to decline in HOT after only 30% of the total trial duration, and was significantly less than in the cool condition from 80% of the trial duration until the finish (Fig. 1). However, rectal temperatures (Fig. 2) were not different until the final kilometre during the trials, suggesting that the observed reduction in power output in the heat could not have been caused by a higher core temperature acting directly on the active skeletal muscles or the brain to cause fatigue, as has been hypothesized [24]. Indeed, the highest power output in both conditions was achieved during the final 5% of the time-trial, when core temperatures were at their highest. The core temperature during the final kilometre of the trial in the cool condition was in fact significantly greater than the core temperatures in the hot condition at 5 and 10 km, when the power output had begun to decline in that trial. Yet, power output was maintained throughout the cool trial and increased by 20% during the final 10% of the trial (Fig. 1). Hence, an elevated core temperature cannot be the direct cause of the lower power outputs achieved in the hot than in the cool condition. Rather, it appears that power output is decreased in the heat in the absence of any thermal distress.

Third, iEMG activity was reduced significantly at 10 and 20 km in the hot condition. This indicates that the recruitment of motor units was decreased even when core temperatures were below 40 °C. In fact, at 10 km, the core temperatures were remarkably similar between conditions (38.4±0.5 °C vs. 38.3±0.4 °C in HOT and COOL respectively, Fig. 2). Therefore, the reduced skeletal muscle recruitment in the hot trial can also not be explained by the direct effects of a "critical" core temperature producing "central fatigue" in the motor regions of the brain, as has previously been hypothesized [19].

Rather, we propose that the early decline in power output in the absence of any thermoregulatory disturbance in the heat forms part of an anticipatory response in the brain, which mediates a reduction in skeletal muscle recruitment to ensure that the rate of heat production is reduced. This would allow relative thermal homeostasis to be maintained so that exercise can be completed safely without the development of premature fatigue or heat stroke, even in severe environmental conditions.

Indeed, the rate of increase in rectal temperature, a measure of the rate of heat storage, was not significantly different between the hot and cool conditions (Fig. 3). We interpret this finding speculatively to indicate that the reductions in skeletal muscle recruitment and power output in the hot condition may have been mediated to ensure that similar rates of heat accumulation occurred in hot and cool conditions. If this is indeed the case, then the rate of heat storage in the body may provide crucial afferent sensory inputs to a central controller, which adjusts work rate and skeletal muscle motor unit recruitment during exercise in both hot and cool conditions.

Others have reported similar findings to our own. Tatterson et al. have shown a reduction in power output after only 15 min of a 30-min, self-paced cycling time-trial in the heat, even though core temperatures rise at similar rates in a hot and temperate environment [35]. They postulated that the brain is sensitive to the rate of increase in arterial blood temperature, and selects a power output relative to the rate of rise in core temperature. However, they did not measure EMG activity to confirm this hypothesis.

Similarly, Marino et al. have shown that lighter runners outperform heavier runners during a self-paced, 8-km time-trial following 30 min running at 70% peak treadmill speed in hot (35 °C) conditions [16]. A significant correlation was also found between the rate of heat storage and body mass during the time-trial, suggesting that the lighter runners store less heat at the same running speed. It was concluded that this reduced rate of heat storage allows the lighter runners to run faster before reaching a limiting rectal temperature [16]. This suggests that the rate of heat storage may contribute to the afferent input responsible for a reduction in work rate in the heat.

Marino et al. [17] have also shown that African runners, who have a lower rate of heat storage at a given running speed than Caucasian runners, were able to outperform the Caucasian runners in hot (35 °C), but not in cool (15 °C) conditions during an 8-km time-trial. The difference in running speed between the groups in the heat was present from the onset of the time-trial, despite rectal temperatures which were only moderately elevated (~38 °C) and not different between groups. It was suggested that the early reduction in running speed in the heat occurs due to an anticipatory exercise response which would "control the exercise work rate by regulating the number of motor units that are recruited or derecruited during prolonged exercise in the heat" [17].

These findings are compatible with the existence of a centrally-regulated pacing strategy that reduces motor command and exercise intensity specifically to prevent excessive heat storage. Presumably, a central controller calculates the optimum rate of heat production and hence heat storage that will allow the self-paced exercise bout to be completed without the development of a harmful level of hyperthermia (Fig. 2) and then regulates skeletal muscle motor unit recruitment to adjust the metabolic rate

accordingly. Indeed, Kayser has proposed that the CNS integrates afferent signals from various sources including the heart, muscles, respiratory system and thermoreceptors, and adjusts motor command to protect the integrity of the organism during exercise [15]. This general model for the role of the CNS during exercise is applicable to exercise in the heat. If this theory is correct, it is not clear how the brain is able to detect the initial increased rate of heat storage in the hot condition. The skin temperatures at all four measured sites were significantly higher in the heat (Fig. 4). The afferent sensory input from the thermoreceptors in the skin must form part of the integrated response which mediates the decreased central recruitment and power output in the heat. That is, a high skin temperature may inform the brain that the capacity for heat dissipation is reduced [18], and so heat production is reduced to prevent body temperature from rising too rapidly to harmful levels.

The exercise-induced increase in muscle sympathetic nerve activity (MSNA) is augmented during muscle heating [28]. The increase in MSNA is attributed to the stimulation of mechanically sensitive muscle afferents that are sensitized by heating [28]. We did not measure muscle temperature directly in this study, though it can be expected that muscle temperature would be elevated to similar or greater levels than rectal temperature, based on previous studies of exercise in the heat [31]. Thus, the sensitization of skeletal muscle afferents may play a role in increased signalling to the CNS during exercise in the heat [28]. A "central programmer", proposed by Ulmer [36], would integrate this and other afferent signals arising from the muscle and peripheral organs and alter movement or force output to optimize performance [36]. This integral control, termed teleoanticipation, would regulate efferent commands based on the afferent feedback from the periphery and knowledge of the "finishing points". It must also be assumed that all the subjects had prior experience of exercise in the heat, so that any anticipatory reductions in power output may occur as part of a learned response.

The reductions in power output and iEMG activity were not associated with reductions in heart rate (Fig. 6) or RPE (Fig. 7), which were similar at all points during the two trials. The final RPE values were near maximum in both conditions, indicating that subjects performed to their own maximal volitional capacity. It is also significant that power output and iEMG activity were reduced in the heat despite RPE values which were similar and well below maximal in hot and cool conditions. Therefore, the rating of perceived exertion or, alternatively, the conscious sensation of fatigue does not merely track changes in power output, but is related to the central neural processes involved in the maintenance of, in this case, thermal homeostasis. It clearly makes no sense for the conscious perception of effort to be reduced at the same time that power output is decreasing (Fig. 1). The athlete's natural response to a falling RPE would be to override this effect consciously, thereby increasing the power output, the rate of heat production, and the probability that homeostatic failure would develop. Thus, for thermal homeostasis to be maintained, the central processes responsible for adjusting power output and muscle recruitment must simultaneously increase the conscious perception of exertion, in order to discourage any conscious overriding of this subconscious control.

We also showed that the power output in both the hot and cool conditions increased during the final 5% of the trial, as previously reported [14, 35]. In the present study, the increase in power output was associated with a significant increase in iEMG activity at the end of the cool, but not the hot trial. This difference was possibly due to methodological limitations. The iEMG activity was measured during the final 20 s of the time-trial, whereas power output was averaged over the final 5% of the trial, and thus reflects an average of the final few minutes of the trial. Another limitation of the present study is that the iEMG activity was measured in one muscle, and it is possible that altered skeletal muscle recruitment patterns in the heat, or the relatively small number of subjects may also explain the lack of a significant increase in iEMG activity in the heat.

Nevertheless, the increased iEMG activity in the cool condition indicates that the athletes were able to increase motor unit recruitment at the end of exercise, despite core temperatures, heart rates and RPE values which were significantly higher than at the start of the trial. This suggests that the afferent inputs that mediate the initial decreases in recruitment and power output can be overridden consciously in the maximal effort at the end of the trial, and supports the existence of a system which adjusts exercise performance by altering efferent motor command during exercise [36]. Such a system would ensure that under exercise conditions, a skeletal muscle reserve is maintained. Indeed, we found that approximately 30% of the available motor units were recruited during exercise (Fig. 5) with an increase of up to 45% in the final sprint, similar to our previous findings [11, 34]. Hence, a cardinal feature of prolonged exercise is the presence of motor unit recruitment reserve; a feature which is not always recognized [23].

In conclusion, power output began to fall within the first 30% of a maximal self-paced time-trial in the heat, reaching significance after 80% of the trial had been completed. Skeletal muscle iEMG activity was also reduced from 10 km during the trial in the hot condition. These decreases were not associated with altered rectal temperature, heart rate or perception of effort compared with exercise in the cool, and occurred well before rectal temperature reached 40 °C. It is proposed that this response occurs as part of a centrally controlled neural mechanism, which anticipates an abnormal elevation in body temperature, and alters skeletal muscle recruitment to allow completion of the exercise bout whilst thermal homeostasis is maintained. Impaired exercise performance in the heat is thus not the result of a limiting core temperature, but occurs as part of the central regulation of skeletal muscle recruitment, which controls the rate of heat storage, thereby preventing the development of thermo-

regulatory derangement during self-paced exercise in the heat.

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Anticipatory Pacing Strategies during Supramaximal Exercise Lasting Longer than 30 s

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ABSTRACT

ANSLEY, L., P. J. ROBSON, A. ST CLAIR GIBSON, and T. D. NOAKES. Anticipatory Pacing Strategies during Supramaximal Exercise Lasting Longer than 30 s. *Med. Sci. Sports Exerc.*, Vol. 36, No. 2, pp. 309–314, 2004. **Purpose:** This study assessed whether pacing strategies are adopted during supramaximal exercise bouts lasting longer than 30 s. **Methods:** Eight healthy males performed six Wingate anaerobic tests (WAnT). Subjects were informed that they were performing four 30-s WAnT, a 33-s, and a 36-s WAnT. However, they actually completed two trials of 30, 33, and 36 s each. Temporal feedback in the deception trials was manipulated so that subjects were unaware of the time discrepancy. Power output was determined from the angular displacement of the flywheel. The peak power (PPI), mean power (MPI), and fatigue (FI) indices were calculated for each trial. **Results:** Power output was similar for all trials up to 30 s. However, at 36 s, the power output was significantly lower in the 36-s deception trial compared with the 36-s informed trial (392 ± 32 W vs 470 ± 88 W) ($P < 0.001$). The MPI was significantly lower in the 36-s trials (714 ± 76 W and 713 ± 78 W) compared with the 30-s trials (745 ± 65 W and 764 ± 82 W) although they were not different at 30 s (764 ± 83 W and 755 ± 79 W). The significant reduction in FI was greatest in the 36-s deception trial. **Conclusions:** The significant reduction in power output in the last 6 s of the 36-s deception trial, but not in the 36-s informed trial, indicates the presence of a preprogrammed 30-s "end point" based on the anticipated exercise duration from previous experience. The similarity in pacing strategy suggests that the pacing strategy is centrally regulated. **Key Words:** WINGATE, POWER OUTPUT, FATIGUE, CENTRAL REGULATION, END POINT

For the last 30 yr, researchers have used the Wingate Anaerobic Test (WAnT), or a variant thereof, as a means of quantifying anaerobic performance in absolute terms of power output, which is then related to the maximum capacities of specific metabolic pathways. Traditionally the WAnT uses a 30-s cycle test protocol, performed against a constant force, in which subjects are instructed to cycle as hard as they can for the duration of the test. The three indices commonly derived from the WAnT are: i) peak power index (PPI), the highest power output obtained during the trial; ii) mean power index (MPI), the average power sustained over the duration of the trial; and iii) fatigue index (FI), the drop-off in power between the PPI and the final power output reading.

It was thought that during the initial 5–10 s of exercise energy is derived solely from alactic, phosphagenic pathways after which the metabolic fuel for the rest of the exercise bout is obtained from anaerobic glycolysis. Subsequent research has shown that, contrary to this belief, lactate accumulation begins within the first 10 s of supramaximal exercise (6) and that mitochondrial oxidative ATP synthesis increases almost immediately at the onset of exercise (24).

Despite this aerobic component of undetermined magnitude, the WAnT is considered to be largely dependent on anaerobic metabolism (27), and the associated fatigue has been mainly attributed to the fall in pH (10) that changes potassium concentration (8) and/or interferes with calcium release (1), impeding the ability of the muscle to contract (2) and resulting in selective fatiguing of the fast twitch fibers (5,15).

The WAnT may not have been designed to study muscle contractility or fatigue (4) but it has been suggested (13) that observing the effects of such all out efforts could provide insight into physiological and neuromuscular capabilities. Although this peripherally mediated fatigue might account for some of the drop-off in power output observed during the WAnT, EMG signal recordings have revealed a decline in iEMG activity toward the end of the test, which suggests the occurrence of central fatigue (17,30). Indeed, the fact that the fall in power in the Wingate test is explained by the falling cadence (19) can really only be explained by central, neural regulation because it is not clear how peripheral fatigue alone can produce the necessary changes in motor recruitment necessary to cause the progressive and marked reduction in cadence. Although the 30-s duration of the WAnT is generally considered optimal (12), a number of

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authors have suggested that it may not be sufficiently long to measure the total anaerobic capacity (9). The difficulty in extending the protocol beyond 30 s is the adoption of pacing strategies by subjects to ensure that they are able to complete the test (3,4). To prevent the adoption of such a conscious pacing strategy, it has been suggested that subjects should not be made aware of the elapsed time (20). More recently, the concept that subjects subconsciously pace themselves during exercise on the basis of prior experience has been developed (28,29).

There are a number of investigations into the competitive pacing strategies adopted during events lasting 1–6 min (11,14) and the optimal pacing strategies over these periods (18). However, to the authors' knowledge, no study has yet evaluated the possible presence of pacing during bouts of supramaximal exercise. The existence of a pacing strategy would suggest that substrate depletion or metabolic accumulation might not be the immediate cause of the power output profile during a WAnT.

Accordingly, the aim of this study was to determine whether deception and temporal manipulation could identify whether a subconscious pacing strategy exists during a standard and modified WAnT lasting between about 30 and 36 s.

METHODS

Eight healthy males volunteered for this study. The age and body mass (mean ± SD) were 22 ± 2.5 yr and 76.5 ± 6.9 kg, respectively. All subjects were physically active and each signed an informed consent before the study. The study was approved by the Research and Ethics Committee of the University of Cape Town Faculty of Health Sciences.

Subjects performed six WAnT on a Monark friction-braked cycle ergometer (814E). Trials were held 1 wk apart at the same time of day (16,25), and the order of the trials was randomized. One week before the start of the trial, subjects performed a habituation Wingate test.

Standardization procedure. A load of 0.09 $kg \cdot kg^{-1}$ body mass was administered by placing calibrated weights on a weight pan, which exerted a resistive force against the flywheel, at the onset of exercise. Workloads were set to the nearest 0.1 kg. Saddle height was recorded on the first visit to the laboratory, and the same height was used in all subsequent trials. Subjects were strapped to the saddle to avoid standing on the pedals. Pedal crank length was constant, and all subjects used cleated cycling shoes. The warm-up was standardized to 2-min unloaded pedaling. Before the start of each trial, subjects were instructed to pedal as fast as possible and to attempt to maintain that cadence velocity for the duration of the test. All tests were conducted from a standing start. The same investigators offered encouragement throughout the trial to minimize motivational differences. Time feedback during the trial was provided on an LCD screen that displayed elapsed time.

Subjects were informed that they were completing four 30-s, one 33-s, and one 36-s trial. However, they actually completed two trials of 30 (30-1 and 30-2), 33 (33-D and 33-I), and 36 (36-D and 36-I) s each. The suffixes D and I denote the deception trial and informed trial, respectively. A computer application altered the rate at which the LCD counter displayed second intervals. Therefore, during the two deception trials, the display time showed a 30-s count for the 33- and 36-s duration of the respective tests.

Data capture. The formula for power (P) generated on the Monark bicycle was derived from the angular velocity of the flywheel (ω), which was calculated every 36° from sensors attached to the flywheel, and the torque (τ) applied to the flywheel:

$$\omega = \frac{\text{rad}}{\text{t}} \quad [1]$$

$$\tau = I \cdot \alpha \quad [2]$$

$$P = \tau \cdot \omega \quad [3]$$

where t is time, I is the moment of inertia, and α is acceleration. Data logging occurred every 0.5 s.

Indices. The PPI was calculated as the highest average power over any 3-s period (4), MPI as the average power over the entire trial, and FI as the fractional decrease in power during the test (23):

$$FI = \frac{PPI - FP}{PPI} \quad [4]$$

where FP is the power averaged over the final 3 s of the test.

Statistical analysis. Power output data for all calculations were averaged over 3 s. Calculations for MPI and FI during the modified trials were determined over the entire duration and over the first 30 s. An analysis of variance was used to assess differences between and within the trials. Once main effects were identified individual differences between the means were located using Tukey's HSD *post hoc* procedure. Significance was accepted at $P < 0.05$. All data were expressed as mean ± SD.

RESULTS

On completion of the study, the subjects were unable to identify on which occasions they performed the deception trials.

Power output. Power output was uncorrected for inertia. There were no differences in power output up to 30 s between any of the trials (Fig. 1). However, in the 36-s trials, the power output was significantly lower at 36 s in the deception trial compared with the informed trial (392 ± 32 W vs 470 ± 88 W; $P < 0.001$).

Peak power index. There were no significant differences in the magnitude of PPI between any of the trials (30-1: 1055 ± 84 W; 30-2: 1076 ± 97 W; 33-D: 1061 ± 98 W; 33-I: 1047 ± 107 W; 36-D: 1056 ± 83 W; 36-I: 1055 ± 74 W) (Fig. 2a), nor did the time at which peak power occurred differ (30-1: 5.8 ± 1.0 s; 30-2: 5.3 ± 1.5 s; 33-D: 5.4 ± 1.1 s; 33-I: 4.9 ± 2.6 s; 36-D: 4.6 ± 1.0 s; 36-I: 4.7 ± 1.0 s) (Fig. 1).

Mean power index. The MPI for the 36-s trials (36-D: 714 ± 76 W; 36-I: 713 ± 78 W) were significantly lower than for either of the control 30-s trials (30-1: 745 ± 65 W; 30-2: 764 ± 82 W)($P < 0.05$) but not different from the 33-s

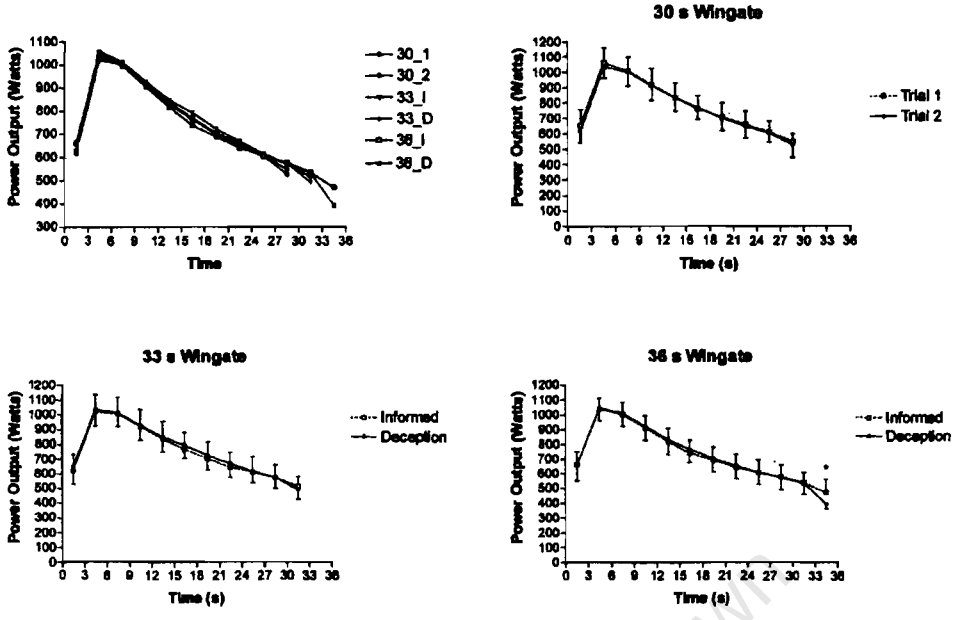

FIGURE 1—Comparison of power output profile for the two 30-, 33-, and 36-s Wingate anaerobic tests.

trials (33-D: 748 ± 87 W; 33-I: 734 ± 100 W) (Fig. 2b). The MPI for the 36-s trials also decline significantly from their value at 30 s (36-D: 764 ± 83 W; 36-I: 755 ± 79 W) where after there were no differences between any trials.

Fatigue index

The FI for the 36-s deception trial (63 ± 4.2%) was significantly greater than all other trials (30-I: 50 ± 7%; 30-2: 49 ± 3%; 33-I: 51 ± 3%)($P < 0.05$) except the 36-s informed trial (56 ± 7%) and the 33-s deception trial (54 ± 3%) (Fig. 1c). There was no difference in the FI at 30 s between any of the trials. The FI in the 36-s deception trial declined significantly from 30 to 36 s (50 ± 10% vs 63 ± 4%)($P < 0.001$).

DISCUSSION

The first important finding of the study was that the power output during the first 30 s of all trials was similar, regardless of the final duration of the trial. This finding is surprising, if it is believed that muscle energy depletion alone acting peripherally, limits such exercise. Rather, it would be predicted that the same amount of chemical energy would allow a faster rate of energy expenditure during the shorter exercise durations. Instead, this finding suggests that power output during the Wingate test is controlled by factors other than purely the magnitude of the skeletal muscle energy reserves and the maximum rate at which such reserves can be depleted.

Indeed, the second novel finding of this study was that power output dropped significantly more over the last 3 s of the 36-s deception trial compared with the informed trial. The occurred even though subjects were not able to consciously differentiate between the duration of the longer deception trials and the standard 30-s Wingate trial.

The finding that subjects were able to perform more work when performing exercise, the duration of which they had been reliable informed about than when misinformed, indicates that central neural factors other than peripheral metabolite accumulation determines the power output profile of the Wingate test.

Indeed, the fall-off in power during the Wingate test has been attributed to the early selective fatiguing of fast twitch skeletal muscle fibers (5) once the optimum velocity for maximal contractions of slower muscle fibers has been exceeded. But it has also been shown that the decline in iEMG activity accounts for nearly 30% of the drop-off in power at the end of supramaximal exercise (17,30). Furthermore, the power output profile of the Wingate test reflects solely the change in the cadence (19), which must be centrally regulated in the brain. Changes in power output generated by the brain could, however, be in response to peripheral metabolic changes in the active muscles.

Indeed, the presence of a central neural component to pacing and fatigue has long been recognized as a factor influencing power output during supramaximal exercise. Pilot studies at the Wingate Institute during the development of the WAnT showed a propensity for subjects to start at

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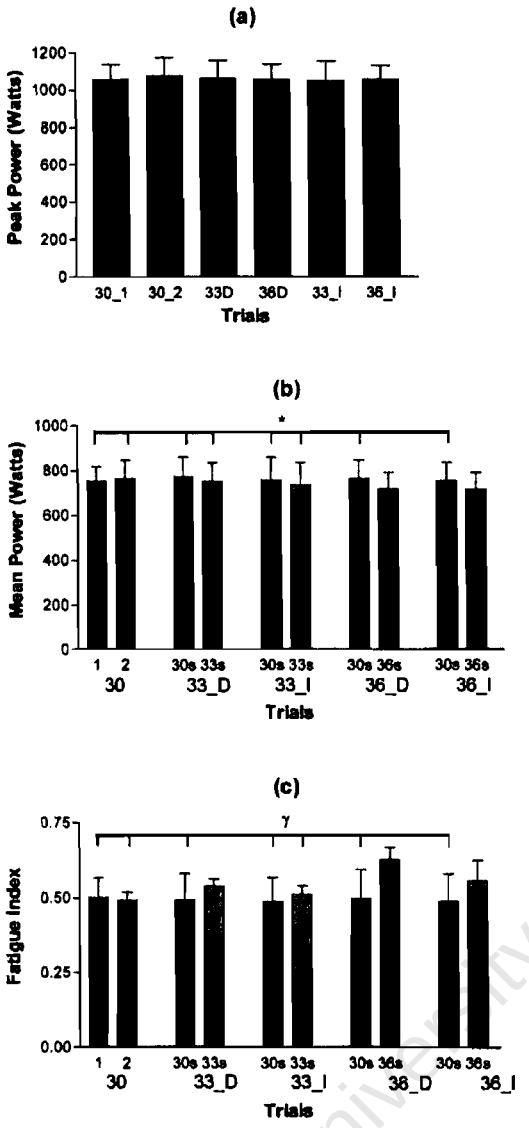

FIGURE 2—Peak power, mean power, and fatigue indices at 30 s and at the completion of the Wingate anaerobic tests; *significantly different from the 36-s deception and 36-s informed trial ($P < 0.05$); ᵞsignificantly different from the 36-s deception ($P < 0.05$).

slower cadences in trials that lasted longer than 30 s (4). This tendency was also observed by Katch and Weltman (20), who remarked that the duration of the trial should not be revealed to the subjects lest they "pace themselves and not produce an initial all-out effort." In a study on elite Alpine skiers (3), trial subjects were instructed to ease up after they had achieved peak power so that they would be able to maintain more constant effort for the remainder of the 90-s trial, implying that some form of pacing is necessary to complete extended supramaximal tests.

An even pace has long been regarded as the most efficient strategy to employ during any exercise, and this belief appears to be supported by evidence that during an even-paced Wingate trial, blood lactate concentrations are lower, blood pH is higher, and recovery is faster, compared with an all-out trial in which the same total amount of work is performed (10). In contrast, Ingen-Schenau et al. (18) argue that in events lasting less than 80 s, the optimal pacing strategy is all out effort, even if this strategy produces a rapid drop-off in power at the end of the race. They suggested that an even-paced strategy should only be used in exercise of a longer duration. Our data do not address this question.

It has been speculated that muscle pH provides the sensory feedback linking central command of motor unit recruitment and intramuscular metabolism (22) so that athletes adjust their pace in order to ensure that a critically low pH is not reached even at the end of a maximum effort (11). This is supported by evidence of a continuous fall in intramuscular pH from 6.94 to 6.82 between 10 and 20 s in all-out exercise (7), mirroring the decline in power output. The fall in power output ensures that the extent of the fall in pH is regulated.

Ulmer (29) extended this concept by proposing the existence of a programmer during exercise that regulates work based upon the remaining duration of an activity. In other words, the effort required in performing an activity is anticipated before the commencement of the activity and the intensity of exertion is regulated according to calculations based on previous experience. This governor acts as a protective regulator of power output to prevent the development of a metabolic crisis that would damage the integrity of the muscle fibers (26).

Although there were significant differences in power output at 36 s when the subjects were deceived as compared with the informed trial, no differences were present at the end of the 33-s trials, indicating that the modification in afferent control, causing a reduction in power in the last 3 s, must occur after 33 s but before 36 s. This is in agreement with the speculation of Hunter et al. (17) that 30 s was too short a duration for a change in recruitment strategies based upon feedback from intramuscular metabolism but predicted that the influence of this feedback loop on central motor control would have to come into effect if the exercise was sufficiently prolonged.

Evidence that the extent of muscle recruitment is controlled centrally during prolonged exercise has been presented by St Clair Gibson et al. (28) in a study that revealed that the fall in power output was mirrored by a reduction in the neural drive despite less than 20% of the muscle mass being recruited. They concluded that the early decline in neuromuscular activity during prolonged exercise explained the reduced power output experienced by their subjects.

During the informed trial, the subjects prepared themselves for an effort that would last 36 s. During the 36-s deception trial, though, the subjects were only primed for a

30-s effort, and despite confirmatory but deceptive evidence in the form of a clock, which was 6 s slow, there was still a disparity between their actual and possible power outputs (Fig. 1). As the subjects were not consciously aware of the deception, this finding indicates that the deception was detected at a subconscious level but not a conscious level, as the reduction in power output over the extra time was not consciously perceived. If the duration of the 36-s trials had been extended beyond 40 s, the subjects may have employed a more obvious coping strategy. However, it is unlikely that subjects would have been deceived, that is they would not have realized that a deception was in place, by such a large (33%) discrepancy between the real and simulated time. Accordingly, this type of experiment may not be possible.

Rather, we conclude that the subjects did detect the time discrepancies but ignored or filtered the conscious knowledge as incorrect based upon what they had been told and the visual cues from the slow-running clock. However, the findings of the present study suggest that the "lag" phase between afferent input and subconscious awareness of discrepancies between expected and actual time must be between 3 and 6 s during an exercise lasting up to 36 s, that is, approximately 12% of the total duration of the activity. More research is needed to determine the degree to which subjects can accurately assess temporal deceptions during exercise.

As peak power was similar and occurred at a similar time point, it seems that the subjects started out at a set work rate, although whether this is paced and submaximal itself cannot be determined from this study. The similar fatigue profiles over the initial 30 s for all the trials suggest that there was no difference in the pacing strategy employed for the different duration trials. However, the sudden decline in power output of the last 3 s of the 36-s deception trial may provide evidence for a preprogrammed "end point" that is different from the ultimate fatigue point. Once the anticipated end point is reached, the power output declines rapidly. It has been demonstrated that even in maximal sprint intervals, subjects maintain a reserve allowing an increase in power output over the last sprint consequent to an increased neural drive (21).

In summary, this study indicates the presence of a preprogrammed "end point" based on the anticipated exercise duration as a result of previous experience in a Wingate test. Furthermore the similarity in pacing strategy in all informed trials regardless of duration suggests that the pacing strategy is centrally regulated and is independent of the total work to be performed, at least for up to 36 s of supramaximal exercise.

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The Conscious Perception of the Sensation of Fatigue

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Abstract

In this review, fatigue is described as a conscious sensation rather than a physiological occurrence. We suggest that the sensation of fatigue is the conscious awareness of changes in subconscious homeostatic control systems, and is derived from a temporal difference between subconscious representations of these homeostatic control systems in neural networks that are induced by changes in the level of activity. These mismatches are perceived by consciousness-producing structures in the brain as the sensation of fatigue. In this model, fatigue is a complex emotion affected by factors such as motivation and drive, other emotions such as anger and fear, and memory of prior activity. It is not clear whether the origin of the conscious sensation of fatigue is associated with particular localised brain structures, or is the result of electrophysiological synchronisation of entire brain activity.

Fatigue is experienced by all individuals on a regular basis. There are many different definitions of fatigue. In medical practice, fatigue is described as a debilitating consequence of a number of different systemic diseases or nutritional deficits.[1] In exercise physiology, fatigue is described as an acute impairment of exercise performance, which leads to an eventual inability to produce maximal force output as a consequence of metabolite accumulation or substrate depletion.[2] In neurophysiology, fatigue is described as a reduction in efferent motor commands to the active muscles resulting in a decline in force or tension as part of a centrally controlled process.[3]

Fatigue is therefore a ubiquitous phenomenon with different meanings in different research fields. However, there is no knowledge at present of how the conscious 'feeling' of fatigue is created, or from where it originates. In this article, therefore, we examine fatigue as a sensation rather than a physical process. The aim of the article is to discuss the concept of fatigue from psychological, anatomical and physiological perspectives, and to describe possible mechanisms and brain regions responsible for the conscious perception of the sensation of fatigue.

1. Conscious Awareness of the Sensation of Fatigue

Before examining the mechanisms responsible for the conscious sensation of fatigue, it is necessary to discuss briefly the more general issue of consciousness itself. There are two basic theories of

consciousness, which have been debated for centuries. The first is the theory of dualism, which suggests that consciousness is a mental state which exists autonomously and is not dependent on brain structures for existence.[4] The second is the theory of monism, which suggests that consciousness is a direct product of activity in specific brain structures.[5,6] While this argument is complex and beyond the realm of this review, the theory of dualism is more difficult to support from a scientific perspective, and remains a philosophical concept (Hallett M, unpublished observation). In this review, we therefore discuss conscious perception of the sensation of fatigue from the monistic perspective.

Consciousness has two distinct components. The first is the 'awareness' of something, for example awareness of activity occurring around an individual. The second is the 'feeling of knowing' of that awareness. This 'feeling of knowing' allows us to have knowledge that the awareness is specific to our own life, and creates the special subjective 'feeling' each individual has which makes us aware that what is going on around us is unique to our own individual participation in that experience. This second component makes consciousness in different individuals a subjective phenomenon, defined as 'qualia',[7] which makes the life of each different individual unique, but which makes consciousness so difficult to examine scientifically. An example of this would be that the sensation of fatigue at any time point is completely unique to the individual perceiving it. While the level of sensation of fatigue associated with different levels of activity can be fairly well quantified in different individuals, at present observers cannot 'feel' the 'exact' feeling of the person being studied when they describe that individual's sensation of fatigue. However, recent work, which will be discussed later in this article, has begun to shed light on the subjective nature of conscious perception.

In relation to fatigue, the first component of conscious perception is easier to define. The conscious sensation of fatigue would occur when alteration to a physical state induced by physical activity leads to changes in activity in brain neural networks, which in turn cause 'awareness' of those alterations. This origin of the conscious perception of fatigue may therefore be determined by examining changes in different brain structures associated with the development of awareness of the sensation of fatigue.

2. Brain Structures Involved in the Sensation of Fatigue

There have been several theories of how the sensation of fatigue is activated in neural networks in different brain structures. In the peripheral model of fatigue, changes in a certain factor in the peripheral organs during physical activity, such as muscle metabolite accumulation,[8-11] substrate depletion[12-16] or cardiac and respiratory limitations,[17-19] stimulate mechanoreceptors[20-22] or metaboreceptors[23-25] resulting in afferent feedback to the brain which induces the sensation of fatigue.[26-28] As there is no conclusive evidence to support any single factor as being directly responsible for the onset of the sensation of fatigue,[29] it is also suggested that a number of different afferent inputs, together with other non-sensory inputs such as psychological and motivational factors, are integrated in brain structures and the ensemble leads to the development of the sensation of fatigue which arises directly from these integrative brain structures.[20,29-32]

This latter hypothesis is supported by three different observations. Firstly, the sensation of fatigue can be altered by hypnosis while individuals maintain constant work output.[33-35] Secondly, the sensation of fatigue is affected by expectations of task demands, being greater at the same absolute timepoint in races of similar intensity but shorter duration compared with those of longer duration (Baden DA et al., unpublished data) and lower when actual exercise duration is shorter than expected.[36] Thirdly, in the clinical condition known as chronic fatigue syndrome, an excessive and debilitating sensation of fatigue is present at rest, and is not related to alteration in physical activity levels.[37-39] These observations suggest that the origin of the sensation of fatigue must be associated with anatomical brain structures responsible for conscious perception,

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rather than from any single peripheral physiological perturbation or altered metabolic state.

The sensation of fatigue is itself a complex phenomenon. It is associated with the conscious perception of changes in body functions, such as breathlessness from increased ventilation, pounding of the heart from cardiac output increase, the sensation of being hot and sticky from temperature increases and sweating, and the sensation of increased muscle activity associated with increased power generation caused by increased physical activity levels.[29] There are also mental cognitive functions associated with the sensation of fatigue. These include level of motivation at the time of the activity, memory of prior exercise sessions and an associated decision-making component based on the relationship between the current sensorimotor input and memory of previous events.[32]

Because of the complex nature of the sensation of fatigue, the regions of the brain from which the sensation of fatigue originates have been difficult to assess, even with the development of modern neuroscience techniques, such as functional magnetic resonance imaging, dynamic electroencephalography (EEG) and repetitive transcranial magnetic stimulation (figure 1). This may be because a number of different brain regions are involved, or because general processes involving energy changes throughout the brain are responsible for the generation of the sensation of fatigue.

The development of the sensation of fatigue is associated with changes in motor activity.[40] As motor function is controlled by the motor and premotor cortex, supplementary motor cortex, basal ganglia and cerebellum,[41-43] changes in neural network activity in any of these areas may be responsible for the generation of the sensation of fatigue. Indeed, it has been suggested that the 'effort of will'[44] or 'sense of effort'[45] is corollary discharge associated with motor activity.[40,46] However, more recent work has suggested that the sensation of effort and the sensation of fatigue may not be generated in the motor cortex and rather originates in motor command centres 'upstream' from the motor cortex.[40,47]

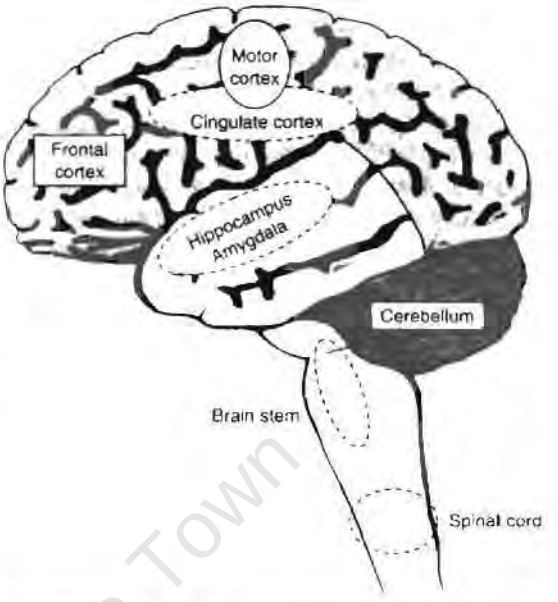

Fig. 1. Putative brain regions associated with the development of the sensation of fatigue.

Fatigue is also related to motivation and emotional state.[48,49] Indeed, it has previously been suggested that fatigue is an emotion itself.[50] Emotional states such as anger, fear and possibly also fatigue, are not free standing psychological concepts, but are distinct collections of chemical and neural responses to particular emotional stimuli that have related physical symptoms, which in some cases can be partially quantified.[50,51] Emotional responses are thought to be triggered by the amygdala and ventromedial prefrontal cortex, and are executed by the hypothalamus and brainstem nuclei.[50] The main targets of the emotional responses are the viscera and musculoskeletal system, but other targets in the brain are also affected including monoaminergic neurons in the brainstem that modulate behaviour and memory formation.[52] Emotional states such as anger and fatigue involve adjustments in homeostatic balance and peripheral physiological changes, such as heart and respiratory rate which can be scientifically measured.[50] Feelings of anger or fatigue may therefore be the mental representations of the physiological changes which characterise these emotions. Functional imaging studies have revealed

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increased or decreased activity in several brain areas including the orbitofrontal cortex, anterior cingulate cortex and insular cortex, when normal individuals experience emotions such as sadness, happiness, fear or anger.[52-57] Therefore, as motivation and drive are affected by all these different emotional states, fatigue may originate in any of these different brain areas associated with emotional responses.

Previous experience and planning of current activity are also important components of the sensation of fatigue. Previous memory of fatigue will allow one to estimate one's reserves and tolerance levels, and allow decision making to occur as to whether to continue, reduce activity or halt the physical activity. Memory formation and decision making involve representations of sequences of events (episodic, personal experiences) within a framework of general semantic knowledge (facts and places), linked by their common events and places.[58] The hippocampus, together with the parahippocampus and surrounding areas of temporal lobe neocortex, synthesise these episodic representations into unique single experiences, such as a specific exercise activity.[58] The transition from immediate to long-term memory is associated with activity in the prefrontal cortex.[59] In the prefrontal cortex, current activity is compared with previously stored memory of previous activity, and the current activity would be altered appropriately if differences between these events were unacceptable as part of decision-making processes in the prefrontal cortex. Working memory is active only for as long as cells in the prefrontal cortex are firing. Therefore, it would be in these prefrontal cortical systems, perhaps, that the origin of the conscious perception of the sensation of fatigue arises from.

Recently, Parvizi and Damasio[60] have suggested that the brainstem and spinal cord may be the area where consciousness is modulated. The reason they proposed that this area was responsible for the origin of consciousness was, firstly, because the reticular activating system, which sets the level of electrophysiological activity in the cortex and most other areas in the brain, arises from the reticular nuclei of the brainstem, and individuals with damage to the brainstem region have impaired consciousness. Secondly, the brainstem is the site of arrival of afferent input from nociceptors, the vestibular system, musculoskeletal system and integrative interneurons, and therefore could be an area where integration of these different signals occurred. Thirdly, there are a number of connections between the hypothalamus and brainstem nuclei, and through these connections knowledge of homeostatic perturbations could be integrated. Fourthly, brainstem nuclei are involved in the dopaminergic, cholinergic and other neurotransmitter systems which alter the mode of processing of other brain structures and areas responsible for mood, memory or perceptual changes. Therefore, these areas in the brainstem and spinal cord may also be associated with the sensation of fatigue.

It is therefore difficult to show that the sensation of fatigue is localised to a single area of the brain, as a number of different cognitive functions and integrative brain regions may be involved with processes that lead to the initiation of the sensation of fatigue. It has also been suggested that no regional classification of the brain is correct for any function, as all areas of the brain are involved during all activities, albeit to different degrees.[61] This concept is encapsulated by the 'binding problem', which describes the problem of binding together representations of different properties of an object or physical state such as it's colour, form or location,[62] and suggests that large areas of the brain must be involved in complex cognitive tasks or motor activities. It has been suggested that large scale synchronisation of oscillatory electrical activity in the neural circuitry of different brain areas or in local brain areas,[63,64] controls the temporal sequences of task activity. This phase synchrony, or coherence of activity in different brain regions is also found to occur in EEG and electromyogram activity during motor tasks, generally in the gamma rhythm range (25–70Hz),[62-64] indicating that central and peripheral neural systems may communicate using synchronisation processes or activity. It is not clear how fatigue influences this synchronisation of electrical activity, or whether alterations in synchronisation patterns induce the sensation of fatigue during func-

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tional activities, and further work is necessary in this field.

Alterations in neurotransmitter concentrations in various brain structures have been suggested to cause fatigue. It is not clear whether neurotransmitter concentration changes are caused by changes in neurotransmitter precursor concentrations in peripheral tissue which cross the blood-brain barrier,[65,66] or whether activation of brainstem structures which control release of neurotransmitters in the higher cortical structures are altered or initiated by fatiguing activity and lead to the release of excitatory or inhibitory neurotransmitters which may alter cognitive function or perception of the fatigue state. For example, monoaminergic nuclei of the reticular formation in the brainstem are responsible for serotonin, dopamine and noradrenaline changes in the cortical mantle, and these neurotransmitters are involved in the modulation of global activity in the cortex, and lead to changes in attentiveness and behavioural responses to external stimuli.[60] Neurotransmitters, such as acetylcholine, have also been found to modulate synchronisation and generation of cortical electrical activity in a concentration-dependent manner.[62] Therefore, neurotransmitter concentration changes may alter the cognitive response to or be involved in the subconscious fatigue generating mechanisms.

Alterations in substrate availability in brain tissue, associated with increased metabolic demands and caused by increased mental activity during exercise, have also been suggested to cause fatigue. For example, it has been postulated that during maximal activity, increased cognitive activity increases brain metabolism, leading to energy demands exceeding production of energy substrates such as brain glucose and lactate.[67,68] However, if brain substrate depletion is the cause of the sensation of fatigue, one would expect there to be a period of time after intense physical activity when all brain function is impaired. As this does not occur,[40] it is more likely that if substrate depletion occurs it would modulate rather than cause the perception of the sensation of fatigue.

In summary, if the sensation of fatigue is a component of cognitive decision making or active setting of exercise intensity as a part of the working memory system and based on prior experience, the most likely region involved would be the prefrontal cortex.[59] If fatigue is a specific type of emotional state, the amygdala or hippocampus or a combination of these areas may be involved.[50,58] If the sensation of fatigue is part of an integrative metabolic regulatory system balancing afferent input with efferent command, the hypothalamus or brainstem and spinal cord regions may be the site of origin.[43,60] Alternatively, fatigue as a sensation may occur as activity processes in the brain which are currently not determined and which involve many different areas of the brain at any one timepoint.

3. Conscious Perception from Subconscious Activities

While we have examined putative structures and processes that may be responsible for the origin of the sensation of fatigue, we have not yet discussed how the sensation of fatigue originates from the underlying neural networks which regulate most functional processes subconsciously. A number of theories have been proposed to explain how consciousness develops, such as the global workspace[69] and neural oscillation theories,[7] but no scientific evidence has been able to clearly substantiate any of these theories and a detailed discussion of each of these is beyond the realm of this review.

However, recently, Damasio[51] has suggested a model for how conscious perception develops from subconscious processes, which may be particularly relevant as a mechanism to describe how the sensation of fatigue originates. In an attempt to describe the association between consciousness and subconscious control processes, Damasio and Parvisi[51,60] suggested that consciousness is underpinned by a subconscious 'proto-self'. In this model, the 'proto-self' controls or maps the physiological changes associated with emotions, such as increased heart rate and sweating, and although this proto-self also operates at a subconscious level, these changes generate 'feelings' which are our conscious response or

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manifestation of these emotional changes. In this model of consciousness, the proto-self is a coherent collection of neural patterns which map the state of physical and physiological structures of the organism. This proto-self becomes the homeostatic set-point of the organism and is a permanent first-order map. When changes in the external environment or internal physiological milieu occur, these changes become a further first-order map. When this altered environment is compared with the proto-self, the differences between the two become second-order descriptive maps which describe the relationship between the proto-self and the altered environment. This second-order map becomes a 'mental' image, which resides at a subconscious level. For the mental image to become a conscious image, the mental image needs to induce a 'feeling' or emotion, which allows our conscious cognitive processes to be aware that a change has occurred which is relevant and requires avoidance behaviour if the emotion or feeling is negative, such as fear or fatigue.

The hypothesis of the proto-self thus centres on a relationship between the changing state of an organism and the sensorimotor first-order maps, or the proto-self, which describes an individual's internal physiological and physical set-point. As changes in the individual occur, another level of second-order mapping creates an account of the events taking place as a consequence of the proto-self/changed environment interaction. The essence of conscious knowledge of these changes occurs when a 'feeling' or emotion, such as fatigue, is induced by this second-order map, which allows responses to the changed state to be initiated. In this model, therefore, because conscious knowledge originates in neural structures associated with the proto-self representation of body states, consciousness therefore is in effect the 'feeling' itself, such as fatigue or other emotional states.

This model may be relevant for describing how the sensation of fatigue originates. For example, at the beginning of an exercise bout, the proto-self first-order map would describe the homeostatic set-points for all metabolic activity at rest in the body, and would serve as the reference point for the activity to follow. As exercise begins, the change in metabolic conditions causes a different first-order map to be created, and the difference between these two maps creates a second-order map which creates a conscious perception of change and thus 'awareness' of the activity. As exercise continues, further second-order maps are created of the ongoing change in metabolic profile, and these metabolic maps must create a cumulative perception of change that eventually is recognised as the conscious perception of the sensation of fatigue (figure 2).

This model is interesting also in that it explains both the 'awareness' of conscious sensations such as fatigue, and the 'feeling of knowing' of the awareness of theses conscious sensations, which as described previously, has traditionally been the more difficult concept to explain. In Damasio's[51] theory of emotion underlying consciousness, physiological changes result in the 'feeling' of emotions, and these feelings ultimately represent the 'feeling' which we attach to consciousness. Therefore, what gives qualia their particular identity are the specific physiological changes which occur at the exact timepoint when a second-order representation is perceived. Damasio's theory may therefore be relevant for understanding how the conscious perception of the sensation of fatigue arises. It is, however, at present still a theoretical model and further work is needed to assess its validity.

It is not clear when the exact point when awareness of change, as described by second-order maps, becomes a conscious awareness of fatigue. It has recently been suggested that vocalisation processes may be necessary for this acknowledgement of altered mapping or evolving second-order states.[70] In this model, inner self-talk alerts one to significant changes in proto-self maps, and this self-talk is associated somehow or as part of a second-order neural network that involves the parts of the cerebral cortex responsible for vocalisation. Further work is needed to examine this theory, looking at these cortical areas specifically using functional imaging techniques during fatiguing activity.

Finally, it must be noted that while the sensation of fatigue represents our conscious knowledge of

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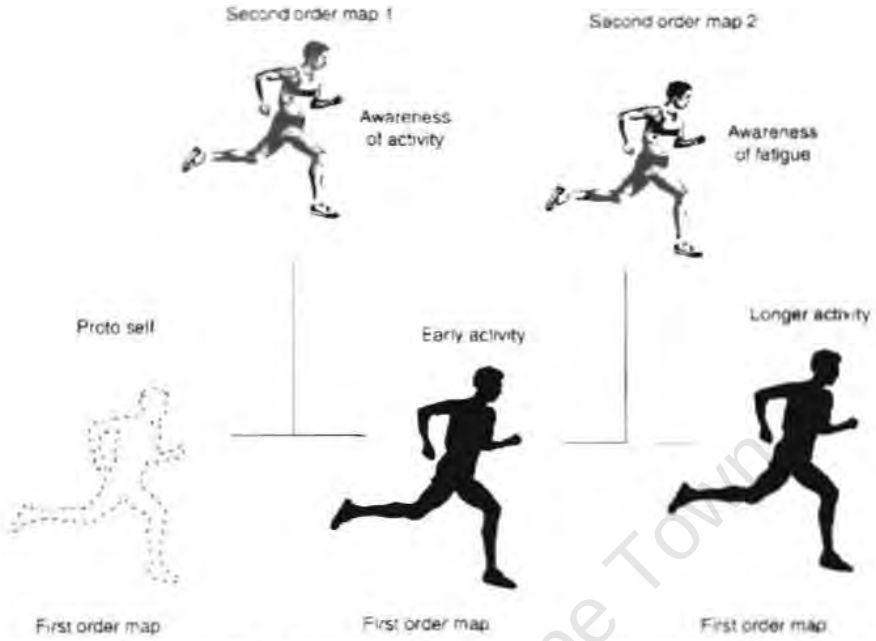

Fig. 2. The relationship between the 'proto-self' and physiological changes associated with increased physical activity and the generation of the conscious perception of the sensation of fatigue

underlying physical activity, the majority of activity is controlled at a subconscious level. For example, when we are running we are not generally aware of individual placement of the feet on the ground, or of co-ordination of limb activity. While a number of different motor tasks are processed by the brain at any one time, we only have a single dominant 'stream' of conscious thought. This may be related to the idea that subconscious neural network activity controlling all subconscious functions such as motor activity occurs in a massively parallel manner, while conscious perception is a completely linear occurrence, and at any timepoint we only have one conscious perception of reality. In the fatigue model therefore, this serial mechanism may be responsible for the dissociation between the conscious sensation of fatigue and underlying subconscious changes in pacing strategy.

4. Future Directions

In this article we have examined briefly both the anatomical origin of the sensation of fatigue and a possible mechanism of how it may originate from subconscious processes in these anatomical areas or functional processes, from a monistic perspective. As described previously, neuroscience techniques have been developed which allow us now to examine brain function in greater spatial and temporal detail. We propose that future research should use these techniques to examine, in detail, changes that occur in different brain regions, or as generalised alteration in brain activity, in order to elaborate on the processes involved in the generation of the sensation of fatigue and the 'feeling of knowing' that we personally feel when fatigued. Fatigue as a model may be relevant therefore to study the broader problem of consciousness, because unlike other emotions such as anger and fear which are difficult to quantify, fatigue has generally been shown to be a reproducible sensation in the laboratory environment[71,73] which can be generated and regulated in the human model using routine exercise testing. Therefore, exercise physiology may have an important role to play in answering questions that

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have traditionally been the domain of philosophers and neuroscientists.

5. Conclusion

In conclusion, we have examined fatigue as a sensation rather than a physiological occurrence. Fatigue is described as conscious awareness originating from subconscious control structures. A model for the development of the sensation of fatigue is described, where the sensation of fatigue originates from a difference between subconscious representations of baseline physiological homeostatic state and the state of physiological activity induced by physical activity, which creates a second-order representation which is perceived by consciousness-producing structures as the sensation of fatigue. In this model, fatigue has a teleological function, and can be classified as an emotional construct. It is not clear whether the origin of the fatigue process is in a particular brain structure, is the result of an integrative process involving a number of different brain regions, or is the result of electrophysiological synchronisation of entire brain activity. Further work is required to determine from which neural processes or brain structures the sensation of fatigue originates.

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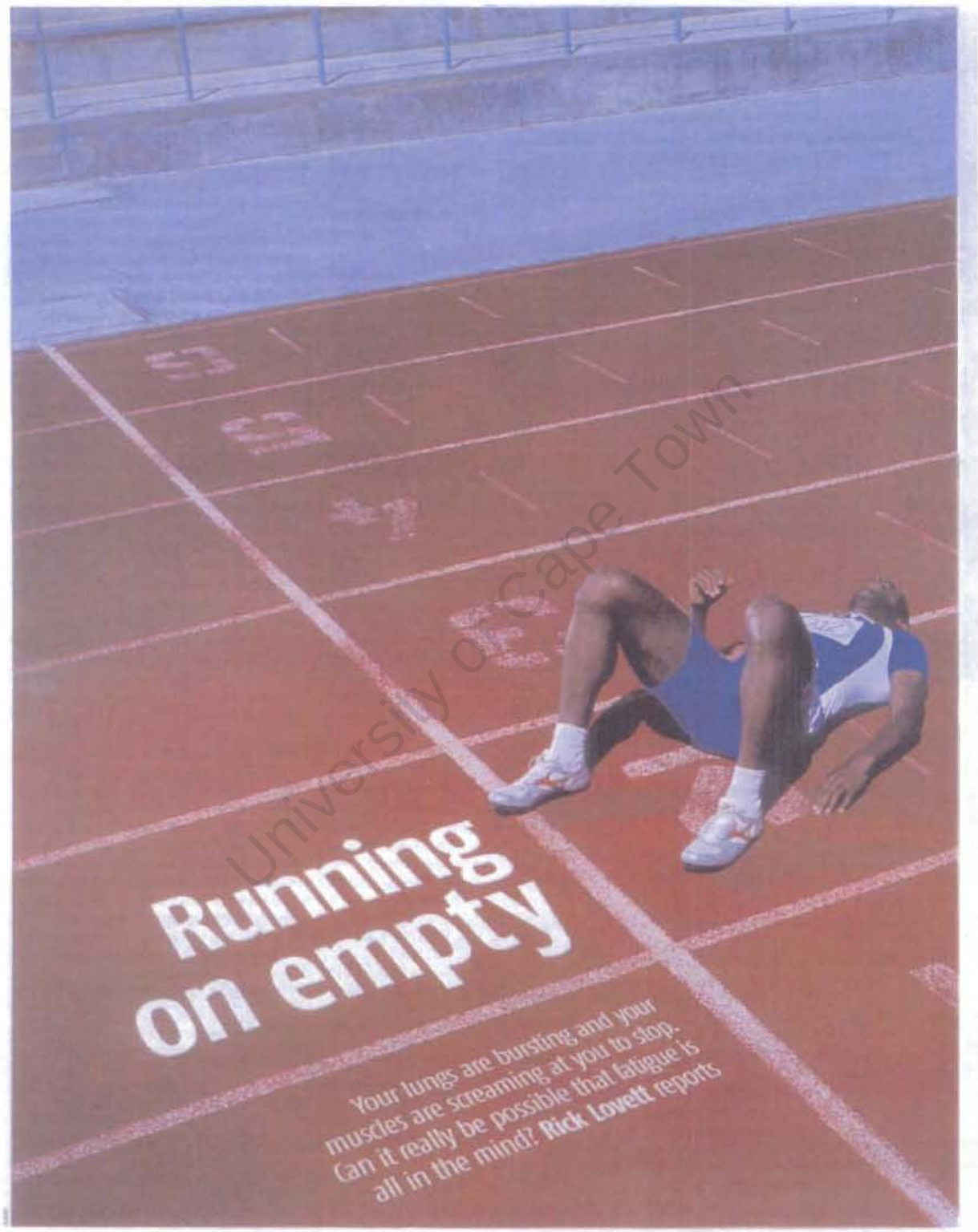


University of Cape Town

"Athletes almost always manage to go their fastest in the last kilometre of a race even though, theoretically, that's when their muscles should be closest to exhaustion"

TIMOTHY NOAKES will never forget the day he encountered the hill from hell. It was 1976 and he was running the gruelling Comrades Marathon, an annual 90-kilometre road race between Durban and Pietermaritzburg in South Africa. About 20 kilometres from home he rounded a bend and saw a steep incline he hadn't known was there. Even before he started climbing, he suddenly began to feel overwhelmingly tired.

At the time it was just a case of gritting his teeth. But Noakes, a professor of exercise physiology at the University of Cape Town, South Africa, soon came to see that hill as an intellectual mountain, too. Why had the very thought of it made him feel so tired?

Conventional wisdom on muscle fatigue can't explain what happened that day. For the better part of a century, scientists and athletes have presumed, not unreasonably, that fatigue originates in the muscles themselves. Precise explanations have varied, but all have been based on the "limitations theory". In other words, muscles tire because they hit a physical limit: they either run out of fuel or oxygen or they drown in toxic by-products.

In the past few years, however, Noakes and his colleague Alan St Clair Gibson have taken a hard look at the standard theory. The deeper they dig, the more convinced they have become that physical fatigue simply isn't the same as a car running out of petrol. Fatigue, they argue, is caused not by distress signals springing from overtaxed muscles, but is an emotional response which begins in the brain.

The essence of their new theory is that the brain, using a mix of physiological, subconscious and conscious cues, paces the muscles to keep them well back from the brink of exhaustion. When the brain decides it's time to quit, it creates the distressing sensations we interpret as unbearable muscle fatigue. This "central governor" theory remains controversial, but it does explain many puzzling aspects of athletic performance, as well as suggesting some revolutionary approaches to training and offering tantalising hints as to the cause and maybe even the cure of chronic fatigue syndrome.

The hill from hell might have set Noakes thinking about fatigue, but it was a more recent discovery that made him start researching it in earnest. He calls this the "lactic acid paradox". Lactic acid is a by-product of exercise, and its build-up is often cited as a cause of fatigue. But when research subjects exercise in a decompression chamber designed to simulate high altitude, they become fatigued even though lactic acid levels remain low. Nor has the oxygen content of their blood fallen too low for them to keep going. Obviously, Noakes deduced, something else was making them tire well before they hit either physiological limit.

Noakes and St Clair Gibson decided to probe further. For their first study, published in 2001 (*American Journal of Physiology – Regulatory Integrative and Comparative Physiology*, vol 281, p R187), they recruited seven experienced cyclists and asked them to pedal 100-kilometre time trials on stationary exercise bikes. On several occasions during the time trial, they asked the cyclists to sprint for 1000 or 4000 metres. Throughout the experiment, the cyclists wore electrical sensors taped to their legs to measure the nerve impulses travelling to their muscles.

It has long been known that during exercise, the body never uses 100 per cent of the available muscle fibres in a single contraction. The amount used varies with the length of the endeavour, but in endurance tasks such as the cycling test the body calls on about 30 per cent, spreading the load by rotating in fresh ones as needed. And because separate nerve filaments send signals to each fibre, sports scientists can determine what fraction of the muscle is being used by measuring the electrical impulse travelling to it.

Noakes reasoned that if the limitations theory was correct and fatigue was due to muscle fibres hitting some limit, the number of fibres used for each pedal stroke should increase as the fibres tired and the cyclist's body attempted to compensate by recruiting an ever larger fraction of the total. But his team found exactly the opposite. As fatigue set in, the electrical activity in the cyclists' legs declined – even during the sprints, when they were striving to cycle as fast as they could.

Plenty in the tank

To Noakes, this was strong evidence that the old theory was wrong. The cyclists may have felt completely done in, he says, but their bodies actually had considerable reserves that they could theoretically tap by using a greater fraction of the resting fibres. This, he believes, is proof that the brain is regulating the pace of the workout to hold the cyclists well back from the point of catastrophic exhaustion.

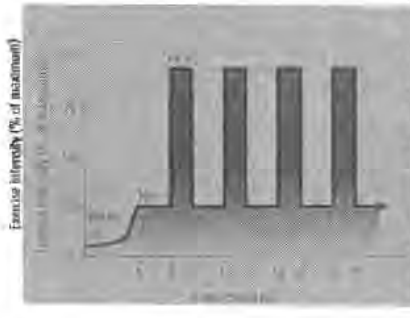
More evidence comes from the fact that fatigued muscles don't actually run out of anything critical. Muscle biopsies have shown that levels of glycogen, which is the muscles' primary fuel, and ATP, the chemical they use for temporary energy storage, decline with exercise but never bottom out. Even at the end of a marathon, ATP levels are 80 to 90 per cent of the resting norm. And while glycogen levels approach zero, they never get there. Post-marathon muscles also still have substantial reserves of other fuels, notably fat.

Still more evidence in favour of the central regulator comes from observations of the closing stages of distance races. Top athletes almost always manage to go their fastest during the last kilometre of a race, even though, theoretically, that's when their muscles should be closest to exhaustion. In particular, Noakes says, the end spurt makes no sense if fatigue is caused by muscles poisoning themselves with lactic acid. If lactic acid build-up is the limiting factor, racers would progressively slow down and would find it impossible to sprint for the finish line.

But with the central governor theory, the explanation is obvious. Knowing the end is near, the brain slightly relaxes its vigil and allows the athlete to tap a bit of the body's carefully hoarded reserves. ▶

FASTER, FASTER

Interval training, where you alternate bouts of high-intensity exercise with active rest periods, can shave minutes off your personal best. But does it work on your body or your mind?



"Why is it that if you set out on a 10-kilometre training run, the first kilometre feels mysteriously easier than the first kilometre of a 5-kilometre run?"

But the central governor theory does not mean that what's happening in the muscles is irrelevant. The governor constantly monitors physiological signals from the muscles, along with other information, to set the level of fatigue. A large number of signals are probably involved, but the ones Noakes is most sure about include the body's remaining stores of carbohydrates, the levels of glucose and oxygen in the blood, the rates of heat generation and heat loss, and the rate at which muscles are working. Where the central governor theory differs from the limitations theory is that these physiological factors are not the direct determinants of fatigue – they are just information to take into account.

Conscious factors can also intervene. Noakes believes that the central regulator evaluates the planned workout, and sets a pacing strategy accordingly. Experienced runners know, for example, that if they set out on a 10-kilometre training run, the first kilometre feels mysteriously easier than the first kilometre of a 5-kilometre run, even though there should be no difference. That, Noakes says, is because the central governor knows you have farther to go in the longer run and has programmed itself to dole out fatigue symptoms accordingly.

This can be verified by putting people on treadmills and telling them they're going to run one distance when in fact you have another planned. When the subjects are given the real story midway through the test, their reported levels of fatigue suddenly adjust to account for the new information.

It also explains Noakes's experience on the hill from hell. "The central governor had been pacing me for another 20 kilometres," he says, "but it had presumed it was going to be flat. Now, it suddenly had to take the hill into account, and it forced me to slow down."

He feels exhausted, but if a life-threatening danger suddenly appeared he'd find the energy to run

St Clair Gibson believes there is a good reason why our bodies are designed to keep something back. That way, there's always something left in the tank for an emergency. In ancient times, an emergency might take the form of a lion or pack of wolves at the end of a long, gruelling hunt. Today, the "wolf" might be a mugger hiding in an alley, or a lightning storm near the end of a long hike. But the same concept applies: life would be too dangerous if our bodies allowed us to become so tired that we couldn't move quickly when faced with an unexpected need.

Drugs and hypnosis

The team also believes the central governor theory helps to explain why hypnosis helps block sensations of fatigue, allowing athletes to work harder. If fatigue were merely the result of hitting the muscles' physiological limits, this shouldn't be possible. But it is. Amphetamines have a similar effect, and again it could be down to the central governor. Blocking the sensation of fatigue with drugs, however, makes it much easier to work yourself to death. Normally, fatigue will force even the most iron-willed competitor to quit before they succumb to heatstroke, but this didn't happen for the British cyclist Tom Simpson, who died after taking amphetamine during the Tour de France in 1967, the year before drug tests started. Ecstasy, Noakes adds, is an amphetamine-like substance that could have the same effect on clubbers.

The theory could also help to unravel the mystery of chronic fatigue syndrome. Perhaps something has interfered with the brain's regulation of fatigue so that you always feel exhausted even though you are not. Successfully puzzling out the workings of the central governor might open the door to a long-awaited cure, Noakes suggests.

St Clair Gibson and Noakes are presently trying to find where the central governor is located in the brain by studying the electroencephalograms (EEGs) of tiring cyclists. "We're finding that a lot of areas of the brain are involved," St Clair Gibson says, "but we haven't yet found the stop switch." However, the mix of such areas is interesting, and includes the frontal lobe (which is involved in decision making), the parietal lobe (which is involved in sensation), and, for some reason, the visual and speech centres.

The central governor theory has found favour with other exercise physiologists.

University of Cape Town

Even when it feels like you're working as hard as you can, only about 30 per cent of your muscle fibres are active

George Brooks at the University of California, Berkeley, for example, recently amended his textbook to include it. But for some it remains controversial.

One critic is Jere Mitchell, a cardiologist at the University of Texas Southwestern Medical Center, Dallas. He points to treadmill tests in which people run up ever-steeper slopes while having their oxygen consumption measured. Shortly before the subjects collapse in exhaustion, their oxygen consumption reaches a plateau beyond which it won't increase, no matter how hard they try to work.

This maximum rate of oxygen consumption, called VO_2 max, can be boosted by increasing the number of red blood cells in circulation – for example, by re-injecting blood that was taken several weeks earlier. This proves that fatigue has nothing to do with any central governor, Mitchell argues. Instead, it kicks in at the point at which the body has bumped into a very real physiological limit – the amount of oxygen the blood can transport.

Peter Wagner of the University of California, San Diego, concurs. He has conducted treadmill tests in which athletes are tested under two different conditions: on normal air, and on pure oxygen. That is enough to produce an 8 to 10 per cent increase in the amount of oxygen going to the muscles, he says, producing a measurable increase the VO_2 max in well-trained athletes.

Noakes and St Clair Gibson, however, argue that the central governor theory can explain both studies. The brain, they say, senses the elevated amount of oxygen in the blood and then "resets" the pace to allow the athlete to work harder, while still maintaining a reserve. "So there is a ceiling of oxygen use," says St Clair Gibson, "but at a level decided by the brain, with a wide margin of reserve for error."

If the central governor theory does prove to be correct, can coaches use it to improve athletes' performance? Noakes's experience on the Comrades Marathon underscores the importance of knowing the course beforehand – particularly its later stages. Top athletes and coaches figured that one out many years ago. In fact, says Brooks, trainers are often ahead of the science. "Coaches, by experience, have discovered things which scientists take longer to understand," he says. But Noakes argues that the central governor theory helps make sense of interval training, a "sharpening" technique in which athletes do repetitive bouts of high-intensity exercise interspersed with recovery breaks (see Graphic, page 43).

In a recent experiment, Noakes took a group of cyclists who had never done intervals before and asked them to add them to their normal training, once or twice a week for six weeks. At the end of this programme the cyclists, who were fast recreational riders but not professional racers, had shaved a startling 15 minutes, or approximately 10 per cent, off their previous times on a 100-kilometre time trial.

Similarly dramatic improvements are often observed when runners are introduced to interval training. Traditional theory says that the improvement is due to physiological changes in the muscle cells that make them better able to use oxygen or tolerate the build up of metabolic waste products. But Noakes doesn't see how major physiological improvements can occur so quickly. And in any case, he says, interval training seems to induce very little, if any, biochemical change in the muscle. He believes that interval training works largely by teaching the central governor that going faster won't do you any harm.

Perhaps, then, the central governor idea can be used to give athletes an important mental edge. Simply telling them that even when they are feeling completely exhausted their bodies actually have a lot in reserve should provide an incredible psychological boost, says St Clair Gibson. "When athletes know that," he says, "it's going to be exciting." ●

Rick Lovett is a writer based in Portland, Oregon

J Appl Physiol 96: 1571–1573, 2004;
10.1152/japplphysiol.01124.2003.

The following is the abstract of the article discussed in the subsequent letter:

Baldwin J, Snow RJ, Gibala MJ, Garnham A, Howarth K, and Febbraio MA. Glycogen availability does not affect the TCA cycle or TAN pools during prolonged, fatiguing exercise. *J Appl Physiol* 94: 2181–2187, 2003.—The hypothesis that fatigue during prolonged exercise arises from insufficient intramuscular glycogen, which limits tricarboxylic acid cycle (TCA) activity due to reduced TCA cycle intermediates (TCAI), was tested in this experiment. Seven endurance-trained men cycled at ~70% of peak O_2 uptake ($Vo_{2\ peak}$) until exhaustion with low (LG) or high (HG) preexercise intramuscular glycogen content. Muscle glycogen content was lower ($P < 0.05$) at fatigue than at rest in both trials. However, the increase in the sum of four measured TCAI (>70% of the total TCAI pool) from rest to 15 min of exercise was not different between trials, and TCAI content was similar after 103 ± 15 min of exercise (2.62 ± 0.31 and 2.59 ± 0.28 mmol/kg dry wt for LG and HG, respectively), which was the point of volitional fatigue during LG. Subjects cycled for an additional 52 ± 9 min during HG, and although glycogen was markedly reduced ($P < 0.05$) during this period, no further change in the TCAI pool was observed, thus demonstrating a clear dissociation between exercise duration and the size of the TCAI pool. Neither the total adenine nucleotide pool (TAN = ATP + ADP + AMP) nor IMP was altered compared with rest in either trial, whereas creatine phosphate levels were not different when values measured at fatigue were compared with those measured after 15 min of exercise. These data demonstrate that altered glycogen availability neither compromises TCAI pool expansion nor affects the TAN pool or creatine phosphate or IMP content during prolonged exercise to fatigue. Therefore, our data do not support the concept that a decrease in muscle TCAI during prolonged exercise in humans compromises aerobic energy provision or is the cause of fatigue.

Linear relationship between the perception of effort and the duration of constant load exercise that remains

To the Editor: Perhaps the study of Baldwin et al. (1) finally establishes that muscle glycogen depletion does not cause fatigue within the muscle by reducing the available energy below a critical amount. This study also proves the logical error in the statement of Conlee (2): " When glycogen runs out . . . the muscle fails from lack of aerobic adenosine triphosphate (ATP) production. However, plausible and attractive this theory is, it is unproven. . . . What is clear is that, in glycogen-depleted muscle, ATP is being used up faster than it can be manufactured, and so force output is diminished." If this logic were correct, then muscle glycogen depletion would lead not to fatigue but to muscle rigor. That is, if the rate of ATP production falls below the rate of ATP use, then there must be a progressive reduction in muscle ATP concentrations leading to skeletal muscle rigor if no other safety mechanism exists.

This logical error, in what has been termed the "energy depletion model of exercise fatigue," has been emphasized previously (5). The essential contribution of Baldwin et al. (1) is to show that some other control mechanism must be present to ensure ATP and total adenine nucleotide pool (TAN) homeostasis during prolonged exercise, as shown by a number of other studies to which the authors refer. Left unanswered is the nature of that control process. However, the authors' data do provide an enticing, novel hint of what that control might be.

Baldwin et al. (1) included data for ratings of perceived exertion (RPE) reported by the subjects during two exercise bouts in which subjects began in either the carbohydrate-replete or carbohydrate-depleted state. The authors do not fully discuss why they chose either to measure or to report these data; they only note that the RPE values at fatigue were identical, despite the exercise lasting for 34% longer (52 min) in the carbohydrate-replete state. It should be noted that, if fatigue is regulated purely by a peripheral control mechanism in the exercising muscles, regardless of its chemical or other nature, it makes no sense for the brain to be informed and hence to perceive that the exercise is becoming progressively more difficult (8). The brain is singularly unable to influence the outcome because it cannot, according to the usual model, overcome the effects of these peripherally acting metabolic events (8).

In contrast, if performance during prolonged exercise is ultimately regulated centrally in the brain (3–9), specifically to ensure that muscle energy homeostasis is maintained and that a critical energy depletion does not occur (5), then the RPE may play some role in that homeostatic process. For example, the rate of increase in RPE may reflect the rate at which crucial fuel reserves are being depleted and hence the duration of the exercise bout that can still be sustained at that particular exercise intensity without threatening homeostasis.

To evaluate this possibility, I plotted the data for RPE reported by Baldwin et al. (1) against *1*) the duration of exercise in the two different conditions (Fig. 1*A*) and *2*) the percentage of time that had been completed, again in both exercise conditions (Fig. 1*B*). The hypothesis is that, if the terminal RPE is the same, then perhaps the rate at which the RPE rises may provide information of how close to the end of exercise the athlete is at any time during the exercise bout. Because manipulation of the size of the starting body carbohydrate stores produced a 34% difference in exercise duration, it seemed probable that a sufficient range of data would be available to evaluate this hypothesis when all data were expressed relative to the percentage of the total exercise bout that had been completed (or remained).

Accordingly, Fig. 1*A* shows that there is a linear relationship between the RPE and the duration of exercise in carbohydrate-depleted and carbohydrate-replete conditions. Hence, the rate at which the RPE increases could indeed serve as a marker of the time left to exhaustion during exercise at a constant workload.

Figure 1*B* confirms this possibility by showing that the linear relationship between RPE and the duration of exercise overlaps for both conditions when the exercise duration is expressed as a percentage of the total exercise time. To my knowledge, this relationship may not have been noticed previously.

One possible interpretation is that the RPE is the real determinant of the fatigue point in this model of exercise, that is, prolonged submaximal exercise at a fixed work rate. This is in keeping with the theory first proposed in the 1930s when it was found that amphetamines, which reduce or abolish the sensations of fatigue, enhance exercise performance (3). Thus it was proposed that exercise terminates when the feelings of discomfort overwhelm the potential rewards of continuing to exercise (3, 4). According to this interpretation, in the study of Baldwin et al. (1), the motivation to continue exercise stopped when a mean RPE of 18.1 units was reached in both conditions.

These findings are compatible with a number of hypotheses, including the following. At the onset of exercise, on the basis of some carbohydrate signal that is increased after a carbohydrate-enriched diet, the subconscious brain calculates the anticipated duration of the exercise that can be safely sustained

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Letter to the Editor

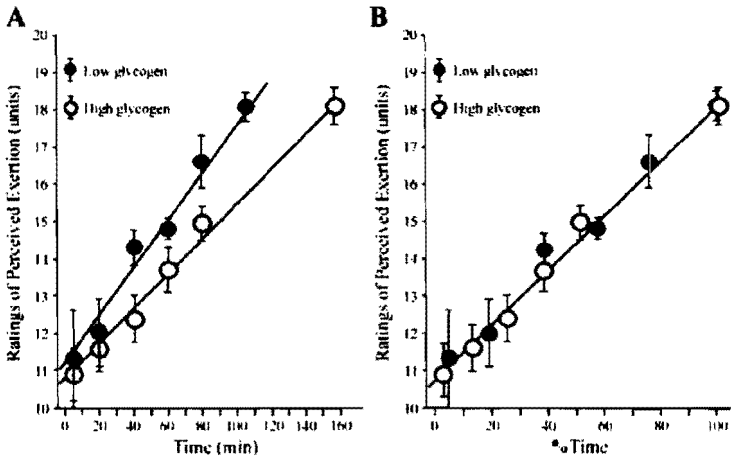

Fig. 1. *A*: plot of ratings of perceived exertion (RPE) against absolute exercise duration (minutes) shows that, regardless of whether exercise begins with low or high muscle glycogen content, there is a linear increase in RPE with exercise duration. However, the rate of rise of RPE is faster during exercise that begins with low muscle glycogen content (carbohydrate-depleted exercise). Note also that exercise terminates at the same RPE in both exercise conditions. *B*: when the RPE for both exercise conditions is plotted against the % of total exercise time (completed or remaining), the data fall along the same line. These data suggest that *1*) the maximal RPE that can be sustained determines the time at which the decision is made to terminate exercise and *2*) the rate at which the RPE increases may determine the duration of exercise specifically to ensure that total energy depletion does not occur in the active muscles during more prolonged exercise. [Data plotted from the relevant information in Table 1 of Baldwin et al. (1).]

without causing absolute whole body energy depletion. Anticipating the maximal RPE that it (or the individual) will tolerate, the brain center responsible for the generation of the RPE then increases that RPE as a function of the percentage of that total exercise time that has been completed (or the percentage of time that remains). Alternatively, some signaling energy substrate, increased by a high-carbohydrate diet, may decline as a linear function of exercise duration, resulting in a linear increase in RPE. The maximum RPE is then reached before complete depletion of that energy substrate.

Because similar RPE ratings at exhaustion occurred even though muscle glycogen contents were significantly different and were higher in the carbohydrate-replete trial, muscle glycogen content could not have been the exclusive determinant of the RPE in this study. Other sensory variables that also clearly did not contribute to this linear increase in RPE with increasing exercise duration were heart rate and oxygen consumption, which were little changed during exercise.

The pivotal importance of the study by Baldwin et al. (1) is that it allows us finally to close the chapter on the concept that a state of absolute energy depletion is ever reached during prolonged exercise, just as it also does not occur during any other form of voluntary exercise (5). The challenge now is to understand how the body anticipates the total duration of the exercise bout that is to be performed and how the increase in the perception of effort is regulated to ensure that skeletal muscle energy homeostasis is not sufficiently disturbed to produce local tissue damage, in particular, the development of skeletal muscle rigor.

GRANTS

The author's research relevant to this topic is supported by the University of Cape Town, the Medical Research Council of South Africa, Discovery Health Pty Ltd, and the National Research Foundation of South Africa through the Technology and Human Resources for Industry Programme initiative.

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REPLY

To the Editor: Our paper (1) focused on the effect of muscle glycogen availability on skeletal muscle energy metabolism and fatigue. As Dr. Noakes indicated, our data do not support the theory that fatigue during prolonged cycling exercise at a constant work rate was caused by an energy crisis within the contracting muscle. However, it should be noted, which we also stated in the paper, that, "We were unable to determine the precise cause(s) of fatigue during prolonged exercise, but this

was not the aim of the study." In particular, our measurement of muscle ATP content only provides information on the average mixed-muscle ATP content but does not elucidate the ATP levels at critical cellular sites within the various fiber types that may be critical in the fatigue process (6). Indeed, in a previous study (4), our group also demonstrated no reduction in the total adenine nucleotide pool during prolonged fatiguing exercise but showed a strong correlation between exercise duration and glycogen use, albeit in a limited number of subjects. We argued, therefore, that the relationship between glycogen content and exercise duration suggested that the maintenance of contractile force is possibly dependent on glycogen availability. Studies in both animals (3, 7) and humans (2) have suggested a link between sarcoplasmic reticulum Ca^{2+} uptake and release and glycogen availability. In addition, topographical localization of glycogen within human skeletal muscle has been observed (5). Therefore, depletion of glycogen in the sarcoplasmic reticulum may possibly lead to a failure of contractile force, although further research in this area is warranted. Hence, based on our present knowledge and techniques, we cannot definitively eliminate the possibility that the fatigue during prolonged exercise is due to a muscle energy crisis, although we agree that this is unlikely. In support of Dr. Noakes' theory on the cause of fatigue, we speculated that the fatigue may have a nervous system component, noting that fatigue was also associated with hypoglycemia. The theory that the onset of fatigue is associated with the perception of effort is extremely interesting and is entirely consistent with our experimental data, as reanalyzed by Dr. Noakes. We eagerly await further research designed to test this hypothesis.

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(d) A statement affirming that this work is the original work of the applicant. Where the work is part of a collaboration, the other contributing authors have been acknowledged.

University of Cape Town

Most of the work to which I have referred in this document was carried out by myself. However all the important conceptual advances that have been achieved by the work that I have presented here, were my creation and, when not undertaken personally by myself, the work was done by staff and students under my direct supervision.

I have also not referred to other work from my Unit to which I might have provided critical input but which has been directed principally by other members of my staff.

Hence the work I have presented here is that which I believe to have been most influenced by my direct input over a prolonged period of at least 15 years.

Full acknowledgement to the contribution of others is given in the relevant publications and in *Lore of Running*.

Professor T.D. Noakes. MBChB, MD, FACSM.

Department of Human Biology. August, 2002.

University of Cape Town

(e) A statement that the candidate has not submitted this work for an equivalent degree at this or any other University.

I hereby affirm that I have not submitted this work for consideration for an equivalent degree at this or any other University.

University of Cape Town

Professor T.D. Noakes. MBChB, MD, FACSM.

Department of Human Biology, August, 2002.

University of Cape Town

(f) Copies of the reports of 3 examiners

University of Cape Town

Expression of thanks

I thank the examiners for allowing their reports to be included in this document.

University of Cape Town

STANFORD UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF HEALTH RESEARCH AND POLICY
DIVISION OF EPIDEMIOLOGY

STANFORD, CALIFORNIA 94305-5405

4 September 2002

Adri Winckler
Deputy Faculty Office Manager
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Dear Mrs. Winckler,

This is to report that I have reviewed three documents submitted by Professor Timothy D. Noakes to the University of Cape Town for candidature towards the DSc(Med) degree. These documents include a) a detailed synopsis of the work on the nature and value of Prof. Noakes' contributions to exercise science, b) a copy of his curriculum vitae, and c) a set of 36 papers authored or co-authored by Prof. Noakes that is considered appropriate for submission towards the degree. I also have reviewed Prof. Noakes' remarkably comprehensive, practical, and useful book, the 4th edition of Lore of Running (Oxford, 2001).

I have known Prof. Noakes and followed his work closely since the late 1970's. I have met with him countless times at medical meetings, have visited him in his laboratory on four occasions (once in 1991, for more than a month), have hosted his visits at Stanford and Harvard Universities, and consider him a close friend. I add a personal note about Prof Noakes: his work and general lifestyle bring boundless energy along with confidence, intellect, and judgment, all coupled with excellent interpersonal and communicative skills.

To outline Prof. Noakes' major research activities in the Medical Research Council of the University of Cape Town, I would characterize his investigations in four areas:

a) Factors that determine exercise performance during high intensity exercise of short duration, and during prolonged exercise lasting 2-10 hours.
b) The role of exercise in disease states.
c) The mechanisms and epidemiology of sports injuries, physical and psychological.
d) Innovative technologies to enhance performance in individual and team sports.

He, together with his colleagues and students, has produced more than 300 scientific publications, many of which have been acclaimed internationally. Exercise scientists of many

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basic disciplines – physiologists, biochemists, medical clinicians, psychologists, epidemiologists, etc. – recognize Dr. Noakes' contributions as scholarly, educational, and of research excellence.

I give special attention to Prof. Noakes' unique textbook, Lore of Running. From the gracious Dedication, through the Acknowledgements, Forward, Preface and Introduction, he has proceeded into the most astonishing collection of scientific and historical data on endurance footracing that I could ever imagine. It is uncanny how he has put Lore of Running together. It represents a truly significant advance over the third edition, published nearly 12 years ago. New data, new theses, new interpretations – all the kinds of needs that called for a new edition – he has provided. Physical exercise scientists from the world around are in his debt.

I believe, Mrs. Winckler, that the materials submitted to the University of Cape Town by Prof. Noakes for the degree of DSc(Med) are certainly appropriate to meet the established written requirements for such a degree at your university. I might add that these materials, likewise, would meet corresponding requirements for the DSc degree from my own universities – Johns Hopkins University School of Hygiene and Public Health, Harvard University School of Medicine and School of Public Health, and Stanford University School of Medicine.

In summary, I give the strongest possible endorsement to the awarding of a DSc(Med) degree to Timothy David Noakes by your magnificent university, the University of Cape Town.

Sincerely,

Ralph S. Paffenbarger, Jr., MD

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September 11, 2002

Adri Winckler
Deputy Faculty Office Manager
Faculty of Health Sciences
University of Cape Town
Anzio Road
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Dear Ms. Winckler:

It is a great pleasure for me to examine the work of Professor Timothy Noakes and make a recommendation regarding the award of a DSc (Med) degree. I have been familiar with Professor Noakes' research for over 20 years, and have followed closely his scientific work over this period

The first of Professor Noakes' research contributions I noticed was his work to refute Bassler's marathon immunity theory. These carefully done and elegantly reasoned papers put to rest Bassler's unlikely notion that a person who completed a marathon was immune from coronary heart disease. I fully agree with the presentation of Professor Noakes' account of this research that is included in his degree submission document.

The second seminal contribution described in the degree submission document is that of the "dehydration myth". If I may be permitted a personal note, I have been a marathon runner for over 30 years, and early in my own research career had investigated the effects of fluid restriction versus fluid *ad libitum* during American football practice. Our results supported the wisdom of the time, which was that dehydration was a major problem during exercise, and the athletes exercising the heat should drink as much as possible. I followed this advice during a 50 mile run in the early 1980s and developed severe hyponatremia by the end of the race. Shortly after my own experience Professor Noakes described 'water intoxication'. His first article caused a revolution in my own thinking and made me realize the Timothy Noakes was a person who was not bound by rigid thinking and the status quo, but that he brought a fresh and open perspective to entrenched issues in sports medicine.

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My admiration and respect for Professor Noakes has grown over time. I completely agree with his description of seminal contributions presented in his degree submission. Again on a personal note, I was at least indirectly involved in one of these contributions—challenging the plateau phenomenon of oxygen uptake. I was President-Elect and program chair for the American College of Sports Medicine meeting in 1996. One of the pleasant responsibilities of that position is to select the Joseph B. Wolfe Lecturer for the annual scientific meeting. This is the most prestigious lecture for the world's largest and most respected meeting on sports medicine and exercise. I selected Timothy Noakes, from all of the leading exercise scientists in the world, to deliver the Wolfe lecture. I was not disappointed. The lecture was a model of careful thought, good organization, clear exposition, and use of data. The lecture was somewhat controversial, as Professor Noakes acknowledges in his submission, and it stimulated additional debate and more publications on the topic in the exercise science literature. I believe that Professor Noakes has once again been shown to be correct. I later proposed him for a Citation Award, which was given by the American College of Sports Medicine at an annual scientific conference.

The examples briefly reviewed above clearly show that Timothy Noakes is an excellent scientist, original thinker, and world leader in sports medicine and exercise science.

I have no doubt about giving my highest endorsement for Professor Noakes award of the DSc (Med) degree. He has sustained a remarkable level of scientific output that meets the highest international standards. He is widely recognized as one of the leading exercise scientists in the world. He also has developed and managed a highly productive group of research scientists and students at the University of Cape Town. I endorse his application with no reservations, and I hope that you will award him this degree.

Regards,

Steven N. Blair
Director of Research

University of Cape Town

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September 18, 2002

Adri Winckler
Deputy Faculty Office Manager
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Dear Mrs. Winckler and colleagues:

You have asked me to assess the works of Professor Timothy D. Noakes who is being considered for the advanced degree of D.Sc. in Medicine. This is a task that I undertake very carefully because of its importance to the candidate and University of Cape Town. At the outset, please know that while I am impressed with many aspects of the case, after careful consideration of the complex issues involved, they have distilled clearly in my mind. Hence, I can write this most enthusiastic and unreserved report. If any fault is to be found with this letter of evaluation, it is with the author, and not with the candidate. First, some background material appropriate to evaluating the voracity of this letter.

I first met Dr. Noakes in March of 1985 in Cape Town at an international meeting titled "Membranes and Muscle.' I was immediately and powerfully impressed by the candidate. You there in the RSA will remember those times better than me, but to state that times were strained and that the nation was isolated would probably be accurate. However, meeting Noakes and others, but especially Dr. Noakes had a powerful and positive impression on me. First off, he was a pleasant chap, which is nice, but not obligatory in assessing a scholar. Next, he was extremely well read, and had diverse interests in science and medicine. Tim was also a fine teacher and mentor to graduate students. As well, he was a physician and gave extensive community service. Amazingly, he was committed to what is called in the United States, "Affirmative Action." There I was visiting from very liberal Berkeley, California, but I could not claim to have a black graduate student. But, in Cape Town, Tim Noakes had such students who he couldn't claim either because of the politics involved, but they were there; Noakes' "investments in the future." And finally, Tim Noakes was an athlete, but he didn't just run marathons; he ran double marathons. Overall, my first impression was of someone with great intellect, extraordinary energy, boundless enthusiasm, and a great future in science and medicine. Now, I am pleased to see the intellectual fulfillment of an individual who I imagine is widely admired in South Africa as he is admired in the United States and around the scientific world.

As athlete, physician and scientist, Tim Noakes brings almost an unfair advantage to the fields of sports medicine and exercise physiology. Noakes is a prodigious investigator and author. With the publication of a fourth, South African edition of LORE OF RUNNING, Tim has surpassed

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even my most lofty assessment of his potential. As a contemporary and classic compendium of running lore, basic physiology, metabolic biochemistry and applied sports medicine, there is simply nothing like it in the world. Only Tim Noakes could have accomplished such a feat as authoring the LORE OF RUNNING, for the work is a testament to Tim as well as a triumph of achievement of one South African who stands as a fine representative of his country. Although the LORE OF RUNNING is a book, and hence, commercial effort, the work validates Professor Noakes' petition for the D.Sc. in Medicine. Like the author, the book is bigger and better than most things and individuals in this life.

My reading of Professor Noakes' self-authored Synopsis of achievements is that the document establishes him as a remarkable integrative physiologist. As already noted, Tim Noakes is a very well-read scientist. Hence, his ability to assess and appreciate problems and issues goes far beyond the abilities of most others. Tim knows the classic literature, and studies the context from which ideas emerge. He is a very good technician, and so appreciates the limitations of data sets and their interpretation. Moreover, and especially, Professor Noakes in integrative and insightful. Not just one phenomenon or system attracts him, not just injury prevention or rehabilitation motivate him, but achieving basic understanding and application of ideas new and old motivate him.

In Professor Noakes' Synopsis of work, four sorts of contributions were emphasized. Had my recommendation been solicited, I might have urged addition of a fifth (integration of metabolic and physiological systems). Still, I see the wisdom in organization of the Synopsis as it progresses somewhat chronologically, and from medical to more theoretical and physiological.

To support my conclusion that the candidate is deserving of the D.Sc. degree, I will focus on the last claim asserting seminal contributions; this is articulation of the "Central Governor Theory" of human exercise performance. There are several reasons for this emphasis on my part. Although modestly brief, the text demonstrates the breadth and depth of the candidate's understanding. As well, there is sufficient overlap between the candidate's work and my own published work on oxygen transport and utilization and substrate partitioning in muscle during exercise that my opinion should be credible on the matter. It is true that in his Synopsis the candidate devoted much of his work on the effects of hyponatremia on exercise performance, and it is true that we hold very similar ideas on the subject. However, for various reasons I have not published in that area because of my commercial involvement. Suffice it to say, as holder of U.S. Patent # 5,420, 107, I do quite well and have royalties, but not reprints to assert authority in the field. None the less, were the Central Governor Theory inadequate to assert a claim of a seminal contribution to science, I could have built a case around the hyponatremia theme.

Professor Noakes' work on the Central Governor Theory sets him apart from most contemporary investigators in biology and medicine who study a single system, gene, disease or physiological processes. In contrast, Professor Noakes' approach is integrative. Though not written in detail in the Synopsis, the candidate refers to the classic studies of Walter Morley Fletcher and Frederick Gowland Hopkins as well as to efforts of Fletcher's student, Archibald Vivian (A.V.) Hill. In 1922 the British gentleman A.V. Hill was to share the Noble Prize in Medicine with the German-Jewish biochemist Otto Meyerhof, and in 1929 Hopkins was awarded the Nobel Prize for his discovery of growth-stimulating vitamins. Those were heady days for physiologists and biochemists who were studying and discovering the physical-chemical nature of metabolism common to living things. Needless to say, their prominence in science and medicine, their

associations and friendships, and events of the times served to institutionalize many ideas in Western biology and medicine. Among those ideas were the nature of muscle contraction and fatigue, and the involvement of oxygen and lactic acid.

In his retrospective analysis of contemporary understanding, and in combination with his own experiences as athlete, scientist and clinician, Noakes traced extant ideas back to seminal papers of the above mentioned luminaries. Fletcher and Hopkins, Hill and Meyerhof as well as others working in the early twentieth century studied electrically stimulated frog muscles. These muscles were not perfused and often held in anaerobic environments. And, even if air or oxygen were present, given size of the muscle studied likely the tissue cores were anoxic. Further, the muscles were severed from the central nervous system (CNS) and built by Nature for only a few twitches. Hence, not merely by reading textbooks and reviews, but by reading and understanding the primary literature, Noakes saw the flaws and gross errors underpinning contemporary muscle and exercise physiology. Still today, even with our advanced techniques we can't demonstrate muscle anaerobiosis during lactic acidosis likely because it (oxygen lack) is simply not present. Regrettably, in contemporary critical care medicine the observation of lactic acidosis is frequently followed by administration of oxygen and bicarbonate.

Those frog hemi-corpus and isolated muscle preparations stimulated electrically long ago by British and German investigators were not only studied deprived of blood, oxygen and nutrients, but more fundamentally they were not recruited to action by the frog's brain. Further, by neither circulatory nor neuronal means could the muscles provide feedback to the animal's CNS. Thus, to an integrative physiologist such a Tim Noakes, those old reports on muscles stimulated in the absence of anything must seem odd, indeed. It is within this context of understanding the 'classic' literature and conducting contemporary studies on metabolite kinetics and human exercise physiology that Tim Noakes extended the Central Governor Theory to include the brain. After all, it is the brain that commands muscular contraction as receives both conscious and unconscious signals about peripheral physiological status.

To many, professor Noakes' ideas make perfect sense, but to others it's unfathomable. My own insight on the matter comes from our work on Pikes Peak (elevation 4,300 m). There, maximal efforts elicit lower muscle and blood lactate levels compared to sea level. That ambient hypoxia gives rise to hypoxemia, but in combination hypoxemia and maximal efforts produce lower lactate levels than at sea level has befuddled many physiologists who have termed the phenomenon the "Lactate Paradox." But, to Noakes' way of thinking, the matter makes perfect sense. The brain, and perhaps also the heart suffer when the environment is dreadful, and mechanisms intrinsic to them accommodate to protect their homeostatic mechanisms, the muscles and perhaps heart not being driven to make maximal efforts. In other words, the candidate's knowledge of multiple systems allowed him to comprehend how they are integrated and unified in function. Retrospectively, to us it now makes perfect sense that a Central Governor acted to restrain the peripheral musculature in men at high altitude. And, although, we did not take our data to be a hint of a general principle of physiology, Tim Noakes did. For that I commend him. With colleagues Noakes not only used hypoxia, but they employed other environmental stresses and conditions including hyperoxia, heat and humidity and prolonged exercise to demonstrate a central limitation of work performance.

I recognize fully that in evaluating Professor Noakes for the D.Sc. in Medicine it is essential to focus on his scholarly efforts. None the less, I feel compelled to note, at least in passing, that his abilities to organize, build and motivate others are remarkable.

In summary, the candidate's impressive and prodigious accomplishments are both qualitatively and quantitatively superior. Hence, my analysis of the case leads me to enthusiastically support the case for awarding a D.Sc. in Medicine to Professor Timothy D. Noakes.

Please accept my sincere best wishes as well as compliments for advancing this case.

Sincerely,

George A. Brooks, Ph.D.
Professor

University of Cape Town

(g) Reproduction of copy for the awarding of the Degree of Doctor of Science in Medicine (Exercise Science) as it appeared in the Faculty of Health Sciences Graduation Ceremony 2002 programme

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DEGREE OF DOCTOR OF SCIENCE IN MEDICINE
In Exercise Science

Timothy David Noakes, MBChB, MD, FACSM

Timothy David Noakes was born in Harare, Zimbabwe in 1949 and educated at Diocesan College in Cape Town. After matriculation he spent a year in 1967/68 as an American Field Service Scholar in the USA, an experience that was to shape his future development as a medical doctor and international scientist. He graduated with an MBChB from UCT in 1974 and with an MD, also from UCT, in 1981 for a doctoral thesis entitled "Exercise and the Heart". Over the past two decades Professor Noakes has built a world-renowned research enterprise, the MRC/UCT Research Unit for Exercise Science and Sports Medicine, and currently holds the Discovery Health Chair in Exercise and Sports Science. Professor Noakes' most important research publications, together with the recently published 4th edition of his book Lore of Running, formed the basis for a portfolio that was examined by a panel of three international experts. He has made seminal contributions during the past 25 years in four separate areas of exercise science.

First, he showed that marathon runners are not immune from heart disease as had been proposed by a Californian pathologist in the early 1970s. This innovative work, which comprised a portion of Professor Noakes' MD thesis, was published in the New England Journal of Medicine, and was his first encounter with some of the myths in sports science. Second, he debunked the dehydration myth: the advice to endurance athletes that they should drink as much as possible, and he produced the first report of water intoxification during prolonged exercise and the first exposition of the physiological mechanism causing that condition. His pioneering publications on this condition, while provoking an outcry among fellow exercise scientists, especially those whose research is supported by the sports drink industry, have effectively changed the face of endurance events. For this work on fluid balance during exercise, Professor Noakes received the Cannes International Grand Prix Award for Research in Medicine and Water in France earlier this year. Third, he has developed a novel approach to the management of exercise-associated collapse in endurance athletes, including the redefinition of the so-called "heat illnesses" of exercise. Based on the hypothesis that collapsed athletes are suffering from hypotension, rather than dehydration, he and his team have developed guidelines for the management of these athletes that have been accepted by the International Marathon Medical Directors Association, located in New York, as the standard for all international races held under their auspices. The fourth seminal contribution of Professor Noakes has been to challenge the "anaerobic" theory of exercise performance, and to postulate the central governor theory in which the brain, by controlling and integrating neuromuscular recruitment, is the primary organ that determines athletic performance. Drawing on insights from the classic studies of Nobel Laureate AV Hill in the 1920s, Noakes has provided a theoretical framework that will fundamentally change our under-standing of exercise physiology.

In the words of one of the examiners: "Noakes' work on the Central Governor Theory sets him apart from most contemporary investigators in biology and medicine who study a single system, gene, disease or process. The candidate's knowledge of multiple systems allows him to comprehend how they are integrated and unified in function. His impressive and prestigious accomplishments are both qualitatively and quantitatively superior."

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(h) Acknowledgements

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We acknowledge too infrequently the women who shape our lives. I learned the English alphabet at my mother's knee on the sands of Glencairn beach, some 50 years ago. My mother's devotion to my education and her faith in me have sustained and inspired me ever since then.

Marilyn Anne has been the single greatest influence on my life. Her purity and generosity of spirit, coupled with a necessarily astute understanding of the person behind the image, forms a foundation for all that we have collectively achieved, including all the elements of our shared lives that made my career possible.

Of the inspiring men in my life, none has been more important than my late father, who taught me that honesty is the first requirement in life. His great sense of humour, his love of a good story skilfully told, and his global view, allied to a disdain for authority and pretense, made him the perfect mentor for a career in science and education. He also had that brilliant foresight to leave me, as a young child, in the care of Thomas Taravinga, my first friend, whose Zimbabwean warmth and brilliant smile I have tried all my life to emulate.

The genius of the late Professor Christiaan Barnard inspired me to study medicine at the University of Cape Town, where I discovered running under the expert tutelage of Drs. Edward (Tiffy) King and Manfred Teichler, all of us inspired by the exploits of Dave Levick. There too, I came under the influence of Professors Lionel Opie and Wieland Gevers, perhaps two of the finest teachers anyone could be privileged to encounter at the same time, anywhere in the world. Together with the iconic Christiaan Barnard, they formed an intoxicating triumvirate. For what more could a young scientist wish? Lionel Opie inspired me to read, taught me how to write and how to use figures to explain complex concepts. He taught a love of books and a reverence for the contribution and genius of the great scientists on whose shoulders we stand. To Wieland Gevers I am indebted for his offhand remark that we should not assume that muscles become anaerobic during exercise, and to his insistence on the term "oxygen-independent" (not anaerobic) metabolism. His special way of teaching – question everything – ultimately led to the research that produced the maverick theory presented in this thesis. That research has been funded by the University of Cape Town and the Medical Research Council for an unbroken period of 26 years.

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Adrian Gore, Neville Koopowitz and Johan van Rooyen of Discovery Health were instrumental in establishing the Chair in Exercise and Sports Science and substantial additional research funding. Without the unwavering support of all these great institutions, the pivotal ideas in this thesis would never have evolved.

I first met the late Dr George Sheehan, the running writer without equal, at the New York Academy of Sciences Conference on the Marathon in New York City in 1976, a pivotal event in my life and which led to the publications on heart disease in marathon runners described in this thesis. His writings, which continue to set the standard against which all else is measured, and the friendship we shared for 15 too-short years, are forever. From Dr Sheehan I learned that two quotes that have fashioned my scientific philosophy:

> "Fifty percent of what we teach you is wrong. Unfortunately we don't know which 50% it is", and:

"Truth passes through 3 phases. First, they tell you that what you say is wrong. Then they tell you that what you say is right, but it is irrelevant. Finally they say that what you say is right, but they have always taught it anyway!"

For the enthusiasm, passion, and faith of those colleagues who were there in the basement in the old Physiology building at the beginning – Mike and Vicki Lambert, Steve Dennis, Andrew Bosch, Wayne Derman and Martin Schwellnus – and whose support and collaborations made this research possible, my sincerest thanks. History will yet judge with great favor the contributions you have already made and those yet to come.

In 1992, South African rugby icon, Morné du Plessis, helped us found the Sports Science Institute of South Africa. The achievement of our collective vision would not have been possible without the substantial patronage of Mr Johann Rupert.

I began my research career certain only that I wished better to understand human physiology during exercise. My fate was to be directed down the two paths that would form the basis for this DSc thesis. The chance events and observations that initiated this research are detailed, perhaps as an example of how science sometimes works. The key it seems to me is to be eternally inquisitive, especially when your instinct tells you that here is something currently unexplained, but really interesting. When it conflicts with conventional wisdom, so much the better. Perhaps the single greatest lesson I have learned in this journey, is the manner in which we use subconsciously registered models to interpret our world and how this means that we each live in quite different "worlds". Understanding the individual worlds of our scientific peers provides the key to understanding why they think as they do.

Finally, I have prepared this thesis for publication to provide a bridge with the past I did not know and a future I will not live to experience. Yet, teachers live on through their students. To all those students who have enriched my life for the past 20 years, my joy is to know that the future is yours.

And your best is yet to come.

Tim Noakes
Cape Town

(Revised from acknowledgements in the 4th Edition of *Lore of Running*)

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