# BLOOD LACTATE LEVELS DURING EXERCISE. THE EFFECTS OF EXERCISE DURATION, BICARBONATE INFUSION AND BETA-RECEPTOR ANTAGONISM.

Thesis submitted to the University of Cape Town

for

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by

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With love to my parents,

and with thanks for their unfailing belief

in my ability to achieve whatever I set out to do.

# INDEX

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Sheila Bertram

August 1985

## DECLARATION

I, S. Bertram, declare that the work on which this thesis is based is original (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

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August 1985

## ABSTRACT

This study examines factors that determine blood lactate accumulation during exercise in order to examine the opposing theories that such accumulation occurs either as a result of muscle anaerobiosis or an "overflow" of oxygen-independent glycolysis.

Three separate studies were conducted; in the first study we compared blood lactate levels measured during progressive and constant intensity exercise lasting six minutes to see whether a single blood lactate turnpoint could be identified, or whether there are in fact multiple turnpoints. The presence of multiple turnpoints would tend to support the theory of blood lactate production due to glycolytic overflow.

In the first study, six trained subjects exercised on a treadmill according to a progressive protocol which started at 8 $km.h^{-1}$ and zero grade, and increased by 0.5 $km.h^{-1}$ every 30 seconds to voluntary exhaustion. Blood lactate samples were collected at 30 second intervals in order to establish the lactate turnpoint, that is, the point at which blood lactate levels increased abruptly. Thereafter, each subject exercised for six minutes at each of eight workloads near to that workload at which the lactate turnpoint occurred in the progressive

treadmill test. Blood lactate levels were again measured every 30 seconds.

This study showed that :

i) The blood lactate levels during the steady-state test were higher at all exercise intensities than those measured at an equivalent treadmill speed in the progressive test.

ii) The blood lactate turnpoint occurred one workload earlier in the steady-state test than in the progressive test.

iii) Blood lactate levels during the steady-state test increased for the first three minutes of each workload for two workloads beyond the turnpoint ("T+2"), but remained constant for the remainder of the exercise at that intensity.

iv) The "T+2" intensity occurred at blood lactate levels of around 4 $mmol.l^{-1}$, with exercise beyond this intensity resulting in a continuous increase in blood lactate levels for the remainder of the exercise.

v) All subjects had great difficulty exercising for the full twelve minutes at the combined "T+3" and "T+4" workloads

during which blood lactate levels rose continuously to reach blood levels of 6 to 8 mmol.$l^{-1}$.

This study allows the following conclusions :

1) That glycolytic overflow is probably responsible for elevated blood lactate levels for exercise up to the "T+2" workload, as shown by stable but elevated lactate concentrations over the last three minutes of these workloads. Had anaerobiosis been present, we would have expected these levels to continue rising throughout the six-minute exercise period.

2) That a number of "lactate turnpoints" exist at workloads between the "T-1" and the "T+2" work intensities.

3) That the "true" lactate turnpoint occurred at blood lactate concentrations of 4 mmol.$l^{-1}$. This turnpoint was irrevocable, and is probably caused by the inability of lactate removal by other tissues to match the increased rates of muscle lactate production resulting from :
i)possible anaerobiosis
ii)glycolytic overflow, or both.

The second study examined blood lactate levels obtained under

acidemic and neutral pH conditions obtained by a bicarbonate infusion to see whether increased buffer concentrations would reduce hydrogen ions available for reduction with pyruvate and therefore result in lower lactate levels. In this study, six subjects performed progressive exercise to exhaustion on a cycle ergometer, starting at 100 $kpm.min^{-1}$ and increasing by 100 $kpm.min^{-1}$ every minute until the subject was unable to maintain a pedalling rate of 50 rpm. Blood lactate, bicarbonate and pH levels, as well as respiratory gases, were measured at 60 second intervals.

A week later this same test was repeated, but with 4.2% sodium bicarbonate infusion at a rate calculated to maintain a constant blood bicarbonate level (26 $mmol.l^{-1}$) and a neutral pH. The rationale for this study was to determine whether the initial lactate turnpoint during progressive exercise could be altered, as it is known that alkalosis increases the rate of lactate removal from muscle. In addition, an adequate availability of bicarbonate would increase the uptake of hydrogen ions thereby reducing the quantity available for reduction of pyruvate to lactate.

This study showed that blood lactate levels tended to be higher during bicarbonate infusion, when blood pH remained neutral and bicarbonate concentrations were maintained at resting levels.

Unfortunately, this could not be proved statistically due to the small number of subjects used in the study. It appears then, that while lactate formation is probably not impeded by the alkaline environment, lactate diffusion from the exercising muscles into the blood may be enhanced by increased blood bicarbonate levels. Supported by the work of Sutton et al (1981), these results suggest that the activity of glycolytic enzymes is enhanced in the non-acidic environment, thereby providing indirect evidence in favour of the glycolytic overflow theory.

The third and final study examined blood lactate levels before and after beta-receptor antagonism with propranolol. Lower blood lactate levels following beta-receptor antagonism would indicate reduced muscle glycogenolysis; the ability to manipulate muscle lactate production in this way would therefore tend to support the view that increased lactate production during exercise is caused by glycolytic overflow and not tissue hypoxia. In this final study, six subjects followed the same progressively increasing treadmill protocol used in the first study before and after they had ingested 80mg. propranolol. Blood samples were collected at 30 second intervals to determine the effects of beta-receptor antagonism on the lactate turnpoint.

This study showed that beta-receptor antagonism caused lower

blood lactate levels and a significantly delayed lactate turnpoint. This is compatible with the theory that the initial rise in lactate levels during exercise is due to the increased production of pyruvate and hydrogen ions which exceed the metabolic capacity of the mitochondria.

CONCLUSIONS :

1) There are multiple blood lactate turnpoints and the workload at which these occur depends on the duration of the testing protocol.

2) Lactate release into the blood may be facilitated by metabolic alkalosis.

3) The blood lactate turnpoint measured during progressive exercise can be manipulated by intervention such as beta-receptor antagonism.

4) Anaerobiosis is an unlikely explanation for the initial lactate turnpoint during progressive exercise since blood lactate levels during prolonged, constant intensity exercise remained constant even at intensities above the initial blood lactate trunpoint.

Further work to confirm these findings would require the measurement of lactate production and clearance rates at workloads near to that which defines the lactate turnpoint.

# CHAPTER ONE

## OUTLINE AND AIMS OF THE STUDY

During exercise of progressively increasing intensity, there is a point where blood lactate levels increase abruptly allowing a so-called lactate turnpoint to be identified. This turnpoint probably occurs as a result of an imbalance in the rates of production of lactate within the exercising muscles, and its oxidation or subsequent metabolism at such alternative sites of lactate uptake as the slow-twitch muscle fibres, the heart and the liver. Current theories are that increased rates of muscle lactate production occur either when there is tissue anaerobiosis (Wasserman and McIlroy, 1964; Saiki et al, 1967; Wasserman et al, 1973) or when the mitochondrial capacity for the oxidation of glycolytically-produced pyruvate and protons is exceeded (Keul et al, 1967; Mazzeo et al, 1982).

At present, the kinetic radio isotope techniques used for measuring the rates of lactate production and oxidation are extremely expensive and are only available in very few laboratories throughout the world. I therefore chose to measure changes in blood lactate levels, and to thereby identify the lactate turnpoint during progressive and steady-state exercise under various conditions as an indication of whether tissue anaerobiosis or glycolytic overflow could explain the blood lactate changes which occur during exercise.

Three different studies were conducted :

1) In the first study, the lactate turnpoint was determined during progressive treadmill exercise as the point where blood lactate levels rose abruptly. Thereafter, subjects exercised for six minutes at a number of workloads near the lactate turnpoint in an attempt to relate the blood lactate turnpoint obtained during the progressive test to steady-state exercise levels.

   In particular, I wished to examine blood lactate levels over each six-minute period to see whether these levels continued to rise or to stabilise for each intensity. The rationale behind this examination was that, since blood lactate accumulation occurs as a result of an imbalance between the rate of lactate production and the rate of lactate uptake, a constant blood lactate level would indicate a balance between production and oxidation. Such a balance would contradict the theory of anaerobiosis because, were anaerobiosis to be the cause of elevated blood lactate levels, we could expect to see continuously increasing blood lactate levels rather than a steady-state concentration.

2) In the second study, the lactate turnpoint was determined during progressive cycle exercise both before and after a bicarbonate infusion which maintained resting blood bicarbonate levels and a neutral pH. The rationale behind

this study was the fact that lactate diffuses more readily out of the muscle cells when there are adequate buffer supplies (Hirche et al, 1972). In addition, we reasoned that an adequate availability of bicarbonate would increase the uptake of hydrogen ions, thereby reducing the quantity available for the reduction of pyruvate to lactate.

A change in post-infusion blood lactate levels would demonstrate an ability to alter the glycolytic production of lactate, thereby supporting the theory that glycolytic overflow is the cause of lactate accumulation during exercise.

3) The final study involved a comparison of blood lactate levels and the lactate turnpoint before and after beta-receptor antagonism with propranolol. The aim was to determine whether beta-antagonism would inhibit glycolysis, thereby reducing lactate accumulation and causing a delayed turnpoint. Following the reasoning described above, if propranolol caused sufficient inhibition of glycolysis, lactate levels would be lower and this too would tend to favour the theory of glycolytic overflow as the cause of rising exercise blood lactate levels.

# CHAPTER TWO

## BLOOD LACTATE LEVELS DURING EXERCISE : A LITERATURE REVIEW.

## 2.1 EARLY STUDIES OF LACTATE PRODUCTION DURING EXERCISE (1907 - 1944).

Fletcher and Hopkins (1907) were among the first researchers to study the content of "lactic acid" (see Appendix One) in muscle, and the factors determining its production and release from muscle. They studied frog hind-limb muscle preparations under a variety of conditions and showed the following :

A) The concentration of "lactic acid" in homogenised, freshly excised hind-limb muscles of frogs was close to zero.

B) Excised, non-contracting whole muscles isolated in a container exposed alternatively to room air, to pure oxygen, to coal gas or to hydrogen showed the following : At room temperature, "lactic acid" production was slowest when the muscle was exposed to oxygen, but increased progressively when exposed to hydrogen and coal gas. During coal gas exposure the rate of "lactic acid" production was four times greater than that measured during exposure to room air. Exposure to hydrogen resulted in "lactic acid" accumulation commencing immediately the muscle was excised.

C) Under "exercise" conditions produced by continuous electrical stimulation of muscle for one and a half to two

hours until the muscle could no longer contract, the following was found : The rate of "lactic acid" production increased to three times resting rates and appeared to establish a "fatigue maximum" of acid release. Once this maximum was reached, muscle contraction ceased, suggesting that the accumulation of "lactic acid" during contraction ultimately prevented further contraction.

D) To study whether there might be oxidative removal of "lactic acid", fatigued muscles were exposed alternately to nitrogen (anoxia), room air and oxygen. After a period of anoxia, the re-introduction of any amount of oxygen resulted in a marked and proportional decrease in the muscle "lactic acid" levels. This decrease was initially rapid, becoming increasingly slow thereafter.

In summary, these studies show that while resting muscle released very small quantities of "lactic acid", this release was increased when muscles were stimulated to contract in room air. "Lactic acid" release was not observed in muscles exposed to an atmosphere of pure oxygen, but was increased under anoxic conditions. After a period of anoxia the re-introduction of oxygen markedly decreased the rate of "lactic acid" production.

The next relevant study was that performed by Ryffel (1909) who measured urinary, sweat and venous blood lactate levels in humans under four conditions :

A) After moderately severe exercise involving a run of approximately 600 metres in two minutes, after which urinary lactate levels were measured; and a run of approximately 700 metres in 2.75 minutes, after which venous lactate concentrations were measured. There was a considerable increase in urinary lactate levels after these short periods of severe exercise, with a corresponding but smaller increase in venous blood "lactic acid" levels. Ryffel also noted that "lactic acid" disappeared more slowly from blood than from urine, there being no lactate in the urine 30 minutes after exercise, whereas blood lactate levels returned to resting levels only after 45 minutes.

B) During continuous exercise involving a 24 hour walking race, blood lactate levels remained low at all times.

C) During exposure to high external temperatures produced by a Turkish bath, sweat lactate levels were extremely high (8 $mmol.l^{-1}$), similar to those measured in urine (6 $mmol.l^{-1}$) and in blood (7 $mmol.l^{-1}$) during severe exercise. Urinary values were not elevated.

D) During exposure to reduced atmospheric oxygen content (hypoxia) produced by placing the subjects in a closed chamber, from which only carbon dioxide was removed, for three and a half hours. Various side-effects of oxygen lack were observed. These included headache, mental confusion, increased respiration and cyanosis, but urinary lactate levels did not rise. Blood lactate levels which were slightly elevated after 15 minutes' hypoxia were markedly elevated after 4 hours' hypoxia, suggesting that the accumulation of lactate under hypoxic conditions is time-dependent.

In 1923, Hill and Lupton described a series of experiments in which subjects performed exercise ranging in intensity from mild (running at 12 $km.h^{-1}$ at zero grade for five minutes) to severe exhausting exercise (violent gymnastic exercises for 30 seconds), and including a wide range of exercises of intermediate intensities. Using the assumption that the recovery "excess" oxygen (that is, the post-exercise oxygen intake which exceeds normal resting requirements) is used entirely for oxidative removal of "lactic acid", Hill and Lupton (1923) calculated that one litre of "oxygen debt" (see Appendix Two) reflected a post-exercise blood "lactic acid" concentration of around 8 gramme-molecules (approximately 8 $mmol.l^{-1}$).

Although the above assumption is now known to be incorrect, Hill and Lupton used the excess oxygen uptake both during exercise and recovery to calculate "lactic acid" production, and came to the following conclusions :

1) During prolonged steady-state exercise, blood "lactic acid" levels attained a steady value until "the exercise reaches a severity greater than can be maintained on a contemporary supply of oxygen". Muscle "lactic acid" increased gradually from the start of exercise, resulting in a simultaneous increase in the rate of oxidation, until a steady-state was reached where the rates of "lactic acid" production and oxidation were balanced - provided the oxygen supply was adequate. These conclusions were drawn from the fact that the post-exercise excess oxygen consumption increased linearly with the duration of the preceeding exercise up to an exercise duration of about 120 seconds (figure 1). Thereafter, the excess post-exercise oxygen consumption remained steady at a value that depended on the exercise intensity.

2) The fact that "lactic acid" was produced even at moderate exercise levels, and that a balance was achieved between "lactic acid" production and removal rates (evidenced by a constant post-exercise excess oxygen uptake regardless of

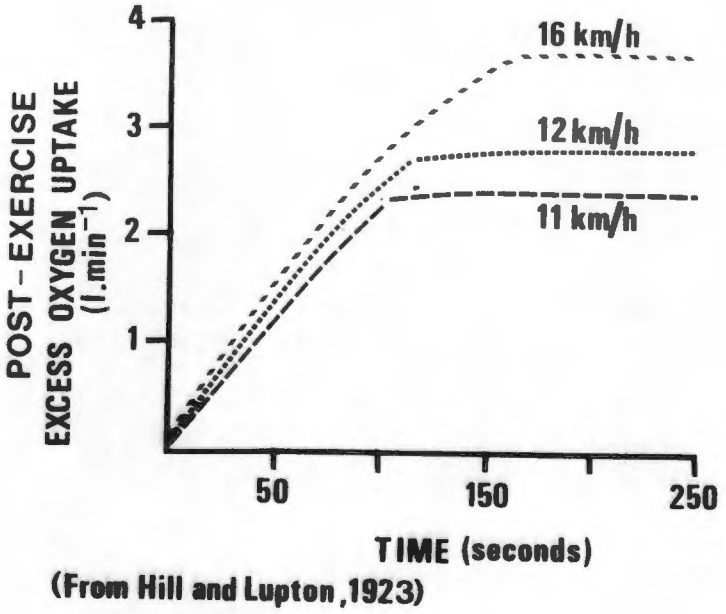



FIGURE 1

The "excess" post-exercise oxygen consumption increased rapidly with the duration of the preceeding exercise and then remained constant during various levels of steady-state exercise. Hill and Lupton (1923) proposed that the excess oxygen uptake was required for oxidation of "lactic acid" produced at all exercise intensities; since the steady-state oxygen uptake varied according to the exercise intensity these authors concluded that the rate of lactate production was also determined by the exercise intensity.

the duration of the exercise) led to the conclusion that "lactic acid" accumulation did not occur only in the absence of oxygen.

3) Similarly, since the oxygen debt (see Appendix II) was higher with higher exercise intensities, Hill and Lupton (1923) concluded that the rate of "lactic acid" production was determined by the exercise intensity.

4) The authors established that there appeared to be some critical running speed where there was a continuous accumulation of "lactic acid" - indicated by a progressive increase in the post-exercise excess oxygen uptake - culminating in exhaustion and cessation of exercise. They concluded that this occurred when the intensity of the exercise exceeded that which could be sustained by aerobic metabolism.

Although all of Hill and Lupton's reasoning is intuitive and based solely on measurement of the excess oxygen uptake after exercise, they put forward the suggestion that severe, continuous exercise was limited by the oxygen supply whilst, during moderate exercise, the rate of "lactic acid" oxidation in the muscles was the major factor limiting performance.

Thus as early as 1923, it was suggested that "lactic acid" was not only produced under conditions of anaerobiosis, but also at all exercise intensities. Hill and Lupton suggested that it was an inability to oxidise the lactate produced that caused the elevated blood lactate levels at low work intensities, rather than muscle hypoxia.

In a subsequent review, Hill, Long and Lupton (1925) discussed the nature of the recovery process after exercise in man, and defined two phases of recovery :

A) The first rapid phase of recovery which they attributed to the resynthesis of glycogen from the "lactic acid" in the active muscles where it had been formed, before the acid diffused into the blood stream. This phase occurred after very mild exertion, when the oxygen supply was adequate for the immediate resynthesis of glycogen from lactate.

B) The second, prolonged phase involving the transfer of lactate from the active muscles into the blood and its' transport to other tissues of the body for "oxidative removal". They believed that this occurred when muscle hypoxia prevented the oxidative resynthesis of lactate to glycogen.

Based on the above definition of the recovery phases, Hill et al. (1925) considered that the difference between moderate and severe exercise was that "moderate" exercise led only to the rapid, first phase recovery pattern, while severe or prolonged exercise involved both the initial rapid phase and the more protracted second phase. They argued that the oxygen supply was always adequate during moderate exercise, allowing for any lactate produced during exercise to be rapidly resynthesised to glycogen. Severe exercise, on the other hand, involved a temporarily inadequate oxygen supply which prevented lactate resynthesis in the exercising muscles so that lactate escaped into the blood and was transported to other organs and tissues. This resulted in a prolonged recovery and extended period of fatigue. This slow process would result in a slower repayment of the oxygen debt.

Jervell (1928) was the next to investigate the concentration of "lactic acid" in the blood during cycle ergometer exercise under the following conditions :

A) Constant workloads at different intensities, each lasting five minutes.

   The "lactic acid" concentration increased at the onset of exercise regardless of the exercise intensity, but this increase was greater at the higher intensities. Thereafter,

if the speed was increased further, there was a further increase in the "lactic acid" levels; if the speed was reduced, "lactic acid" levels decreased.

Jervell concluded that the venous "lactic acid" concentration depended on the amount of work done per minute, and that when the work done was greater than that which could be supported by the available oxygen supply, venous lactate levels would increase. Similarly, a decrease in the venous lactate concentration was taken to indicate that lactate was being resynthesised to glycogen, thereby indicating that the oxygen supply exceeded the requirements of the cells.

B) Constant workload lasting 15 minutes.

Up to an intensity of 130.8 watts, venous lactate levels increased very slightly and remained constant until the work intensity was again increased, when there was a further rise in blood lactate concentrations. This was again interpreted as indicating that oxygen intake was less than the oxygen requirements - the greater the work output per minute, the more quickly would the oxygen deficiency develop and therefore the more rapid the rise in venous lactate concentrations.

C) Constant workload lasting 20 - 60 minutes.

Having concluded that the elevated blood lactate concentrations were determined by the exercise intensity, Jervell proposed that during moderate, long-term exercise no significant increase in blood lactate would occur. However, his results showed an increase in blood lactate levels under these conditions and, since at moderate exercise levels the oxygen requirement was submaximum, Jervell suggested that this must result from a circulatory deficiency. He theorised that the circulation of blood did not increase to the same extent as the demand for oxygen, resulting in relative muscle hypoxia at the onset of exercise.

D) Exercise with different oxygen concentrations in the inspired air.

Venous lactate levels increased only when a gas mixture containing 7.5% or less oxygen was inspired; this increase did not occur when mixtures containing 10%, 20% or 100% oxygen were inspired.

Owles (1930) carried Hill, Long and Lupton's classification of exercise one step further by studying the blood lactate levels during light exercise. He studied two subjects who walked around a track at 6.5 - 7.2 $km.h^{-1}$ for 30 minutes. Venous blood samples were taken immediately after exercise stopped, and after

five minutes' rest. Similar tests were performed during exercise of an equivalent intensity on a cycle ergometer, with blood samples being taken at rest, five minutes before the end of exercise, and immediately after exercise. While blood lactate levels did not increase above resting values during the walking test, levels were slightly elevated on the cycle, even though both exercises were conducted at the same oxygen uptake value. Owles considered that this was due to muscular adaptation to a particular exercise type, implying that trained muscle fibres produced less lactate than did untrained fibres.

In another study, one subject walked at different speeds, ranging from 6.5 - 8 $km.h^{-1}$. It was found that blood lactate levels increased as exercise intensity increased, and Owles concluded that there was a certain critical level of exercise intensity below which no increase in blood lactate levels occurred, but above which lactate levels were elevated. This level varied with exercise type and with training, and was different for different subjects. This is the first study clearly demonstrating a so-called "lactate turnpoint", which might therefore be referred to as the "Owles point".

In contrast to the assumptions of Hill et al. (1923), Owles showed that the oxygen debt in very light exercise bore no relation to blood lactate accumulation, because although an

oxygen debt was incurred at all exercise intensities, there was no increase in blood lactate levels during light exercise. Like all previous workers, he also concluded that muscles did not release lactate as long as their oxygen supply remained adequate.

Margaria, Edwards and Dill (1933) furthered the investigation of the relationship between blood lactate levels and the oxygen debt. A single subject participated in a series of experiments in which he exercised for ten minutes at workloads ranging from walking at 7.5 $km.h^{-1}$ at zero grade, to running at 14 $km.h^{-1}$ on a 4% grade. Blood lactate levels did not increase at workloads requiring less than 60% $VO_2max$, although the oxygen debt increased in proportion to the workload. Above this exercise intensity, blood lactate levels continued to increase. This apparent "lactate turnpoint" occurred at an absolute oxygen uptake of approximately 2.4 liters $min.^{-1}$, and the authors calculated that the lactate levels did not rise until the oxygen debt exceeded 3.0 liters $min.^{-1}$ (see figure 2).

Margaria et al. (1933) concluded that muscle lactate concentration depended on an equilibrium between the rates of lactate formation and removal. They suggested that the rate of lactate removal could not be increased during exercise since the oxygen tension in the working muscles was lower than in resting

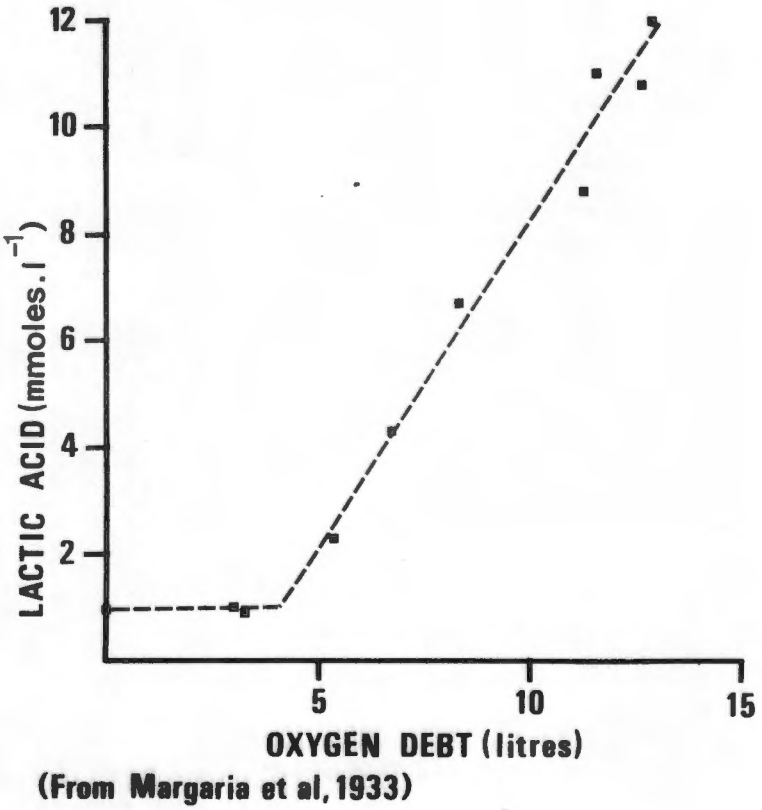



FIGURE 2

Blood lactate levels remained low up to a work intensity of 60% $VO_2$ max., and thereafter continued to increase, with the "lactate turnpoint" only occurring once the oxygen debt exceeded three litres.

muscles. Therefore since blood lactate levels remained low at workloads up to 60% $VO_2max.$, they concluded that muscular work below this intensity was accomplished without the production of lactate.

Cook and Hurst (1933) studied subjects walking for 30 minutes at 6.5 $km.h^{-1}$ and measured venous blood lactate levels at rest and immediately after exercise. In the case of men accustomed to walking for at least an hour daily, there was no increase in blood lactate levels until the speed of walking was increased beyond a "comfortable" pace, at which speed a rise in blood lactate levels occurred. With men not accustomed to walking for prolonged periods, blood lactate levels rose at speeds below 6.5 $km.h^{-1}$. They concluded that the threshold of exercise at which the lactate content began to increase was dependent "on the 'fitness' or 'training' of the individual".

Bang (1936) was the first researcher to study, in detail, blood lactate levels during and after moderate or severe, prolonged or short-term exercise in man. Subjects exercised on a cycle ergometer at various loads, ranging from 117.7 watts (moderate exercise) to 176.6 watts (severe exercise). Fingertip blood samples were drawn approximately every 45 seconds for the determination of blood lactate levels.

During moderately severe exercise, a sharp increase in the lactate concentration occurred shortly after the start of exercise. Bang called this the "primary rise" and attributed it to a phase of hypoxia at the onset of exercise, as had Jervell (1928). Contrary to previous results, Bang found that during steady-state low intensity exercise, lactate levels decreased after about five minutes of exercise, continuing to decrease whether the exercise was continued or discontinued. This finding was used by Bang to support the idea of an initial use of "anaerobic" energy supplies causing blood lactate levels to rise, whereas the falling blood lactate levels indicated that no further lactate was being produced and that the excess lactate was being resynthesised to glycogen. Since the rate of lactate resynthesis to glycogen was greater than the rate of lactate production, a fall in the blood lactate concentrations would result.

During "severe" exercise, Bang observed a "secondary" rise in the lactate levels which he suggested could be due to the recruitment of an increasing number of muscle fibres as the subject became fatigued (see figure 3).

In the next experiment, a single athlete exercised at four different workloads ranging from 176.6 - 264.9 watts for 20 - 90 minutes, depending on the intensity of the exercise. These

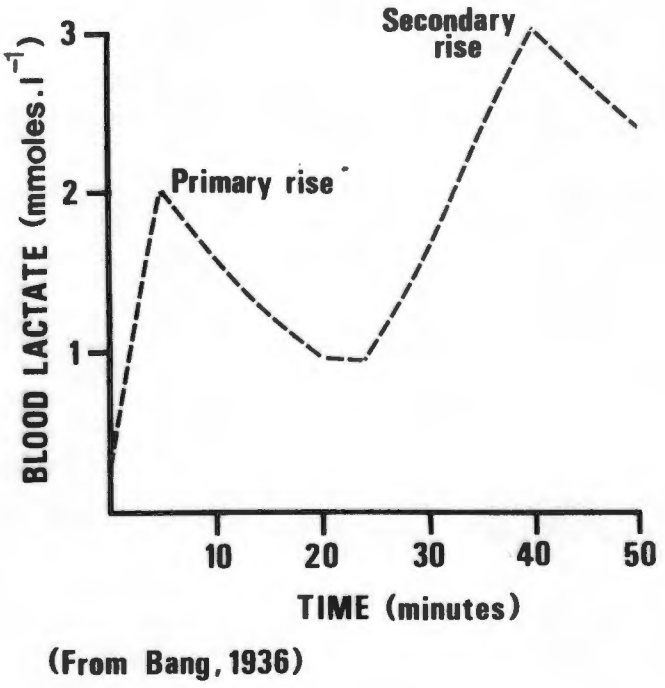


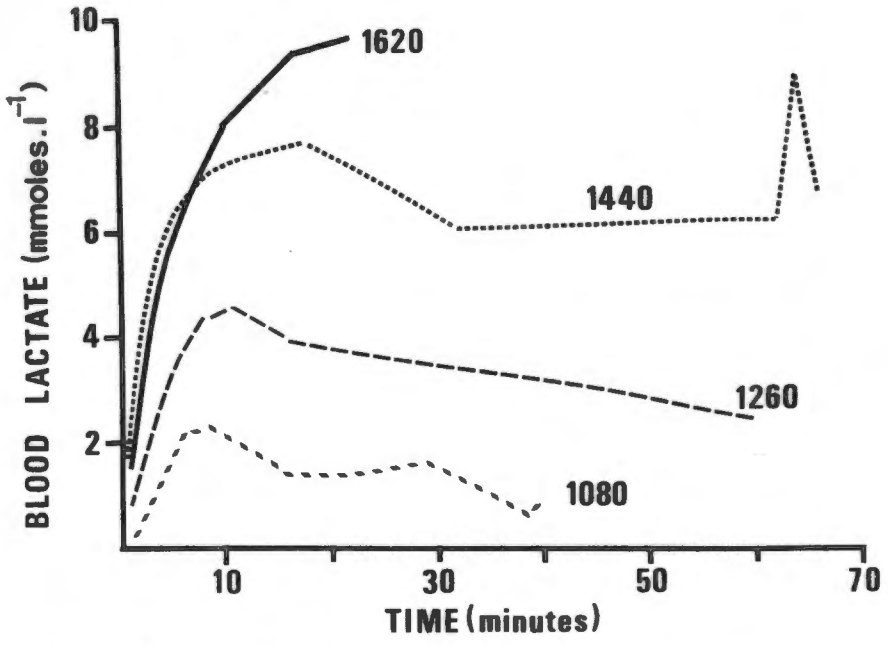

FIGURE 3

During moderately severe exercise, blood lactate levels increased at the start of exercise ("primary rise"), and then decreased over the remainder of the exercise period. During severe exercise, this primary rise was at times followed by a "secondary rise", and was attributed by Bang (1936) to increased fibre recruitment rather than to hypoxia.

studies showed that the rate of increase of blood lactate levels was proportional to workload, and that the peak lactate levels reached were higher for each workload (see figure 4).

In common with all previous workers, Bang considered that the increased lactate levels were due to muscle cell anaerobiosis resulting from inadequate tissue oxygenation during severe exercise. As a result, lactate production continued throughout exercise and did not decrease, as occurred during steady-state exercise of a lower intensity and longer duration.

The effect of the duration of the exercise on blood lactate levels was also studied. Very low or even basal levels were observed at the end of an exhausting 24 kilometer run . After exercise of short duration, blood lactate levels rose during the first five minutes of recovery, and Bang considered this to be due to the slow rate of diffusion of lactate from the muscles into the blood. This post-exercise rise did not occur in recovery from moderate exercise. Bang concluded that, since maximum lactate levels were observed only after exercise lasting approximately seven munutes, exercise lasting only five minutes would result in lactate levels which continued to rise during the recovery period. He suggested that there is an initial "pooling" of lactate in the muscles at the start of exercise which must be removed during recovery, resulting in a delay in




(From Bang, 1936)

FIGURE 4

Blood lactate levels increased in proportion to the intensity of exercise, as previously postulated by Hill and Lupton, 1923 (see figure 1).

the diffusion of lactate from the muscles into the blood.

Bang also studied the effect of training on the lactate curves of two subjects, and found that after two months' training, blood lactate levels remained low during exercise intensities which had previously caused marked elevation. Bang listed three factors that could possibly explain this effect of training :

A) Well-trained individuals worked more economically and did not employ untrained muscles.

B) The oxygen supply to the muscles was improved by training as a result of an increased number of muscle capillaries.

C) In trained individuals, oxygen uptake rose more rapidly so that a steady-state was reached sooner than in untrained individuals.

Bang thus explained his findings on the basis that training reduced the degree of anaerobiosis during exercise.

In summary, Bang refuted Hill and Lupton's theory (1923) of continuous lactate production and removal during exercise and suggested instead that lactate production occurred only when there was an inadequate oxygen supply, which could occur either

at the start of exercise or in the course of very strenuous exertion. On the other hand, the actual rise in blood lactate levels was directly related to the intensity of exercise, resulting in step-like increases in blood lactate concentration with increasing workloads, (see figure 4). This was considered to be due to increased fibre recruitment and anaerobiosis as the exercise intensity increased. This is in direct contrast to Margaria et al's concept (1933) of a single turnpoint (see figure 2).

Robinson and Harmon (1941) similarly studied the effects of training on the blood lactate response to exercise. Observations were made on nine subjects before training started, and at regular intervals over a six week training period. The exercise tests involved two protocols of moderate exercise lasting 10 - 15 minutes, and one four minute run to exhaustion. They found that the resting lactate levels were not altered by training, but that during both submaximal and exhaustive exercise, the lactate levels were much lower after training. Trained subjects were also able to exercise for much longer, reaching higher final lactate values (18 $mmol.l^{-1}$ compared to 13 $mmol.l^{-1}$ at exhaustion). Thus training prevented the initial lactate rise and allowed the athletes to continue exercising despite much higher blood lactate levels. The researchers concluded, as had Bang, that training had improved both the oxygen supply to the

tissues and the ability of the fibres to utilise oxygen, resulting in less muscle anaerobiosis.

Crescitelli and Taylor (1944) studied blood and urine lactate responses to exercise in a group of men of various fitness levels. They found that during prolonged submaximal exercise lasting 15 minutes, blood lactate levels increased rapidly at the onset of exercise, reached a peak and then decreased without attaining a constant blood level. This is similar to Bang's findings during submaximal exercise (see figure 3). No post-exercise increase occurred after submaximal exercise, and levels dropped as soon as the exercise was stopped. These results were interpreted as an indication that equilibrium between the rates of production and resynthesis of lactate was not attained during the submaximal exercise. They suggested, as had Bang in 1936, that an inadequate oxygen supply at the start of exercise caused the initial increases in blood lactate levels, but that once steady-state had been reached lactate removal was more rapid than production resulting in decreased lactate levels.

During maximal exercise, as before blood lactate levels rose from 4 $mmol.l^{-1}$ to 24 $mmol.l^{-1}$, and increased even further during recovery, returning to resting levels only 30 - 90 minutes after the cessation of exercise. Urine lactate levels

increased after both submaximal and maximal exercise, with the major increase occurring 10 - 20 minutes after exercise ended. By 40 - 50 minutes, the urinary lactate levels had returned to resting levels. Fit subjects had lower urinary lactate excretion, lower post-exercise blood lactate levels, lower heart-rates, a higher oxygen consumption and a lower ventilation rate, apparently supporting Robinson and Harmon's suggestion (1941) that trained subjects had an improved ability to prevent muscle anaerobiosis.

In summary, these early studies provided the following information :

A) All researchers explained the increased blood lactate concentrations on the basis of "anaerobiosis" caused by an inadequate oxygen supply within the exercising muscles. Bang (1936) also suggested that the recruitment of untrained fibres could cause elevated blood lactate levels as the subject became fatigued, even when the oxygen supply to the exercising muscles was adequate.

B) Blood lactate levels during exercise are influenced by the intensity of effort, remaining at basal levels up to a certain workload (Owles, 1930; Margaria et al, 1933) and thereafter increasing as work intensity increased. Hill and

Lupton (1923) showed that lactate levels during moderate exercise increased and then remained constant at a level which depended on the exercise intensity, or increased continuously during severe exercise. Jervell (1928) also found that lactate levels increased at the onset of exercise regardless of the exercise intensity, and continued to increase with an increasing exercise intensity. During moderate exercise, levels decreased if the exercise intensity was reduced or remained constant.

C) Blood lactate levels are influenced by the duration of exercise. Ryffel (1909) and Bang (1936) found that blood lactate levels did not increase during prolonged low intensity exercise. On the basis of their studies of oxygen debt, Hill and Lupton (1923) hypothesised that blood lactate levels are always elevated during prolonged exercise but remain constant at a level dependent on the exercise intensity. On the other hand, Bang (1936) and Crescitelli and Taylor (1944) found that during prolonged exercise, blood lactate levels reached a peak and then decreased during the remainder of the exercise period without ever reaching a steady-state. The main reason for the discrepancies is that Hill and Lupton based these hypotheses on observations of the excess post-exercise oxygen uptake rather than actual blood lactate measurements. Since the

elevated post-exercise excess oxygen uptakes occured at all exercise levels, they would not have been able to pick up a drop in lactate levels which may have occurred at the lower exercise intensities (as observed by Bang, 1936, and Crescitelli and Taylor, 1944).

D) Blood lactate levels are influenced by training.
Cook and Hurst (1933) demonstrated that the blood lactate levels started to increase at lower workloads in untrained than in trained subjects. Bang (1936) and Robinson and Harmon (1944) found that while there were no differences in basal blood lactate levels between trained and untrained subjects, lactate levels at equivalent workloads were significantly lower in trained subjects. During exhaustive exercise, trained subjects were able to exercise for longer than untrained subjects, despite higher final blood lactate levels.

E) The post-exercise oxygen debt was attributed to the oxidative resynthesis of glycogen from lactate.

In the following sections, we shall look more carefully at the more recent research on each of these observations.

## 2.2 MORE MODERN STUDIES OF THE BIOCHEMICAL BASIS FOR ELEVATED BLOOD LACTATE LEVELS DURING SUBMAXIMAL AND MAXIMAL EXERCISE: ANAEROBIOSIS VERSUS GLYCOLYTIC OVERFLOW.

As the exercise intensity increases, so the increased utilisation of ATP results in elevated intracellular ADP, Pi and AMP levels. These in turn activate glycolysis by stimulating the activity of the key glycolytic enzymes, glycogen phosphorylase and phosphofructokinase (Newsholme and Start, 1973). Increased glycolytic flux generates increased amounts of pyruvate. In the presence of sufficient oxygen, pyruvate enters the mitochondria where it is oxidised in the Krebs cycle. However, during hypoxia or anoxia, the mitochondrial oxidative capacity is reduced and pyruvate may accumulate in the cytoplasm where, under the action of lactate dehydrogenase, the following reaction occurs :

$$\text{PYRUVATE} + \text{NADH} + H^+ \longrightarrow \text{LACTATE} + NAD^+$$

The importance of this reaction is that it regenerates NAD, allowing glycolysis to continue (see diagram 1).

Similarly, it is possible that when glycolysis is maximally stimulated, as occurs during maximal exercise, the substrates for lactate dehydrogenase, pyruvate and hydrogen ions, may accumulate and, under the action of that enzyme, be converted preferentially to lactate, rather than enter the mitochondria, even though the muscle is not hypoxic. This formation of lactate

# GLYCOLYSIS

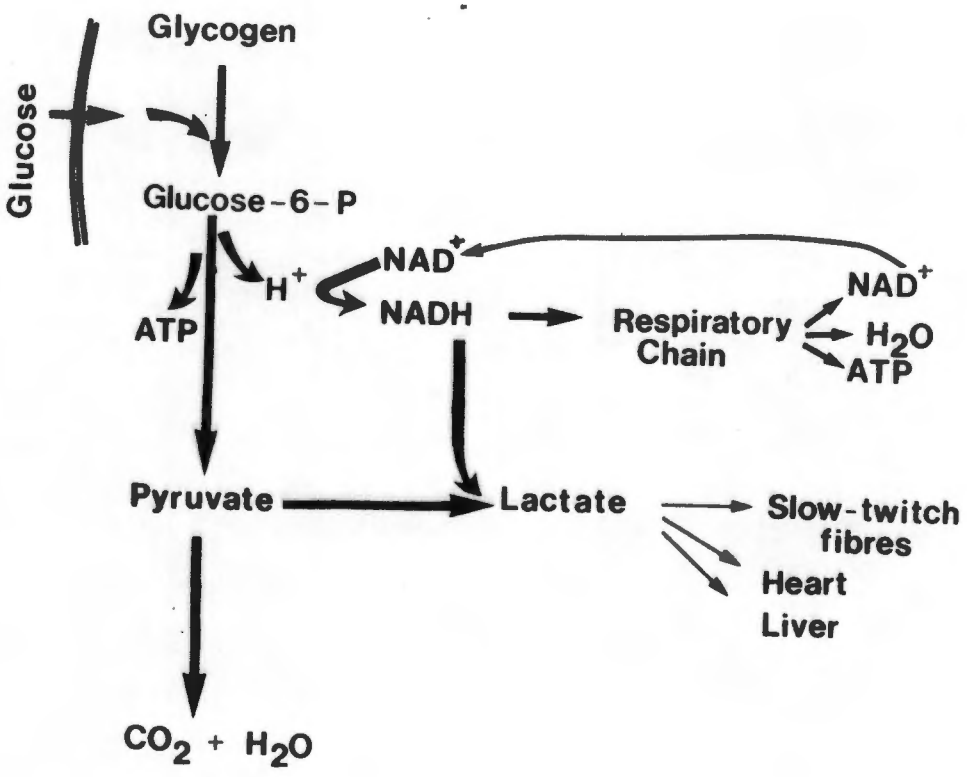



DIAGRAM 1

Schematic representation of glycolysis.

occurs because the mitochondrial capacity to oxidise pyruvate appears to be exceeded under such conditions of maximal glycolytic stimulation.

These two different possibilities identify the two major schools of thought explaining why lactate is produced during exercise :

A) The anaerobic school : those who believe that an insufficient supply of oxygen to the working muscles causes increased rates of lactate production during exercise.

B) The glycolytic overflow school : those who believe that tissue anaerobiosis does not occur during exercise, but that during maximal exercise the mitochondrial capacity for pyruvate and proton transfer is exceeded, resulting in the preferential formation of lactate.

A) <u>ANAEROBIOSIS.</u>

Fletcher and Hopkins (1907) showed convincingly that an insufficient oxygen supply to resting or exercising muscles in isolated tissue caused an increased rate of lactate formation, and that the re-introduction of oxygen after a period of anaerobiosis resulted in a marked decrease in the rate of lactate production. Ryffel (1909) also established that blood lactate accumulation under hypoxic conditions at rest was

time-dependent, since lactate levels which were only slightly elevated after 15 minutes' hypoxia were markedly elevated after four hours' hypoxia.

Hill and Lupton (1923) hypothesised that elevated lactate levels during exercise were due to muscle hypoxia occuring when the exercise severity reached an intensity greater than that which could be maintained by the available oxygen supply, and the majority of subsequent researchers have accepted this explanation (Hill, Long and Lupton, 1925; Margaria et al, 1933; Bang, 1936; Robinson and Harmon, 1941; Crescitelli and Taylor, 1944; Wasserman and McIlroy, 1964; Wasserman et al, 1973).

More direct evidence for this hypothesis comes from the studies of Lundin and Strom (1947) who measured blood lactate levels during steady-state exercise while subjects breathed air containing oxygen at concentrations varying from 10 - 50%. In all of the experiments, blood lactate levels reached a steady-state at some stage during the 50 minute test, in spite of a decreased oxygen content in the inspired air. However, the fact that the blood lactate levels were significantly higher at low oxygen partial pressures, at the same work intensity (147.2 watts), was interpreted by the authors as indicating tissue hypoxia, causing increased lactate production (see figure 5).

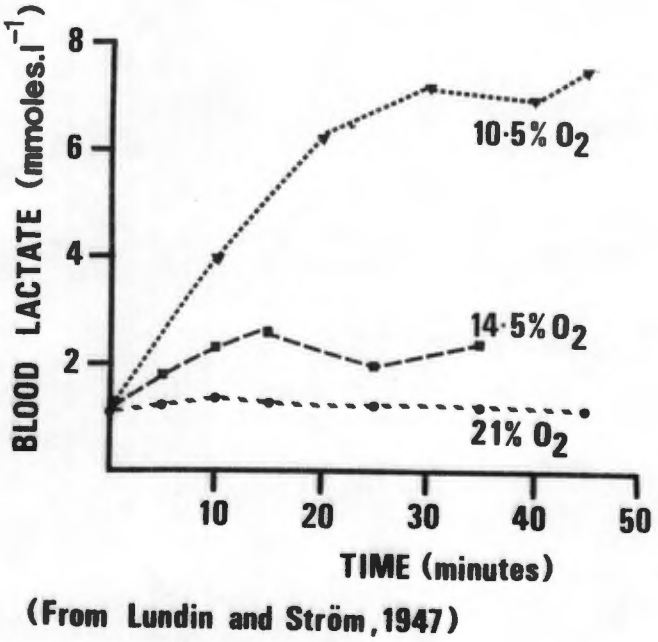



FIGURE 5

Blood lactate levels during exercise at 550.5 watts were significantly higher in subjects who inspired air with a reduced oxygen content.

In contrast, Asmussen, Dobeln and Nielsen (1948), who exercised subjects under hypoxic conditions by having them breathe a 12% oxygen-nitrogen mixture, found that during steady-state exercise the lactate concentration was in fact practically unchanged and even slightly lower when breathing 12% oxygen, as compared to room air or 100% oxygen. During maximal work, lactate concentrations were the same whether the subjects breathed normal room air or 100% oxygen, but were distinctly higher when 12% oxygen was inhaled.

The authors considered that the difference in blood lactate levels observed between the steady-state test and the maximal test when inspiring 12% oxygen was due to varying diffusion times. They suggested that levels observed during the steady-state test were the same as those measured during the maximal test because the latter test lasted for a shorter time. This resulted in there being less time for the lactate to diffuse out of the muscles and into the blood. This conclusion was made even though lactate levels were measured for three to six minutes after exercise, at which time maximal lactate levels are usually recorded (Freund and Gendry, 1978) and which should be sufficient time for lactate to diffuse into the blood if the intra-muscular concentration is high enough. Thus it seems likely that the different levels were not due to an inadequate diffusion period after exercise.

A further interesting finding in that paper was that the lactate levels were the same whether 21% oxygen or 100% oxygen was breathed, which tends to negate the idea that an insufficient oxygen supply results in an increased lactate concentration. Were this the case, subjects should have been able to continue exercising while breathing 100% oxygen without increasing blood lactate levels. The authors chose to ignore this observation, however.

Linnarson, Karlson, Fagraeus and Saltin (1974) investigated the probability of a relationship between hypoxia, blood lactate and muscle lactate levels by exercising subjects at inspired oxygen tensions ranging from 13.2 kPa through 19.9 kPa to 28.3 kPa (normal resting = 20 kPa). Performance time increased significantly as oxygen tensions increased, while lactate accumulation in the working muscles varied inversely with the inspired oxygen tensions during submaximal exercise; that is, muscle lactates were highest at an inspired oxygen tension of 13.2 kPa (7 $mmol.l^{-1}$) and lowest at 19.9 kPa (3 $mmol.l^{-1}$). Similarly, blood lactate concentrations paralleled muscle lactate concentrations so that blood lactate levels were highest during hypoxia (4 $mmol.l^{-1}$) and lowest during hyperoxia (2 $mmol.l^{-1}$.

These authors also measured the glycolytic intermediates

(glucose-6-phosphate and pyruvate) which did not decrease with decreasing inspired oxygen tension, indicating that glycolysis was not stimulated under conditions of hypoxia. They concluded that tissue hypoxia and not glycolytic overflow explained lactate formation at the start of exercise, since less oxygen was used at the lowest oxygen tension during the first four minutes of submaximal work, and this corresponded to the highest blood lactate levels.

Finally, Jorfeldt et al. (1978) demonstrated a relationship between intramuscular lactate concentrations and low femoral venous saturation levels, with muscle lactate levels increasing as venous saturation decreased. However, they did not measure the oxygen content in the mitochondria, and it may well be that even at low venous oxygen saturations the mitochondria still have sufficient oxygen for normal function.

Not all research, however, supports a relationship between hypoxia or "anaerobiosis" and lactate production. Hill and Lupton (1923) suggested that since a steady-state in lactate levels could be attained during prolonged steady-state exercise, anaerobiosis alone could not explain increased rates of lactate production. Saiki, Margaria and Cuttica (1967) also observed steady-state lactate concentrations during submaximal exercise and concluded that no lactate was therefore being produced. As a

decrease in lactate levels occurred in some cases, they suggested that this indicated that the oxygen supply was more than adequate, even at exercise intensities of up to 70% $VO_2max$.

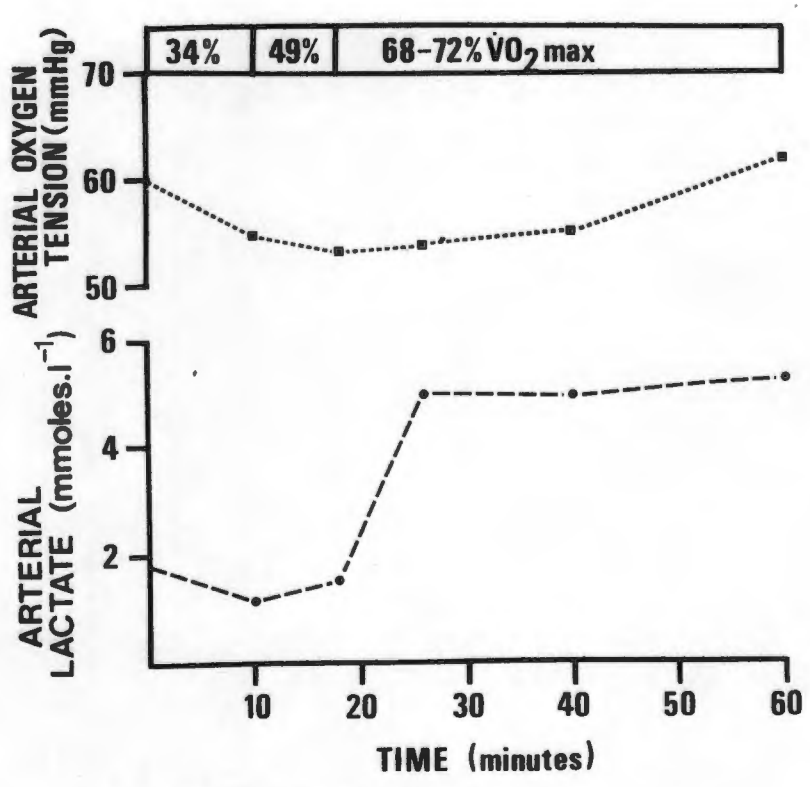
Whipp and Wasserman (1969) studied only gas parameters during exercise without relating them to either blood or muscle lactate levels. On the basis that arterial oxygen tensions did not decrease during moderate exercise, they argued against the anaerobiosis theory of lactate production during exercise. They did however consider that diffusion may be a significant factor limiting oxygen transport during high intensity exercise. This in turn would stimulate glycolysis causing blood lactate concentrations to rise. They suggested that tissue oxygen deficiency was not due to inadequate oxygen transport to the muscles, but might be due to diffusion limitations within the muscle.

Dempsey, Thompson, Forster, Cerny and Chosy (1975) examined subjects exercising on a treadmill at 250 meters and 3100 metres altitude. Subjects walked continuously for nine minutes at 34% $VO_2max$., nine minutes at 49% $VO_2max$., and to exhaustion at 68% $VO_2max$. Arterial oxygen content decreased in the first 18 minutes of exercise while workload was increasing, whereas arterial lactate levels actually decreased slightly from 1.8

mmol.$l^{-1}$ to 1.5 mmol.$l^{-1}$. This would apparently indicate little relationship between the available oxygen supplies and the rate of lactate production, since a fall in arterial oxygen tension should be followed by an increase rather than a fall in the blood lactate concentration. Conversely, during the last 40 minutes of exercise at 68%$VO_2$max., arterial oxygen tension gradually increased to 0.4 - 0.5 kPa above starting levels, while lactate levels rose sharply from 2 mmol.$l^{-1}$ to 4 mmol.$l^{-1}$ and then remained constant for the duration of the test (see figure 6).

The working muscle was able to continue exercising, even though venous oxygen tensions were as low as 1.3 - 2 kPa, without significant increases occurring in the glycolytic rate. Dempsey et al. (1975) concluded that capillary oxygen tensions at sea level and at 3100 metres altitude would have provided a more than adequate diffusion gradient, even without acclimatisation, for subjects to maintain a steady-state level of aerobic energy production during prolonged exercise at workloads requiring up to 72% $VO_2$max.

Subsequently, Dempsey, Hanson, Pegelow, Claremont and Rankin (1982) reported that during steady-state exercise beyond the "lactate turnpoint", the arterial oxygen tension remained within 0.7 kPa of resting levels, and that arterial oxygen saturation




(From Dempsey et al, 1975)

FIGURE 6

At low exercise intensities, both arterial lactate levels and arterial oxygen content decreased, whereas both these parameters increased at higher exercise levels. This appears to refute the theory that inadequate tissue oxygenation cause elevated blood lactate levels during exercise.

fell only three to five per cent due to hyperthermia and metabolic acidosis. However, this mild desaturation was usually offset by increased oxygen extraction by muscle, as shown by lower venous oxygen content.

Dempsey et al. (1982) also found that exercise-induced arterial desaturation occurred only in heavy work requiring more than 85% $VO_2$max., and therefore elevated blood lactate levels at submaximal exercise intensities were not likely to be caused by an inadequate oxygen supply.

Dempsey et al. (1982) also tested 20 trained runners during a maximal treadmill test and found that, in all cases, arterial oxygen tension decreased slightly after the first 30 seconds of exercise, but that sufficient hyperventilation occurred to partially compensate for the metabolic acidosis and to raise the alveolar oxygen levels. Although these researchers did not study blood lactate concentrations, their conclusions are pertinent to the theory of anaerobiosis because they showed that arterial hypoxaemia during maximal exercise is mild and is not a consistent finding during short-term, high intensity work.

Thomas, Gaos and Vaughan (1965) found that blood lactate levels rose during exercise without an increase in the oxygen debt and suggested the following reasons, besides anaerobiosis and

increased lactate production, for the development of an oxygen debt:

A) Hyperthermia, resulting in an elevated oxygen consumption.

B) Restoration of oxygen stores within the body.

C) An increased oxygen consumption as a result of an increased work of breathing.

Davis, Bassett, Hughes and Gass (1983) first exercised subjects on a progressive protocol until exhaustion. This caused lactate levels to be about seven times higher than resting concentrations, and these levels subsequently decreased when subjects exercised at intensities far exceeding the "anaerobic threshold" (around 45% $VO_2$max.). They concluded that sufficient oxygen was available for lactate removal during exercise at up to 75% $VO_2$max.; higher exercise intensities caused blood lactate levels to rise sharply. These results are therefore not consistent with either the hypothesis that oxygen availability or a limited oxidative capacity within the muscle is responsible for the onset of "anaerobic" glycolysis at the anaerobic threshold.

In a more recent study, Hogan, Cox and Welch (1983) examined

blood lactate levels during progressive exercise at different inspired oxygen tensions, and found that the blood lactate levels were significantly lower during hyperoxia (60% oxygen), and significantly higher during hypoxia (17% oxygen) when compared to normoxia, even though the oxygen uptake was the same at any workload - regardless of the oxygen content of the inspired air. This further suggests that anaerobiosis does not explain muscle lactate production.

To summarise then, the major findings concerning the theory of anaerobic production of lactate during exercise are:

A) Lactate production can occur as a result of an inadequate oxygen supply which stimulates anaerobic glycolysis in vitro:

Fletcher and Hopkins (1907) established that an inadequate oxygen supply under either resting or exercise conditions resulted in a more marked accumulation of lactate. It appears that these results have influenced a majority of subsequent workers, including Hill, Long and Lupton (1925); Margaria et al, (1933); Bang, (1936); Wasserman and McIlroy, (1964); Saiki et al, (1967); and Wasserman et al. (1973).

Further support for this interpretation comes from Lundin and Strom (1947) and Asmussen et al. (1948) who showed that

blood lactate levels during exercise increased as inspired oxygen tension decreased.

B) On the other hand, others have shown that blood lactate accumulation and an inadequate oxygen supply are not necessarily related :

The major observation to support this is that the mild arterial hypoxaemia that occurs during severe exercise is insufficient to constitute a limitation in the oxygen supply to the muscles (Whipp and Wasserman, 1969; Dempsey et al, 1975; Dempsey et al, 1982). Similarly Thomas et al. (1965) examined lactate accumulation and the oxygen debt and concluded that hypoxia was not a direct cause of elevated lactate levels. Thomas et al (1965) proposed alternative causes of the oxygen debt, in particular hyperthermia, restoration of oxygen stores and an increased work of breathing.

B) <u>GLYCOLYTIC OVERFLOW.</u>

Jobsis (1963) and Keul, Doll and Keppler (1967) found that lactate was released from muscle during exercise even in the presence of high venous oxygen tensions. Doll et al. (1968) reported venous oxygen tensions of 2.8 kPa during strenuous exercise when muscles were producing large amounts of lactate, and concluded that lactate production was not the result of

muscle hypoxia.

Saltin et al. (1976) reported that lactate release from an endurance trained leg was significantly less than from the untrained leg at the same submaximal exercise levels, even though the blood flow and oxygen consumption were the same for both legs.

Ivy et al. (1981) considered these results and proposed that the accumulation of blood lactate during submaximal work was not due to muscle hypoxia, but was caused by an imbalance between pyruvate oxidation and "anaerobic" glycolysis. Holloszy (1973) stated that these findings should not be a surprise in view of the high levels of lactate dehydrogenase in skeletal muscle compared to relatively low mitochondria affinity for pyruvate. He reasoned that since pyruvate can be converted either to lactate or oxidised via the citric acid cycle, the comparatively high levels of LDH would result in an increased conversion of intracellular pyruvate to lactate when pyruvate and hydrogen levels increased. Although he did not discount the possibility that muscle hypoxia might occur during strenuous exercise, from the biochemical evidence Holloszy concluded that "it would be most remarkable if well-oxygenated skeletal muscle did not produce considerable lactate during rapid glycolysis". He also questioned the theory that lower lactate levels found in trained

as compared with untrained subjects are due to better oxygen delivery to the working muscles. If lactate production was caused by a limiting muscle oxygen supply during submaximal exercise, he reasoned that training would reduce lactate levels by increasing oxygen uptake at the same submaximal work levels. This, however, is not found. The majority of research shows that oxygen uptakes remained unchanged or slightly decreased during submaximal exercises after training (Williams et al, 1967; Wyndham et al, 1969), even though blood lactate levels are reduced. Similarly, an increased blood flow to the exercising muscles could not be responsible for improved oxygen supply since reduced muscle blood flow has usually been found after training (Holloszy and Booth, 1976; Klausen et al, 1974). However it should be noted that increased capillarisation occurs with endurance training, and this may result in improved oxygen delivery to exercising muscles even in the face of a reduced skeletal muscle blood flow (Andersen and Henriksson, 1977).

Finally, Jones and Ehrsam (1982) have argued that, since exercise can be maintained for prolonged periods with constant, albeit elevated, blood lactate levels, the muscle could not be hypoxic, but must instead have an increased glycolytic rate. This evidence is supported by the results of Doll et al. (1968) and Dempsey et al. (1975) discussed in the previous section. In both cases, reduced arterial oxygen tensions were observed, but

without the concomitant increases in blood lactate concentrations that were expected. Jones and Ehrsam (1982) concluded that lactate production does not necessarily result from tissue hypoxia but indicates instead that rapid glycolysis is occurring with possible changes in muscle fibre-type recruitment patterns. The concept that different fibre-type recruitment patterns explain elevated blood lactate levels is the third popular biochemical theory explaining lactate production during exercise. This will be discussed in detail subsequently.

In support of these arguments, several studies have shown that lactate production occurs during submaximal exercise, even when the oxygen uptake remains constant. For example, Hubbard (1973) found that during prolonged steady-state exercise, oxygen uptake remained relatively constant, while blood lactate levels were maintained at two to four times their resting concentrations. With the use of radio-actively labelled lactate, Hubbard showed that lactate was rapidly removed from the blood even though the blood lactate concentration remained elevated, indicating that lactate was being continuously produced and oxidized while the oxygen uptake remained constant. She therefore queried the theory of anaerobiosis on the basis of the following three observations :

1) Resting muscles produce lactate.

2) Exercising muscles produced lactate even during steady-state, submaximal exercise when the oxygen uptake remained constant.

3) Venous oxygen content remains almost constant during submaximal exercise.

She proposed that lactate levels increased because the mitochondrial capacity for pyruvate oxidation was inadequate, and not because there was tissue hypoxia.

Using one-legged exercise to manipulate glycogen stores in a single leg, Gollnick, Pernow, Essen, Jansson and Saltin (1981) examined lactate levels in relation to the substrates oxidised during exercise under normal dietary conditions, with one leg having low initial glycogen levels, and with lipolysis inhibited. They found that during exercise, the muscles with low glycogen levels extracted lactate from the blood while the leg muscles with normal glycogen levels released lactate, indicating that the glycogen stores influenced lactate production. The finding that lactate was extracted from the blood by one leg and released by the other leg at the same exercise level, when oxygen supply to both legs was the same, led them to conclude that lactate is not produced only as a result of anaerobiosis.

that lactate is not produced only as a result of anaerobiosis.

To determine the metabolic fate of lactate during exercise, Mazzeo, Brooks, Budinger and Schoeller (1982) injected labelled lactate into two subjects at rest, during "easy" exercise lasting two hours at 53% $VO_2max.$, and during "heavy" exercise lasting 45 minutes at 74% $VO_2max.$ Resting blood lactate levels remained constant at around 1 $mmol.l^{-1}$ throughout the test; during "easy" exercise, blood lactate concentrations rose slightly above rest and then remained constant (8 $mmol.l^{-1}$) in one subject, but decreased gradually in the other. Analyses of respiratory gases showed that the rate of oxidation of lactate was higher during heavy exercise, and the authors suggest that the extent of lactate oxidation was related to both the blood lactate concentration and to the intensity of exercise. Even during rest and "easy" exercise, lactate production and oxidation occurred, and Mazzeo et al. (1982) concluded that tissue hypoxia was not the only circumstance under which lactate was produced.

In summary, the majority of researchers favour the theory that glycolytic overflow explains the increased rate of production of lactate during submaximal exercise :

A) Jobsis (1963) and Keul et al. (1967) reported lactate

release even in the presence of high venous oxygen tensions, while, conversely, Doll et al. (1968) and Dempsey et al. (1975) showed that low oxygen tensions were not accompanied by elevated lactate levels.

B) Mazzeo et al. (1982) found that lactate was both produced and oxidised while the oxygen uptake remained constant. Jones and Ehrsam (1982) concluded that the muscle could not be hypoxic if exercise could be maintained for prolonged periods with elevated but constant blood lactate levels.

C) Williams et al. (1967) and Wyndham et al. (1969) reported reduced blood lactate levels as a result of training, even though oxygen uptake was unchanged, or even slightly reduced at that workload. Saltin (1976) went one step further when he compared lactate release and oxygen consumption between an untrained leg and a trained leg, and found that the trained leg released less lactate even though the oxygen consumption was the same in both legs. While this finding introduces the effect of training adaptations on blood lactate levels, it adds weight to the theory of glycolytic overflow in preference to "anaerobiosis".

## 2.3 STUDIES OF FACTORS INFLUENCING BLOOD LACTATE LEVELS DURING EXERCISE.

### A) THE INTENSITY OF EXERCISE.

#### I) Blood lactate levels during progressive exercise of increasing intensity. Evidence for single or multiple "lactate turnpoints".

As reviewed, Hill and Lupton (1923) postulated that the lactate concentration increased at the point where the exercise intensity caused tissue hypoxia, and Owles (1930) was the first researcher to demonstrate this "lactate turnpoint". He studied blood lactate levels in a subject exercising at various intensities and showed a definite point where the lactate concentration increased abruptly. Margaria et al. (1933) demonstrated this curve in relation to the oxygen debt (see figure 2), establishing that up to exercise intensities involving 66% $VO_2$max. venous lactate levels remained constant, but above that exercise intensity, the lactate concentration increased rapidly as a result, they thought, of "anaerobic" metabolism.

Wyndham, Strydom, Williams and von Rahden (1962) studied the rise in blood lactate concentrations above basal levels in relation to oxygen uptake and workrate, and their findings

supported Margaria et al's concept (1933) of a distinct turnpoint. Wyndham et al (1962) studied highly trained mine workers on a cycle ergometer and established that workloads greater than 55% $VO_2max$. caused blood lactate levels to rise. According to these workers, "anaerobic metabolism" occurred where the oxygen supply to the working muscles was insufficient for the rate of energy expenditure, resulting in elevated blood lactate levels. This level of 55% $VO_2max$. was consequently established as the point at which the lactate concentration increased markedly.

Costill (1970) examined the relationship between workload and blood lactate levels in trained distance runners. Each subject ran a series of five minute tests at speeds ranging from 17 - 21 $km.h^{-1}$; blood lactate concentrations measured five minutes after exercise were used to construct a representative lactate curve. Costill showed that, with trained runners, blood lactate levels rose only when the exercise intensity was greater than 70% $VO_2max$. This value is higher than that established by Wyndham et al. (1962) and can be explained by the superior fitness of Costill's runners (see earlier).

In 1973, Wasserman, Koyal, Whipp and Beaver used an incremental cycle ergometer test in an attempt to develop a non-invasive test for the detection of the "anaerobic threshold" by relating

it to respiratory gas exchange variables. 85 subjects pedalled at workloads that increased by 15 watts per minute and expired air flow, expired carbon dioxide and oxygen tensions, plus heart-rate were all recorded continuously. Some subjects had arterial pH measured, as well as arterial lactate levels. The "anaerobic threshold" was determined by non-linearity in carbon dioxide production and in minute ventilation, and by changes in the respiratory exchange ratio, and in blood bicarbonate and lactate concentrations.

They found that there was a curvilinear increase in blood lactate levels which only occurred above a critical work level in normal subjects. Wasserman termed this point of curvilinear increase the "anaerobic threshold" as it appeared to be coincident with a decrease in the blood bicarbonate concentration and in blood pH levels. Respiratory measurements in the study indicated that the occurence of metabolic acidosis (defined as the "AT") was coincident with the same work levels predicted from the lactate and bicarbonate concentrations.

Davis, Vodak, Wilmore, Vodak and Kurtz (1976) also studied incremental exercise of three different types, including arm cranking, cycling and treadmill walking. They defined the "AT" according to Wasserman et al. (1973) and found that before the "AT", lactate levels rose slightly (which the authors refer to

as "hovering around 10 and 11mg.100ml$^{-1}$), whereas 30 seconds after the "AT" lactate levels showed a definite curvilinear increase. In this study, the AT occurred at 55% $VO_2$max.

Mader et al. (1976) introduced the concept that an exercise intensity resulting in a lactate concentration of 4 mmol.l$^{-1}$ constituted the upper limit of exercise, above which lactate levels continued to rise. They found that up to a lactate level of 4 mmol.l$^{-1}$, prolonged exercise resulted in constant or falling lactate concentrations. Exercise intensities causing blood lactate levels to rise above this concentration resulted in a continuous rise in blood lactate levels. As a result, Mader et al. (1976) established a single turnpoint based on the blood lactate levels, as opposed to a specific workrate (% $VO_2$max.).

Stegmann, Kindermann and Schnabel (1981) exercised subjects to exhaustion and found that this type of incremental exercise led to a curvilinear increase in blood lactate levels. They defined the individual AT as the point where the rate of lactate oxidation matched the rate of lactate diffusion into blood, and found that this threshold occurred at around 4 mmol.l$^{-1}$ in untrained subjects.

Yoshida, Takeuchi and Suda (1982) compared changes in arterial and venous blood lactate concentrations in the forearm during

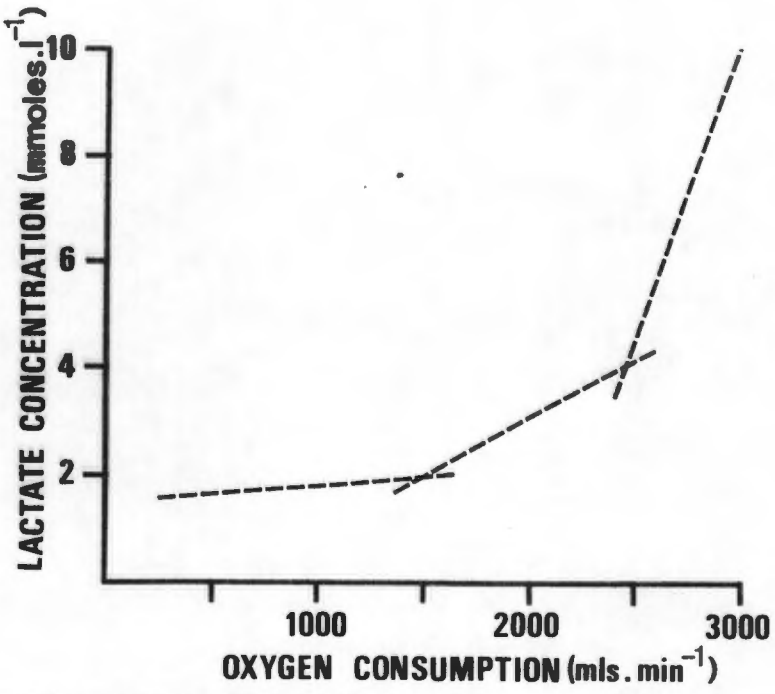
incremental cycle ergometer exercise. They found that while levels increased at a specific %$VO_2$max., arterial lactate concentrations increased earlier (37% $VO_2$max.) and to higher levels (8 mmol.$l^{-1}$) than the venous lactate levels (55% $VO_2$max. and 6mmol.$l^{-1}$ respectively). They suggested that the lower venous lactate concentrations were due to lactate utilisation by inactive forearm muscles.

In contrast to these studies showing a single lactate turnpoint, Bang (1936) established a second turnpoint which occurred during exercise at a very high intensity (see figure 3). Since then, the presence of more than one turnpoint has been demonstrated by a number of researchers. For example, Wells, Balke and van Fossan (1957) also identified two turnpoints (figure 7) and described their lactate accumulation curve according to three different components, namely :

a) An almost flat component where lactate levels remained within the range of normal resting values;

b) A gradually rising phase during which lactate levels increased to almost twice resting levels; and

c) A sharply increasing slope where lactate levels rose to six times resting values.



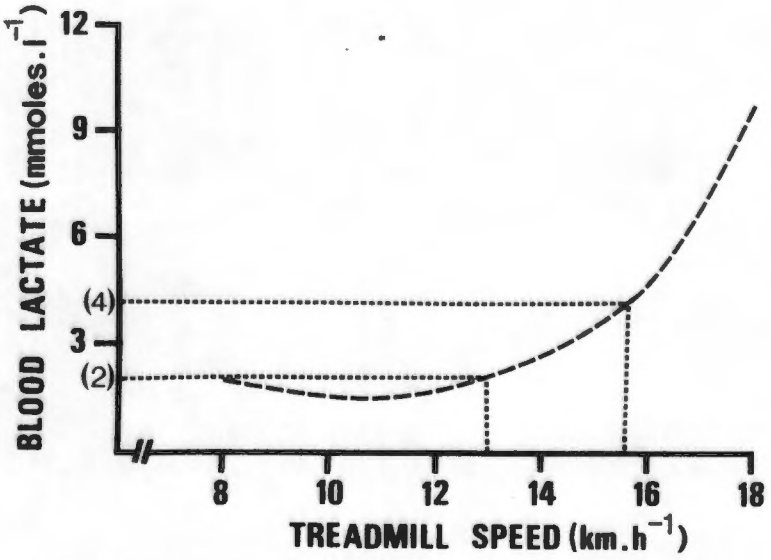

(From Wells et al, 1957)

FIGURE 7

Two lactate turnpoints were identified, with lactate levels increasing sharply once the 4 mmol.l$^{-1}$ concentration was reached.

In 1979, Kindermann, Simon and Keul studied cross-country skiers who worked to exhaustion on a treadmill starting at 5% grade and 8 $km.h^{-1}$, with the speed being increased by 2 $km.h^{-1}$ every three minutes. In these subjects, the steep rise in blood lactate levels occurred at exercise intensities above 80% $VO_2max.$, corresponding to blood lactate levels of 4 $mmol.l^{-1}$ (see figure 8), bearing striking similarity to the results of Wells, Balke and von Fossan (1957). The AT, as defined by Wasserman (1978), occurred at a blood lactate level of 2 $mmol.l^{-1}$, and was the point where these lactate levels showed their first significant rise. They suggested that workload intensities which result in blood lactate levels of around 2 $mmol.l^{-1}$ mark the upper limit of exclusively aerobic metabolism, and propose that this limit be referred to as the "aerobic threshold". They referred to exercise levels causing blood lactate levels between 2 $mmol.l^{-1}$ and 4 $mmol.l^{-1}$ as the "aerobic-anaerobic transition period", while the 4 $mmol.l^{-1}$ level is defined as the "anaerobic" curve, resulting in the steep part of the curve.

Davis and Gass (1979) investigated changes in the lactate levels during three repeated incremental tests, the third of which followed a three minute period of maximal exercise that caused blood lactate levels to be elevated at the start of the second test. In the first test, venous lactate levels only began to



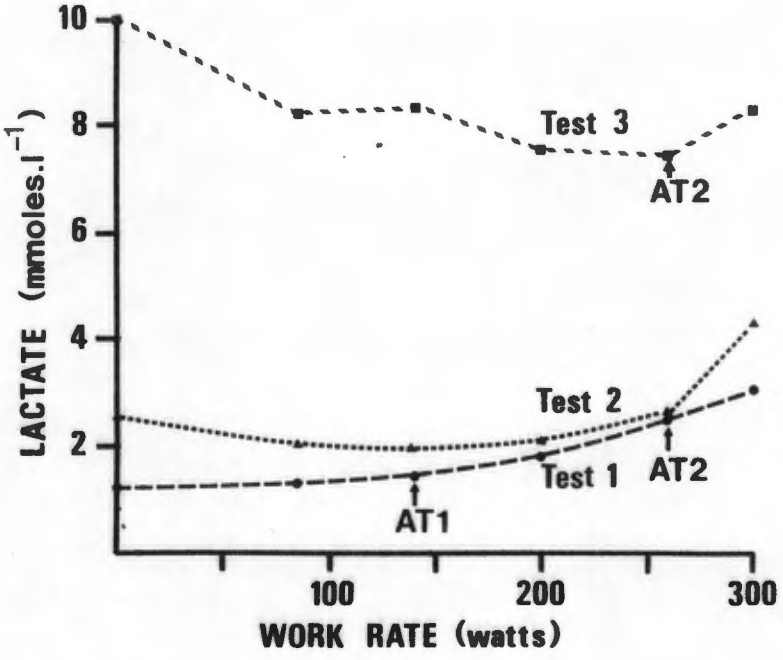

From Kindermann et al, 1979

FIGURE 8

Blood lactate levels start to rise steeply at running speeds that cause blood lactate levels to exceed 4 mmol.l$^{-1}$.

rise above a workload of 140 watts; in the second test, which started directly thereafter so that starting lactate levels were twice those in the first test (figure 9), the workload of 140 watts corresponded to a change from a decrease in the initially high lactate levels to an increase in these levels. This workload of 140 watts was defined by the authors as being the first anaerobic threshold (the AT1). In test three, starting lactate levels were ten times those observed in test one, and levels continued to decrease until a workload of 260 watts was reached, and thereafter they rose. Workrates above 260 watts were characterised by rapid lactate increases in all three tests, and this level was defined by Davis and Gass as the second anaerobic threshold, the AT2.

These authors concluded that the direction and magnitude of changes depended on the initial lactate levels, since a range of workrates was associated with either an increase or a decrease in venous lactate levels. They also postulated that workrates below the AT1 (140 watts) resulted in no increases in venous lactate levels; workrates between the AT1 and AT2 would result in an increase which would plateau during prolonged steady-state exercise at that particular load. Intensities above the AT2 would result in a continuous, work-limiting increase with no plateau in blood lactate levels.




(From Davis and Gass, 1979)

FIGURE 9

Davis and Gass (1979) identified two blood lactate turnpoints, one at 140 watts (AT1) indicating what they considered to be a transition from purely aerobic to partially anaerobic metabolism, and one at 260 watts (AT2) indicating purely anaerobic metabolism.

In 1980, Skinner and McLellan summarised events occurring during progressive exercise from low to maximal intensities, and defined three phases similar to those of Davis and Gass (1979) outlined above:

a) Phase One, characterised by a linear increase in oxygen uptake with little lactate formation. This phase primarily involves aerobic metabolism.

b) Phase Two, involving exercise at 40 - 60% $VO_2max.$, and an initial rise in lactate to twice resting levels (2 $mmol.l^{-1}$). The authors suggest that this level be referred to as the "aerobic" threshold since changes in blood lactate levels are apparently related to an increased recruitment of type II fast-twitch glycolytic fibres, and to an imbalance between the rate of production and oxidation of pyruvate.

c) Phase Three, in which exercise at intensities between 65 - 96% $VO_2max.$ causes a rapid rise in lactate concentrations to levels above 4 $mmol.l^{-1}$. The authors suggest that this is the true "anaerobic threshold" since they believe that the sharp rise in lactate and the "breakaway" ventilation are related more to anaerobiosis and recruitment of type IIb skeletal muscle fibres which are more predisposed to hypoxia.

In summary, there appear to be two different concepts about the lactate turnpoint :

a) A single turnpoint occurring at a specific exercise intensity.

The theory behind this concept is that lactate levels only begin to increase under "anaerobic" conditions, that is, when the exercise intensity becomes greater than can be maintained by the available oxygen supplies. The level at which lactate levels begin to rise appears to be between 55% and 75% $VO_2max.$, with the higher turnpoint occurring in trained subjects.

b) Two turnpoints, resulting in a tri-phasic curve.

The initial increase is generally attributed to increased recruitment of predominantly glycolytic, type IIb skeletal muscle fibres as the subject becomes fatigued, while the second more marked turnpoint is attributed to "anaerobiosis"in which the rate of oxygen delivery is insufficient to support an increased rate of pyruvate oxidation.

Alternatively, as exercise intensity increases, the cytoplasm may become flooded with pyruvate and NADH favouring lactate production as a result of "glycolytic

overflow". Similarly, maximal lactate utilisation rates at other sites (such as the liver) may be surpassed so that above a certain exercise intensity, lactate will accumulate progressively in the blood (Donovan and Brooks, 1983).

B) THE DURATION OF EXERCISE.

I) Lactate levels during prolonged exercise of constant intensity.

a) Low intensity exercise (up to 50% $VO_2$ max).

Ryffel (1909), Owles (1930) and Cook and Hurst (1933) all found that lactate levels remained constant at near resting concentrations during prolonged exercise at very low intensities. However Hill and Lupton (1923) and Margaria et al. (1933) postulated that lactate levels increased during low intensity, prolonged exercise, but that they would usually remain constant as long as the same exercise intensity was maintained.

More recently, Hermansen and Stensvold (1972) studied lactate levels before, during and after 30 minutes of exercise at various intensities (30% - 80% $VO_2$max.). As with Owles' results (1930), no increase was observed in the blood lactate concentrations during prolonged exercise at 30% $VO_2$max.

In contrast to these findings of constant blood lactate levels during low intensity submaximal exercise, numerous researchers have shown that there is an initial increase in the blood lactate concentration, followed by a steady decrease towards the basal levels over the remainder of the exercise period. Rowell

et al. (1966) studied subjects exercising for 60 - 70 minutes at 6 $km.h^{-1}$ and zero grade, which they classified as mild exercise. Arterial and venous blood samples drawn at rest, after ten minutes' exercising, and every seven minutes thereafter showed that lactate levels peaked at around 2 $mmol.l^{-1}$ during the first ten minutes, and then decreased towards resting levels over the remainder of the exercise session. Essentially the same findings were made by Scheen, Juchmes and Cession-Fossion (1981).

Davis and Gass (1981) established the AT1, AT2 and respiratory AT in the maximal progressive test described earlier, and then exercised subjects for 30 minutes at each of the threshold levels. At workloads corresponding to the AT1, the lactate concentrations increased to 2 $mmol.l^{-1}$ and then decreased to remain steady at around 1.5 $mmol.l^{-1}$ for the remainder of the test.

Simon, Young, Gutin, Blood and Case (1983) studied exercise lasting 30 minutes at an intensity just below the anaerobic threshold (46% $VO_2max.$). Lactate levels rose from resting levels of 1.2 $mmol.l^{-1}$ to 2 $mmol.l^{-1}$ in the first eight minutes and then decreased towards resting levels over the remainder of the exercise period. These results are therefore similar to those observed by Bang (1936) who identified a

"primary rise" in lactate levels during moderately severe exercise, followed by a decrease in lactate levels after about five minutes of exercise.

The effect of low intensity exercise on blood lactate levels can therefore be summarised as follows :

i) Blood lactate levels remain at, or near, basal levels (Ryffel, 1909; Owles, 1930; Cook and Hurst, 1933; Hermansen and Stensvold, 1972).

ii) Lactate levels increase and remain constant for the duration of the exercise period (Hill and Lupton, 1923; Margaria et al, 1933).

iii) Lactate levels increase at the onset of exercise, but then decrease gradually towards basal concentrations as the exercise continues (Bang, 1936; Rowell, 1966; Davis and Gass, 1981; Simon et al, 1983).

b) Moderate intensity exercise (50 - 75% $VO_2$ max).

Saltin and Stenberg (1964) studied subjects exercising for 180 minutes at 75% $VO_2$ max., with venous blood samples being taken before and during exercise. Lactate concentrations increased at the start of exercise to around 4 $mmol.l^{-1}$ and then fell

steadily to around 2 mmol.$l^{-1}$ at the end of exercise. These results agree with those obtained by Bang (1936) and by Crescitelli and Taylor (1944) during prolonged exercise but at a very low exercise intensity. It would appear then that the subjects tested by Saltin and Stenberg (1964) were extremely fit, since they showed similar lactate concentrations while exercising at 75% $VO_2$max. to those subjects who exercised at a "low" intensity (below 50% $VO_2$max.) in other studies.

Besides studying exercise at low intensities, Rowell et al. (1966) also studied subjects exercising for 60 - 70 minutes at "heavy" exercise intensities. Arterial and venous blood samples showed that after peaking at around 4 mmol.$l^{-1}$ in the first ten minutes, these concentrations diminished to approximately half these peak values and remained constant over the remainder of the exercise period. Similar results were found by Saiki, Margaria and Cuttica (1967) who exercised subjects at 70 - 80% $VO_2$max. for 15 minutes. Blood lactate levels increased in the first two to five minutes (to 2.5 mmol.$l^{-1}$) and then decreased over the remainder of the exercise period (figure 10). From these results, they concluded that no appreciable production of lactate occurred at submaximal workloads (70% $VO_2$max.) once a steady-state level of oxygen consumption had been reached, with lactate formation being limited to this first phase of exercise during contraction of the oxygen debt. The fall in lactate

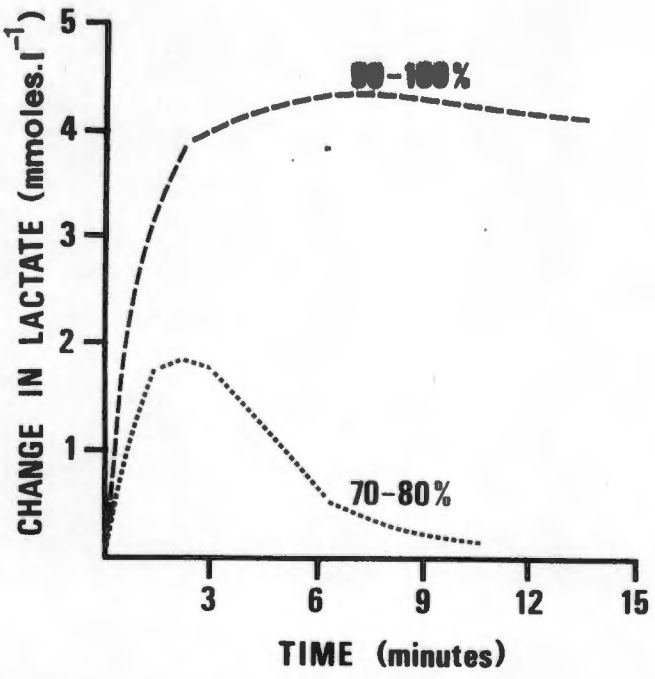



FIGURE 10

During prolonged, moderate intensity exercise (70 - 80% $VO_2$ max.), blood lactate levels increased initially and then decreased.

During high intensity exercise, blood lactate levels rose earlier and to higher concentrations, but peaked later than during moderate exercise; lactate levels then remained constant for the duration of the exercise period.

levels was taken to indicate that the oxygen consumption during steady-state was sufficient for both provision of energy and for repayment of the "lactacid oxygen debt" contracted at the onset of exercise. Interestingly, the authors conclude that no lactate was produced during submaximal, steady-state exercise even though lactate levels remained elevated above resting concentrations for the duration of the exercise.

Costill and Fox (1969) examined marathon runners on a treadmill and during a marathon race, running in both cases at marathon pace, and found that in both tests near resting venous blood lactate concentrations were obtained five minutes after exercise, indicating no significant increases in lactate levels during prolonged exercise.

Nagle et al. (1970) studied blood lactate levels in runners exercising for 40 minutes at 74% - 79% $VO_2max.$, and found that lactate levels increased to approximately 4 $mmol.l^{-1}$ within the first ten minutes, and then levelled off to remain constant over the remainder of the exercise period.

Hermansen and Stensvold (1972) also studied lactate production during prolonged exercise lasting 30 minutes at 60% $VO_2max.$ and found that, as with exercise at 30% $VO_2max.$, no significant increase in the lactate concentrations was observed.

Thus the majority of researchers studying moderate intensity exercise (Wasserman, van Kessel and Burton, 1967; Nagle et al, 1970; Hermansen and Stensvold, 1972; Kindermann et al, 1979; Scheen et al, 1981) have observed that lactate levels increased initially and then remained constant throughout the remainder of the exercise period.

In contrast, a number of researchers found that lactate levels rose, and continued to rise, during the exercise period. Costill (1970) examined blood lactate levels in subjects running at 15 $km.h^{-1}$ for two hours, with venous blood being drawn before, at 30 minute intervals during the run, and after exercise. Lactate levels increased slightly in the first ten minutes (3 $mmol.l^{-1}$), with an equivalent 3 $mmol.l^{-1}$ rise taking place over the remainder of the run, indicating "more-or-less" steady-state conditions.

In 1982, Myhre, Hartung and Tucker investigated changes in blood-borne substrates and plasma volume occurring during prolonged exercise. Subjects were tested during a marathon run at about 66% $VO_2max.$; venous blood samples were taken before the race, at the 16 and 32 kilometre marks and immediately after the marathon. By the 16 kilometre mark, blood lactate levels had increased slightly (1 $mmol.l^{-1}$ - 3 $mmol.l^{-1}$), and these continued to increase slightly to the end of the race

(4 mmol.$l^{-1}$). At least half of the increase in blood lactate levels occurred during the first 16 kilometres, although levels continued to rise gradually throughout the race.

Scheen et al. (1981) exercised subjects for 20 minutes at a "severe" exercise intensity and found that, above 65% $VO_2max.$, lactate levels showed a sustained increase over the duration of the exercise period.

In summary, the effect of prolonged exercise at moderate intensity on lactate levels may be categorised as follows :

i) Lactate levels do not increase at low exercise intensity or at moderate intensities in fit subjects (Ryffel, 1909; Margaria et al, 1933; Cook and Hurst, 1933; Costill and Fox, 1969).

ii) Lactate levels increase at the onset of more intensive exercise and then decrease over the remainder of the exercise period (Bang, 1936; Crescitelli and Taylor, 1944; Saltin and Stenberg, 1964; Rowell et al, 1966; Saiki et al, 1967; Scheen et al, 1981).

iii) Lactate levels increase and remain constant during exercise of a constant but slightly higher intensity (Hill and

Lupton, 1923; Wasserman et al, 1967; Saiki et al, 1967; Nagle et al, 1970; Hermansen and Stensvold, 1972; Scheen et al, 1981).

iv) Lactate levels continue to rise throughout the exercise period (Nagle et al, 1970; Hermansen and Stensvold, 1972; Scheen et al, 1981).

c) <u>High intensity exercise (above 75% $VO_2$ max).</u>

Results obtained during high intensity exercise show two main categories of results - constant blood lactate levels after an initial rise, or a continuous increase in the lactate concentration throughout the exercise period.

Wasserman, van Kessel and Burton (1967) examined the lactate concentration during "heavy" and "very heavy" exercise intensities over a 50 minute period. Lactate levels increased to around 4 $mmol.l^{-1}$ during heavy exercise, and to 8 $mmol.l^{-1}$ during very heavy exercise. In each case lactate levels plateaued and remained constant, but did so at different times and at different concentrations depending on the exercise intensity (see figure 11).

Saiki et al. (1967) exercised subjects at 90 - 100% $VO_2max.$, and found that lactate levels rose earlier than during the test

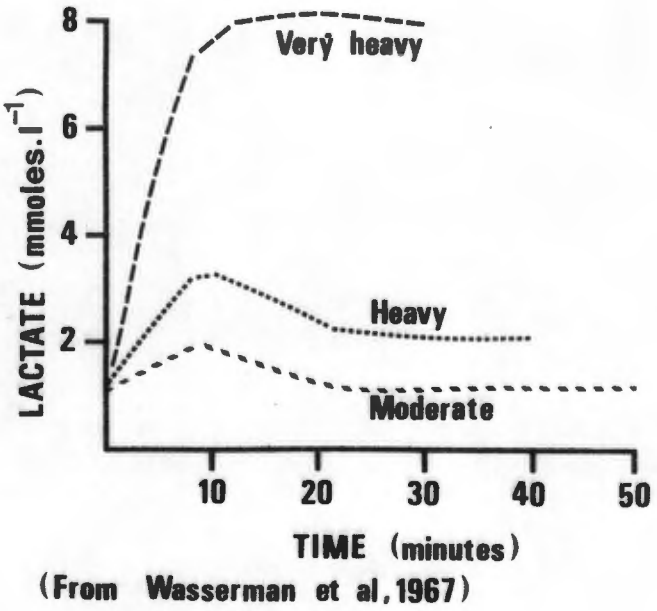



FIGURE 11

During prolonged exercise, blood lactate levels increased at the onset of exercise and then levelled off to remain constant for the duration of the exercise period at blood levels which depended on the exercise intensity.

at 70 - 80% $VO_2max$. described earlier (figure 10). The lactate concentration also increased to a higher maximum value (4 $mmol.l^{-1}$ compared to 2.5 $mmol.l^{-1}$), but peaked later than in the lighter workload. Lactate levels then remained constant rather than decreased during the remainder of the exercise period.

Nagle et al. (1970) also studied blood lactate levels during 30 minutes' running at 82% - 89% $VO_2max$. to determine the effect of intensity and duration of the exercise on the "aerobic and anaerobic processes". Venous blood samples collected three minutes post-exercise showed that blood lactate levels rose in proportion to the oxygen demand, and at exercise intensities above 80% $VO_2max$. lactate levels continued to increase.

In summary, studies of blood lactate levels during high intensity exercise have produced two sets of results :

i) Blood lactate levels increase and then remain constant at a level depending on the exercise intensity (Wasserman et al, 1967; Saiki et al, 1967).

ii) Blood lactate levels continue to rise throughout the exercise period (Nagle et al, 1970).

C) THE EFFECT OF TRAINING ON BLOOD LACTATE LEVELS.

Williams, Wyndham, Kok and Von Rahden (1967) found that training shifted the lactate turnpoint from 46% - 62% $VO_2max.$, (see figure 12), and suggested that this occurred because the oxygen supply to the working muscles increased with training (as a result of increased blood flow). Wyndham, Strydom, van Rensburg and Benade (1969) next examined highly trained subjects, and found that compared to untrained subjects, the lactate turnpoint in the trained subjects occurred at workloads higher by 10% $VO_2max.$ than in the untrained subjects.

Karlsson, Nordesjo, Jorfeldt and Saltin (1972) measured muscle and blood lactate levels at rest, during prolonged submaximal exercise and during maximal exercise before, after three and again after seven months' training. After three months' training, muscle lactate levels during submaximal exercise decreased from 7 $mmol.l^{-1}$ to 4 $mmol.l^{-1}$, and fell even further to 3 $mmol.l^{-1}$ after seven months of training. During maximal exercise, however, peak muscle lactate levels were the same after three months' and higher after seven months' training, indicating an increased ability to continue exercising at high muscle lactate concentrations.

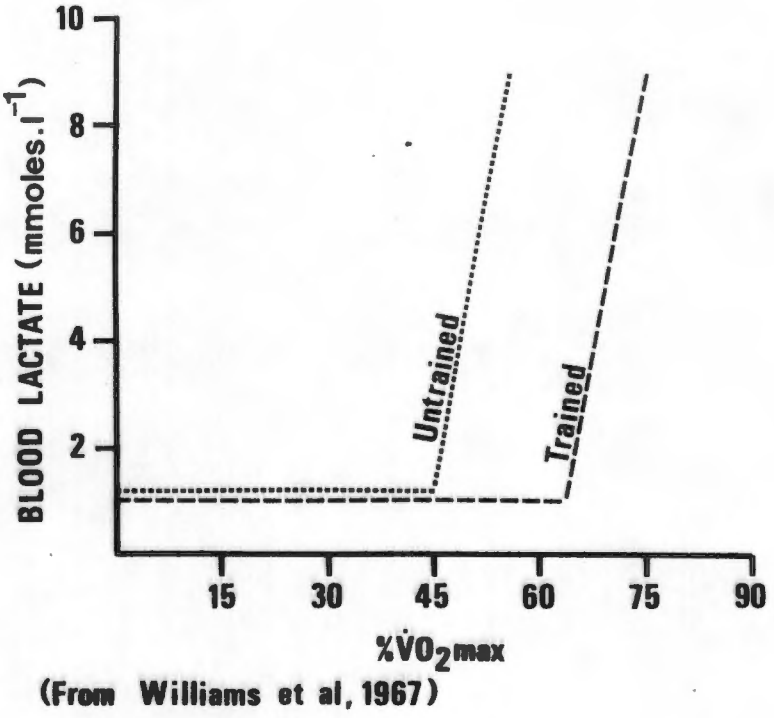



FIGURE 12

Training resulted in a shift in the lactate turnpoint to a higher percentage $VO_2$max.

During submaximal exercise, blood lactate levels were related to muscle lactate levels, and Karlson et al. (1972) suggest that the low levels recorded at the same exercise levels could result from increased uptake and utilisation of lactate as a fuel (due to differences in fibre-type recruitment) or from a reduced production rate in the trained muscles.

Robinson, Prior and Newton (1973) compared trained and untrained young men during exhausting, short-term intermittent exercise and after a continuous run at 17 $km.h^{-1}$. After the continuous run, blood lactate levels were higher in the trained (21 $mmol.l^{-1}$) than in the untrained subjects (15 $mmol.l^{-1}$), and these values increased by 11% and 27% respectively during intermittent exercise. They suggested that the rest periods during the intermittent exercise allowed diffusion of lactate from the muscles so that much higher blood lactate concentrations could accumulate. Robinson et al.(1973) concluded that trained persons tolerated higher blood lactate levels (as previously shown by Karlson et al, 1972), and that this was probably brought about by improved circulation which removed lactate from the working muscles.

Klausen, Rasmussen, Clausen and Trap-Jensen (1974) measured lactate production before and after arm or leg training, and found that resting levels before and after training were

similar, but that the lactate concentrations during exercise were significantly lower in the trained muscles. After training, venous-arterial lactate differences were significantly lower in the trained muscles, and these authors suggested that a local muscular training effect occurred which decreased the rate of lactate production. These results contrast with those of Robinson et al. (1973) and Karlson et al. (1972) who found higher lactate levels in the trained state.

These differences can be explained on the basis of different testing protocols - Klausen et al. (1974) tested subjects during prolonged submaximal exercise, whereas Robinson et al. and Karlsson et al. (1972) found higher lactate levels during maximal exercise. Karlsson et al. (1972) also measured lactate levels during submaximal exercise, and their results at these intensities support Klausen et al's observations (1974) of lower blood lactate levels after training.

Saltin, Nazar, Costill, Stein, Jansson, Essen and Gollnick (1976) trained subjects with one leg performing endurance training and the other sprint training, or with a combination of either endurance or sprint training with one leg while the other leg remained untrained. Endurance training caused a marked decrease in the femoral arterial and venous blood lactate concentrations during submaximal exercise, but only in the

vessels draining the trained limb. Post-exercise blood lactate levels were only significantly increased after the sprint training. The sprint-trained leg tended to have higher muscle lactate levels when compared with an endurance trained leg, while the non-trained leg had even higher lactate concentrations than either the sprint- or endurance-trained legs.

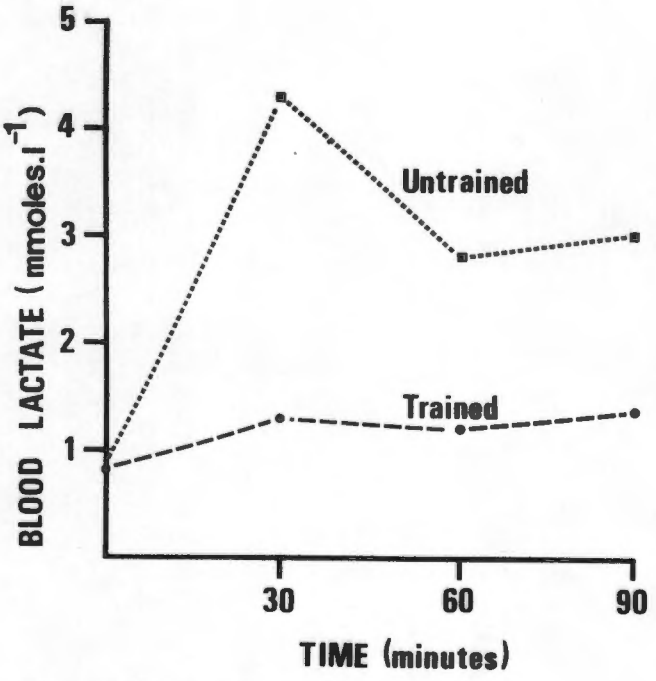
Both muscle and blood lactate levels therefore decreased with training. The higher peak lactate levels recorded with the sprint trained leg was considered to indicate an increased "anaerobic capacity" resulting from an increased fast-twitch fibre area. Alternatively, as suggested by Robinson et al. (1973) and Karlsson (1972), this could indicate improved lactate tolerance in the exercising muscles. Saltin et al. concluded that training induced a specific adaptation pattern, according to the type of training programme followed.

Henriksson (1977) examined local muscular adaptation to an eight week training programme, involving one-legged cycling at 70% $VO_2max$. for 45 minutes a day, three times a week. Blood lactate levels were lower after training, but only during submaximal exercise (70% $VO_2max$.) and not during maximal exercise. Lactate release from the untrained muscles was higher than the release from trained muscles, and after prolonged exercise the trained muscles showed net lactate uptake, although

muscle lactate concentrations were the same in both the trained and the untrained legs. He suggested that the differences in lactate uptake and release indicate different levels of lactate metabolism, and results from changes in muscle oxidative capacity as a result of training. An increased oxidative capacity would reduce the tendency for pyruvate to be converted to lactate, and in this way cause less lactate to be produced.

Winder, Hickson, Hagberg, Ehsani and McLane (1979) examined the metabolic changes which occurred over a nine week training programme, and found that blood lactate concentrations at the same absolute workload were much lower in the trained than in the untrained state (figure 13).

Denis, Fouquet, Poty, Geyssant and Lacour (1982) examined changes in the lactate turnpoint over a ten-month endurance training period, and found that the turnpoint changed from 72% to 79% $VO_2max$. Similarly, the level at which a blood lactate concentration of 4 $mmol.l^{-1}$ occurred increased from 72% to 83% $VO_2max$. Although the lactate turnpoint shifted, the actual turnpoint concentrations showed no significant changes (4 $mmol.l^{-1}$ before training compared to 3.5 $mmol.l^{-1}$ after training). Maximum lactate concentrations were not significantly altered by training, and the shift in the turnpoint only became significant after 20 weeks of training.



(From Winder et al, 1979)

FIGURE 13

Training reduced blood lactate levels at the same absolute workloads.

Finally, Donovan and Brooks (1983) examined whether the lower lactate levels after training were due to a decreased rate of lactate production resulting from an increased oxidative capacity, or to an increase in the rate of lactate removal from blood. They found that the rate of lactate production in endurance-trained rats was not different to that in untrained rats. However the lactate clearance rate was significantly higher in trained rats. This finding is not compatible with the theory that less lactate is produced by trained muscles.

In conclusion, it would seem that there are two major effects of training on blood lactate concentrations :

I) Trained athletes have lower blood lactate levels than do untrained athletes working at the same % $VO_2max$.

II) The lactate turnpoint "shifts to the right" so that it occurs at higher work intensities in trained than in untrained athletes.

Maximal blood lactate concentrations do not appear to be significantly altered with training, although Karlson et al. (1972), Robinson et al. (1973), and Klausen et al. (1974) all reported higher maximum lactate concentrations after training. They suggest that this indicates an improved lactate tolerance.

Most workers are of the opinion that the lower blood lactate levels in trained athletes during submaximal exercise occur because training improves tissue oxygenation and oxidative capacity by increasing the myoglobin content, and the size and the number of mitochondria (Hollman, Rost, Liesen, Dufaux, Heck and Mader, 1981). In contrast, Donovan and Brooks (1983) suggest that, in rats, it is not the rate of lactate production but its rate of removal from blood that is altered by training.

## D) DIFFERENT TYPES OF EXERCISE.

### I) Exercise type.

Davis, Vodak, Wilmore, Vodak and Kurtz (1976) found that lactate accumulation occurred at a significantly lower workload during arm cranking than during cycling or treadmill exercise. They suggested that this was due to the smaller muscle mass of the arms as well as the fact that subjects were more used to cycling or running and, as such, were "more trained" in these tests. They also suggested that arm exercise resulted in different muscle fibre recruitment patterns which, as will be discussed, may affect blood lactate levels.

Stamford, Weltman and Fulco (1978) compared one-legged and two-legged cycling and found that blood lactate levels were the same at low work levels, but that beyond a workload of 50 watts, one-legged cycling resulted in higher lactate concentrations (see figure 14). They suggested that these differences were not related to the size of the exercising muscle mass, but may be due to the involvement of a greater proportional utilisation of maximal aerobic capacity during one-legged exercise.

Finally, Lavoie (1982) compared blood lactate levels during cycling and swimming and found that blood lactate concentrations during a 45 minute exercise period were significantly higher in

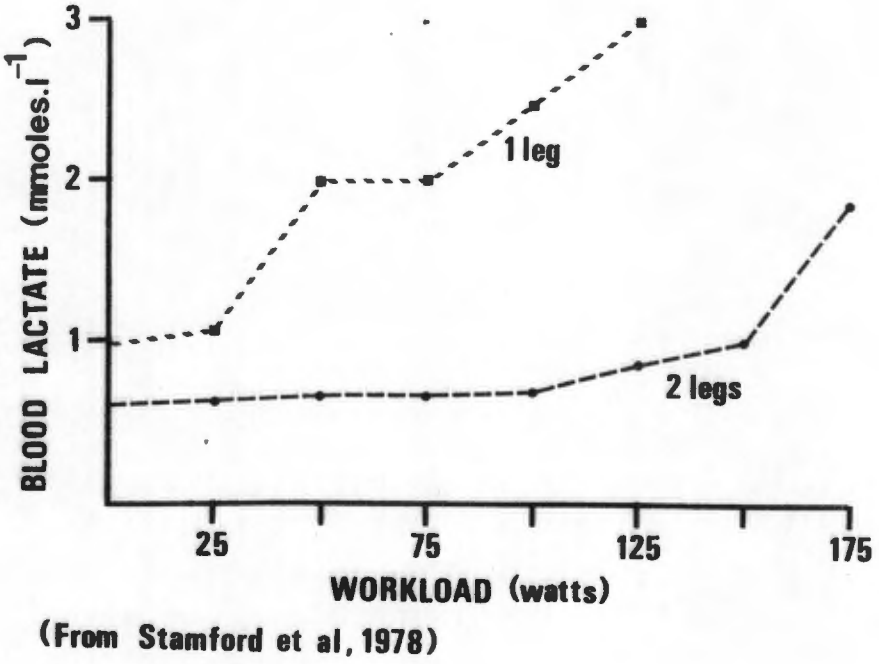



FIGURE 14

Blood lactate levels are lower during two-legged exercise than during one-legged exercise, even at very light workloads.

swimming than in cycling. They proposed the following three causes for this difference :

a) Leg muscles used for cycling have a greater respiratory capacity due to greater daily endurance work (training and familiarity with the task).

b) Lactate utilisation was elevated when the larger muscle groups were exercising.

c) Differences in skeletal muscle fibre recruitment patterns - swimmers tend to have a higher relative carbohydrate oxidation rate, possibly as a result of different fibre-type recruitment patterns.

Thus it appears that there are definite differences in blood lactate concentrations during different types of exercise. The explanation for these differences is unknown, but these differences are probably influenced by those factors outlined by Lavoie (above).

II) Exercise at various threshold intensities.

Davis and Gass (1981) established the AT1, the AT2 and the respiratory AT in a maximal progressive test described earlier, and then exercised subjects for 30 minutes at each of the

threshold levels. Exercise at work-rates between the AT1 and AT2 (considered moderate exercise) resulted in moderate increases in lactate levels, followed by maintenance of steady-state levels of around 2 $mmol.l^{-1}$.

Stegmann, Kindermann and Schnabel (1981) defined the individual anaerobic threshold (IAT) as "the workload corresponding to the steady-state between diffusion of lactate into blood and maximal elimination from the blood and exercising muscles". In 1982, Stegmann and Kindermann exercised subjects for 50 minutes at their IAT and at the 4 $mmol.l^{-1}$ lactate threshold established by Mader et al. (1976), to see whether a steady-state in lactate metabolism occurred at both these thresholds. These researchers found that they could distinguish between three distinct groups:

a) The largest group (15 subjects) in whom blood lactate concentrations were lower than 4 $mmol.l^{-1}$ at the IAT. All subjects completed 50 minutes at the IAT. After an initial increase, lactate levels stabilised at around 3 $mmol.l^{-1}$; however none of the group could exercise for 50 minutes at the 4 $mmol.l^{-1}$ lactate threshold since at that workload, lactate levels continued to increase to around 10 $mmol.l^{-1}$. These levels were similar to those associated with exhaustion in a maximal incremental test.

b) A considerably smaller group (3 subjects) in whom the two thresholds were identical. In both cases, subjects were able to exercise for 50 minutes with lactate levels remaining steady at around 4 $mmol.l^{-1}$.

c) In one subject, the IAT was higher than 4 $mmol.l^{-1}$ and again in both tests the exercise was maintained for 50 minutes. Prolonged exercise at the 4 $mmol.l^{-1}$ intensity resulted in a slight drop in the lactate levels (3 $mmol.l^{-1}$) which then remained constant for the duration of the exercise. With exercise at the IAT, lactate levels initially increased considerably to 12 $mmol.l^{-1}$ and then decreased to remain constant at around 9 $mmol.l^{-1}$.

Stegmann and Kindermann (1982) concluded that since prolonged exercise at the IAT produced a steady-state in blood lactate concentrations, the IAT identified the maximum exercise intensity at which lactate production exactly matched its rate of oxidation.

In a subsequent study, Schnabel, Kindermann, Schmitt, Biro and Stegmann (1982) examined the metabolic responses to prolonged exercise at the IAT to see whether a steady-state production of lactate was associated with a steady-state in other metabolic functions. Subjects exercised for 50 minutes at their IAT, with

lactate levels remaining steady at around 4.6 mmol.$l^{-1}$ after 20 minutes. Blood levels of glycerol, insulin, growth hormone, cortisol, adrenaline and noradrenaline all changed initially and then remained relatively constant throughout the execise period. Schnabel et al. (1982) concluded that exercise at the IAT could be tolerated for at least 50 minutes with a relative steady-state in energy metabolism, even though this was at a high % $VO_2max$.

Simon, Young, Gutin, Blood and Case (1983) examined exercise lasting 30 minutes at a work-rate just above the AT (57% $VO_2max$.), the AT being defined as the highest oxygen consumption beyond which lactate began to accumulate. At this work load, the lactate concentration rose sharply in the first ten minutes and then remained constant at around 3 mmol.$l^{-1}$ for the duration of the test.

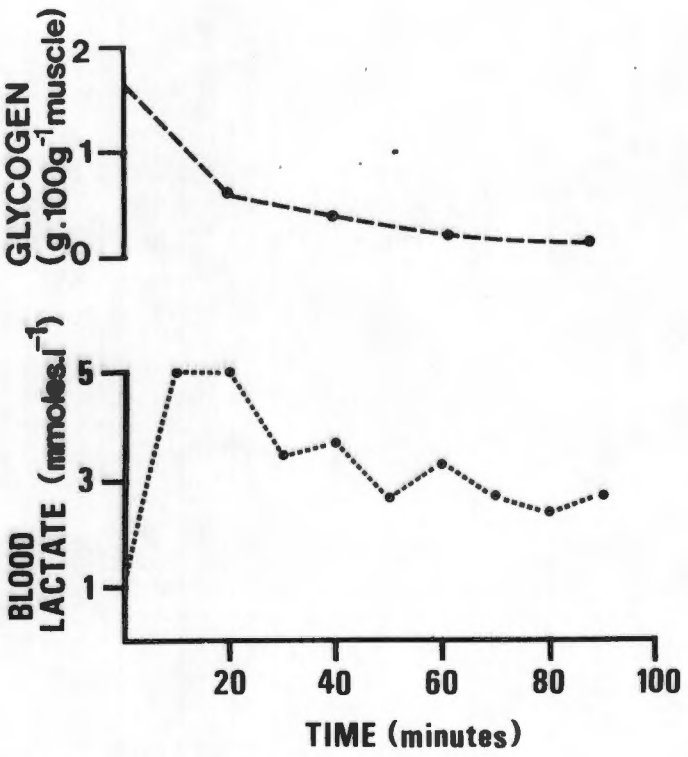
These authors included in their study an examination of exercise lasting 30 minutes at an intensity just below the "respiratory compensation threshold" (RCT), where the RCT is defined as the point where the ventilation increased disproportionately to the rate of the carbon dioxide production causing a fall in the expired carbon dioxide.

## E) THE EFFECTS OF DIET AND SUBSTRATE AVAILABILITY.

Since glucose and glycogen are the precursors of lactate production, a greater carbohydrate availability could cause a greater potential for lactate production during exercise.

Hermansen, Hultman and Saltin (1967) studied ten trained and ten untrained subjects exercising at 77% $VO_2$max. for four periods of 20 minutes each, with 15 minutes rest between each exercise bout. Blood lactate levels peaked in the first work period (6 mmol.$l^{-1}$) and then decreased in subsequent exercise bouts. There was a pronounced decrease in muscle glycogen during the first work period. The rate of glycogen depletion fell in these subsequent exercise bouts (see figure 15).

Bergstrom, Hermansen, Hultman and Saltin (1967) examined the effect of different diets on muscle glycogen content and the relationship between glycogen content and capacity for prolonged exercise. Nine subjects exercised for as long as possible at 75% $VO_2$max. after three days of a mixed diet, after three days of a fat plus protein diet, and again after three days on a high carbohydrate diet. Blood lactate levels were significantly lower after the protein diet, both at rest (0.8 mmol.$l^{-1}$ compared to 1.7 mmol.$l^{-1}$ after the carbohydrate diet) and during exercise (2.5 mmol.$l^{-1}$ compared to 4.9 mmol.$l^{-1}$ after the




(From Hermansen et al,1967)

FIGURE 15

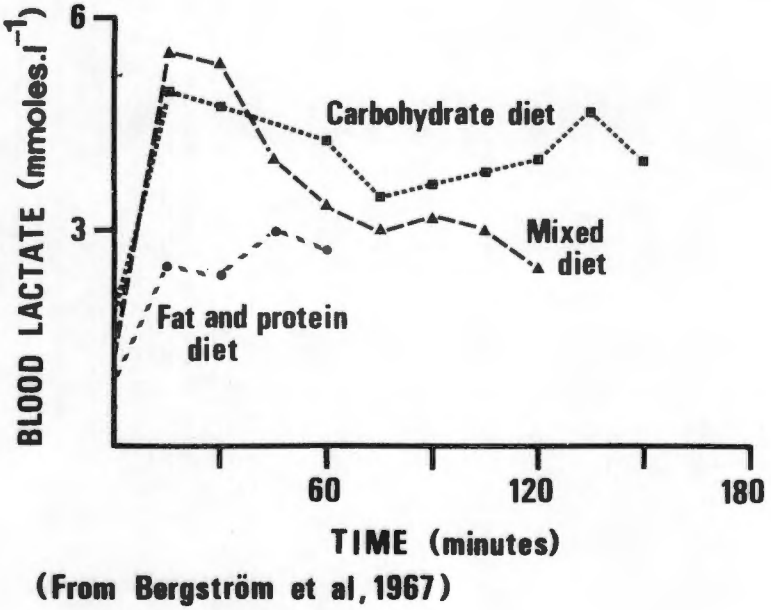
Peaking lactate levels occurred after the first exercise bout, corresponding to the most rapid rate of glycogen depletion.

carbohydrate diet - figure 16).

Pernow and Saltin (1971) exercised subjects to exhaustion before and after a diet consisting entirely of fat and protein, and found that not only did endurance time decrease dramatically (by 20 minutes) after the protein diet, but blood lactate levels during exercise were also much lower following glycogen depletion (1.2 $mmol.l^{-1}$ compared to 7.0 $mmol.l^{-1}$). Similarly Costill, Coyle, Dalsky, Evans, Fink and Hoopes (1977) found that blood lactate levels were significantly lower during exercise following "fat loading" which involved eating a fatty meal four to five hours before exercise. Thirty minutes before the test, heparin was injected intravenously to promote lipolysis. The lower blood lactate levels were compatible with free fatty acid inhibition of glycolysis resulting in a muscle glycogen-sparing effect.

Similarly, Jansson (1980) exercised subjects at 65% $VO_2max.$ after a fat-rich diet and after a carbohydrate-rich diet and found that both the arterial and muscle lactate concentrations were significantly lower after the fat-rich diet, both at rest and during exercise (figure 17).

Ivy, Costill, van Handel, Essig and Lower (1981) showed that subjects who exercised after taking 75 grams of glucose in water



(From Bergström et al, 1967)

FIGURE 16

Blood lactate levels during exercise were influenced by the pre-exercise diet and were lowest when pre-exercise muscle glycogen levels were lowest (fat and protein diet) and highest when muscle glycogen levels were highest (carbohydrate diet).

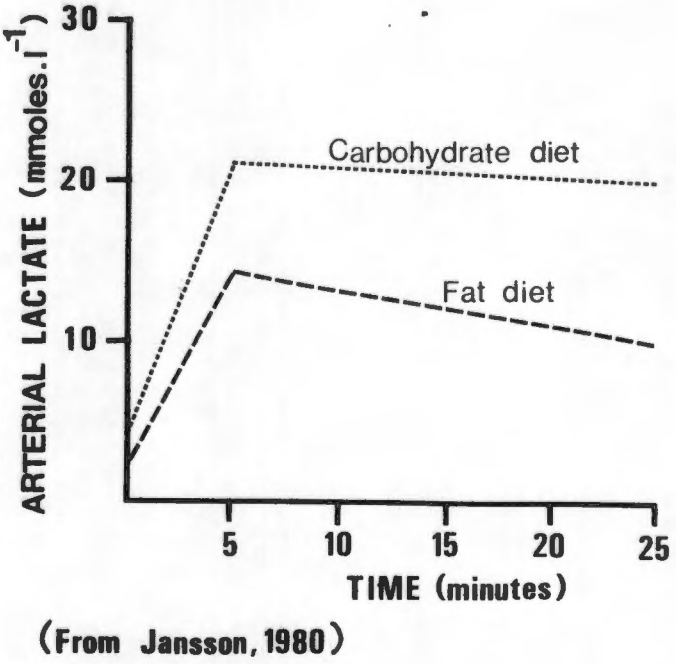



FIGURE 17

Both muscle and arterial lactate levels (not shown) were lower both at rest and during prolonged, moderate intensity exercise after a fat diet than after a carbohydrate diet.

had significantly greater blood lactate concentrations (9.2 $mmol.l^{-1}$) than they did under control conditions (7.3 $mmol.l^{-1}$) or after eating a fatty meal combined with heparin injection to increase blood free fatty acid levels (7.7 $mmol.l^{-1}$). They concluded that while lactate production increased at similar rates in the control and glucose tests, lactate production was significantly reduced in the fat trial. Elevated free fatty acid levels decreased the rate of lactate production and caused a significant shift in the lactate turnpoint which increased from 54% to 60% $VO_2max$. They suggested that the lower blood lactate levels found in trained as opposed to untrained subjects at the same relative workloads may be due to an enhanced capacity for fat oxidation in the trained subjects.

Jacobs (1981) tested subjects on a muscle fatigue test involving knee extensions following glycogen depletion, after a four day fat/protein diet and again after a four day carbohydrate diet. In contrast to Bergstrom et al. (1967), Jacobs found that the different diets did not affect resting muscle lactate levels but in common with all the previous researchers, blood lactate levels were significantly lower after the fat diet and after glycogen depletion, than after the control test.

Wiswell, Girandola, Bulbulian and Simard (1978) found that

subjects who performed the same exercise bout before and after a two-hour run to induce muscle glycogen depletion showed a 45% decrease in blood lactate concentrations in the glycogen depleted state.

Gollnick, Pernow, Essen, Jansson and Saltin (1981) examined the substrates oxidised by legs whose glycogen content had been manipulated by prior one-legged exercise, and found that muscles with low glycogen content took up lactate, while muscles with normal glycogen levels released lactate at the same workload. Similarly, Hughes, Turner and Brooks (1982) studied subjects before and after glycogen depletion, and found that not only were blood lactate levels 40% lower in the depleted state, but that the lactate turnpoint occurred 25% later even though subjects could not exercise for as long as they had during the glycogen replete test.

In summary, it appears that the greater the available glycogen stores, the higher will be the lactate concentration during exercise. Conversely, the higher the lipid availability (in combination with low glycogen stores), the lower will be the blood lactate concentrations during exercise. However, since glycogen depletion diminishes the ability to perform prolonged exercise, these lower blood lactate levels are not necessarily desirable.

## F. SKELETAL MUSCLE FIBRE-TYPE AND FIBRE-TYPE COMPOSITION.

It is well established that there are two basic skeletal muscle fibre types in human muscle. Slow-twitch (Type I) fibres are characterised by a high myoglobin content, abundant mitochondria and large lipid droplets, all of which enhance the fibre's capacity for oxidative energy production. Fast-twitch (Type II) fibres have fewer mitochondria, a large glycogen content and increased glycolytic capacity (Essen et al., 1975). Based on these differences, it becomes apparent that muscle fibre-type may play a significant role in determining blood lactate levels. For example, a muscle which is predominantly composed of slow-twitch fibres has less potential for lactate production than does a muscle containing a large percentage of fast-twitch fibres.

### I) Lactate levels in individual fibres.

Essen and Haggmark (1975) examined lactate accumulation in relation to fibre type during exhausting exercise of short duration. At rest and after ten seconds of exercise the lactate concentration was the same in both fibre types (1.8 $mmol.l^{-1}$ and 2.8 $mmol.l^{-1}$ respectively). At exhaustion, however, although lactate levels had risen in both fibre types, they were higher in the fast-twitch (23 $mmol.l^{-1}$) than in the slow-twitch fibres (18 $mmol.l^{-1}$). These results were

attributed to the greater glycolytic capacity of the fast-twitch fibres.

Tesch, Sjodin and Karlsson (1978) reported lactate concentrations of 22 $mmol.l^{-1}$ and 15 $mmol.l^{-1}$ in fast-twitch and slow-twitch fibres respectively after exhausting exercise. The lowest muscle lactate concentration occurred in the subject with the greatest percentage of slow-twitch fibres, and the highest levels were recorded in a subject whose muscles consisted mainly of fast-twitch fibres. Tesch et al. (1978) concluded that fast-twitch fibres are better able to produce lactate than are slow-twitch fibres, and suggested that this is due to the different metabolic profiles described earlier.

Jacobs and Kaiser (1982) measured the lactate levels in fast- and slow-twitch fibres following an incremental cycle test to exhaustion and found no significant difference. Muscle fibre composition was not related to muscle lactate levels, nor to the muscle-blood ratios. To explain their unexpected result, Jacobs and Kaiser (1982) suggest that the four minutes at each workload could have allowed diffusion of lactate from the muscle to the blood, or from the one muscle fibre type to the other, or even the use of lactate as an oxidative substrate for contraction.

II) Blood lactate concentrations in relation to skeletal muscle fibre-type distribution.

Tesch (1980) examined lactate accumulation in different muscles after short-term maximal exercise, and found that the lactate concentration was related to the percentage of fast-twitch fibres. Thus muscles containing high percentages of fast-twitch fibres accumulated more lactate than did those with high percentages of slow-twitch fibres. Subjects with a high percentage of fast-twitch fibres were able to exercise at higher intensities than those with a high percentage of slow-twitch fibres, and Tesch concluded that this indicated a higher "anaerobic" capacity in these subjects.

III) Lactate turnpoint in relation to muscle fibre-type distribution.

Ivy, Withers, van Handel, Elger and Costill (1980) examined the relationship between the percentage of slow-twitch muscle fibres in the vastus lateralis muscle and the lactate turnpoint in a group of 13 subjects performing incremental exercise to exhaustion on a bicycle ergometer. They found that the percentage of slow-twitch fibres was significantly related to the lactate turnpoint in that the greater the percentage of such fibres, the later the turnpoint occurred. They concluded that there may be a cause-and-effect relationship between the

percentage of slow-twitch fibres and the lactate turnpoint and that, consequently, the ratio of slow-twitch to fast-twitch fibres may exert a genetic influence over the turnpoint, controlling the range within which the turnpoint can shift with training or de-training.

Sjodin and Jacobs (1981) also found a significant relationship between the percentage of slow-twitch fibres and the exercise intensity at the lactate turnpoint in trained marathon runners. In cyclists, Tesch, Sharp and Daniels (1981) found the same relationship. Komi, Ito, Sjodin, Wallenstein and Karlsson (1981) also found a significant relationship between the percentage of slow-twitch fibres and blood lactate levels during prolonged exercise at the "lactate turnpoint". They concluded that a higher percentage of slow-twitch fibres would result in a higher lactate turnpoint, since the greater proportion of slow-twitch fibres would result in a slower rate of lactate production.

In summary, the consensus of opinion is that fast-twitch muscle fibres produce more lactate than do slow-twitch fibres due to their higher glycolytic potential. Consequently, the greater the amount of slow-twitch fibres, the lower will be the blood lactate concentrations during exercise and the later the lactate turnpoint.

## G. CATECHOLAMINES AND BETA-RECEPTOR BLOCKADE.

The catecholamines (adrenaline and noradrenaline) are primarily involved with metabolism of fats and carbohydrates, as well as with cardiovascular changes during exercise. Circulating catecholamines have two major metabolic effects :

I) Lipolysis of adipose tissue triglyceride to free fatty acids. This is important in this context because high blood free fatty acid levels during exercise reduce the rate of glycolysis and therefore are likely to influence the rate of lactate formation.

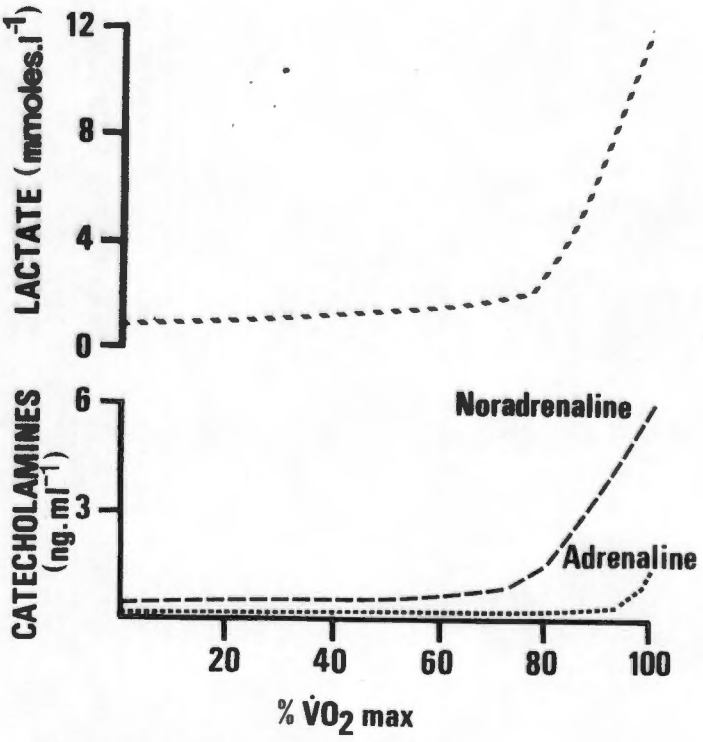
II) Stimulation of liver glycogenolysis resulting in increased glucose release from the liver and therefore potentially an increased rate of glycolysis in the active muscles (Newsholme and Start, 1973).

Catecholamine release increases with exercise depending on the duration and intensity of the workload (Howley, 1976; Christensen et al., 1979). Haggendal, Hartley and Saltin (1970) studied blood noradrenaline levels during submaximal and maximal exercise and found that these levels showed only a slight increase during exercise below 75% $VO_2max$. Above this exercise intensity, there was a sharp rise in blood noradrenaline levels.

These authors also reported that catecholamine levels during exercise were much lower in trained than untrained subjects, as also found by Winder, Hickson, Hagberg, Ehsani and McLane (1979) who studied catecholamine responses to exercise before and after a nine week training period. They found that within three weeks of the start of the training program, catecholamine levels fell during exercise.

In a series of research articles between 1980 and 1982, Lehmann and various co-workers examined catecholamine levels during exercise and compared men and women, men and boys, young and old subjects and trained and untrained subjects. Studying medium distance runners after a ten kilometre race, after a 55 metre sprint and on the treadmill at varying speeds, Lehmann, Keul, Schmid, Kindermann and Huber (1980) found that catecholamine levels increased slightly up to about 80% $VO_2max.$, and thereafter showed a rapid, ten-fold increase. Furthermore, catecholamine levels increased parabolically in relation to running speed and showed a close relationship to the lactate turnpoint (figure 18).

Lehmann, Keul and Korsten-Reck (1981) compared adults with boys during graduated treadmill exercise, and reported the same findings except that catecholamine levels during exercise were higher in boys than in adults.




(From Lehmann et al, 1980)

FIGURE 18

Blood lactate, noradrenaline and adrenaline levels all increase at the same running speed and show very similar turnpoints.

Similarly, Lehmann, Keul, Berg and Stippig (1981) found higher exercising catecholamine levels in women than in men, while Lehmann, Keul, Huber, Bachl and Simon (1981) found that noradrenaline and lactate levels were significantly higher in elderly subjects. Since the older subjects did not reach the same maximal lactate levels as the younger subjects, Lehmann et al. (1981) concluded that noradrenaline levels during exercise showed a direct relationship to age and to decreased physical performance.

Haggendal et al. (1970), Winder et al. (1979), and Lehmann, Keul, Huber and da Prada (1981) reported that both lactate and catecholamine levels were lower in trained than in untrained subjects at the same relative submaximal workloads, although there were no differences in concentrations after maximal exercise. A direct relationship was found between catecholamine and lactate concentrations; submaximal exercise was characterised by low lactate and low catecholamine levels while higher intensity exercise was characterised by rapid increases in both catecholamine and lactate levels. Although lactate and catecholamine levels showed a constant relationship with each other, this relationship became less exact during higher exercise levels and especially during recovery.

Thus it appears that there is a definite relationship between

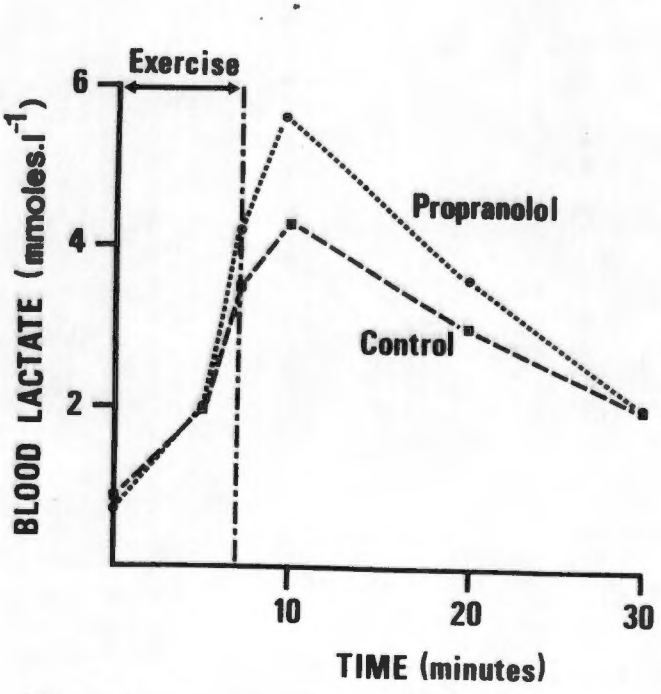
catecholamine release during exercise and increased muscle lactate production. It also appears that the closest relationship exists between noradrenaline specifically and lactate levels which show virtually identical "turnpoints".

The close relationship between blood lactate and noradrenaline levels suggests that beta-blockade may alter the lactate turnpoint, particularly as muscle glycogenolysis may be activated by beta-stimulation (Day, 1975).

Frisk-Holmberg, Jorfeldt, Juhlin-Dannfelt and Karlsson (1979) were amongst the first to study the effects of long-term beta-blockade with alprenolol. Patients exercised at 50% $VO_2max$. under control conditions, and again four hours after ingestion of propranolol. Resting and maximal exercise heart rate decreased by about 30%, during exercise with alprenolol. Whereas resting blood lactate levels were unchanged, blood lactate levels during exercise were significantly lower during beta-blockade (2.3 $mmol.l^{-1}$ compared to 3.4 $mmol.l^{-1}$). However, based on estimated muscle lactate concentrations (which apparently increased during alprenolol treatment) and higher muscle-blood lactate ratios, Frisk-Holmberg et al. (1979) suggest that the lower blood lactate levels indicate impaired translocation of lactate from muscle to blood as a result of beta-blockade, rather than due to inhibition of glycogenolysis.

Twentyman, Disley, Gribbin, Alberti and Tattersfield (1981) tested subjects before and two hours after propranolol ingestion both during a progressive incremental test to exhaustion and during steady-state exercise lasting six minutes at 50% and 70% $VO_2max$. In all cases, propranolol resulted in lower heart rates, increased blood glucose levels, and lower plasma free fatty acid levels. The highest blood lactate levels were recorded after propranolol ingestion, which contradicts findings of Day (1975) and Frisk-Holmberg et al. (1979). These researchers concluded that the higher lactate levels indicate an increased level of "anaerobic" metabolism caused by changes in peripheral muscle perfusion, with propranolol reducing muscle perusion, and increasing glycogenolysis and glucose metabolism in preference to fat oxidation (figure 19).

Uusitupa et al. (1982) have evaluated the metabolic consequences of beta-blockade during prolonged exercise lasting 30 minutes. In contrast to previous workers who found that beta-blockade either increased or decreased blood lactate levels, Uusitupa et al. (1982) found that the exercise-induced elevation in blood lactate levels was not significantly influenced, even though the rate of muscle glycogenolysis, assessed by muscle glycogen concentrations before and after exercise, tended to be slightly decreased.



(From Twentyman et al, 1981)

FIGURE 19

Blood lactate levels during exercise following beta-blockade with propranolol were higher than during a control test, which is contrary to the earlier findings of Day (1975) and Frisk-Holmberg et al. (1979).

In summary, catecholamines, particularly noradrenaline, appear to closely mirror the elevated blood lactate levels which occur during exercise :

a) Haggendal et al. (1970) showed that noradrenaline levels rose gradually up to an exercise intensity of 75% $VO_2max.$, and thereafter increased sharply. Similar results were found by Wyndham et al. (1962), Wasserman et al. (1973), Davis et al. (1976), Stegmann et al. (1981) and Yoshida et al. (1982) who all measured blood lactate levels during a progressive exercise protocol.

b) Haggendal et al. (1970), Winder et al. (1979) and Lehmann et al. (1981) all showed that both blood lactate and catecholamine levels were much lower in trained than in untrained subjects.

Since catecholamine effects are mediated via the beta-receptors, it would be reasonable to assume that beta-blockade during exercise would result in lower blood lactate levels. This was in fact shown by Frisk-Holmberg et al. (1979), but not by Twentyman et al. (1981) and Uusitupa et al. (1982) who both showed that lactate levels did not decrease following beta-blockade.

## 2.4 ADDITIONAL CONSIDERATIONS CONCERNING THE LACTATE TURNPOINT.

### A) THE RELATIONSHIP BETWEEN MUSCLE AND BLOOD LACTATE CONCENTRATIONS.

When blood lactate levels are measured during exercise, it is frequently assumed that these levels correlate with intramuscular lactate concentrations and with the rate of lactate production in the exercising muscles. It is necessary therefore to consider whether blood lactate levels accurately reflect the levels of muscle lactate.

Diamant, Karlsson and Saltin (1964) measured muscle and blood lactate levels at rest and after exhausting cycle exercise and found that there was a marked gradient between muscle and blood lactate concentrations which was most pronounced immediately after exercise (19.0 $mmol.l^{-1}$ in muscle compared to 11.0 $mmol.l^{-1}$ in blood). Only after 30 minutes of rest had the gradient disappeared (figure 20). Muscle lactate levels decreased asymptotically immediately on cessation of exercise, whereas blood lactate levels continued to rise for the first ten minutes and only then began to drop. Resting muscle lactate levels were also higher than blood lactate levels in all subjects (3.0 $mmol.l^{-1}$ and 1.4 $mmol.l^{-1}$ respectively).

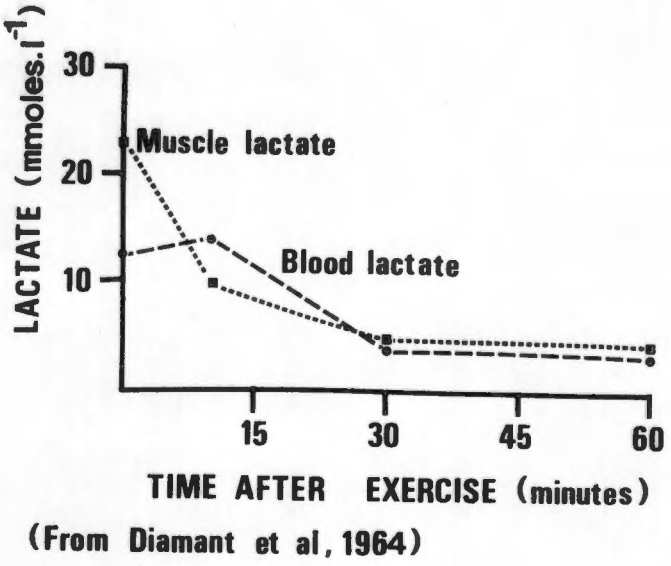



FIGURE 20

Muscle lactate levels were higher than blood lactate levels immediately after exercise, and only paralleled each other 30 minutes after the cessation of exercise.

Agnevik, Karlson, Diamant and Saltin (1969) measured muscle lactate levels in exercising muscle in relation to the oxygen debt, and also found that post-exercise muscle lactate concentrations were higher than blood lactate concentrations. Muscle lactate levels fell rapidly immediately after exercise, whilst blood lactate levels increased slightly for the first ten minutes, and then decreased gradually for up to 60 minutes after exercise.

Karlsson and Saltin (1970) measured muscle lactate and phosphagen concentrations after maximal exercise. As found by the previous workers, peak post-exercise blood lactate levels were always lower than muscle levels (13.4 $mmol.l^{-1}$ compared to 16.0 $mmol.l^{-1}$ at the highest intensity). Whether the workload was exhausting or not, both blood and muscle lactate accumulation increased until exhaustion. Lactate accumulation during the highest intensity was double that at the lowest load, and Karlsson and Saltin (1970) suggest that these lower levels may be due to either lower lactate production, or to increased lactate oxidation rates due to increased recruitment of fibres which use lactate as a fuel. They suggest that while lactate production is dependent on the exercise intensity, lower blood lactate levels measured during short-term maximal exercise when compared to prolonged exercise at an equivalent intensity occurred because there was too little time for lactate to

diffuse out of the muscle into the blood, or for it to be used as a substrate in non-exercising muscles.

Karlsson (1970) measured blood and muscle lactate concentrations at rest, after submaximal exercise lasting ten minutes, and after maximal exercise lasting three to five minutes. Muscle lactate levels were higher at rest (2.3 $mmol.l^{-1}$ compared to 1.6 $mmol.l^{-1}$), during submaximal exercise (10.4 $mmol.l^{-1}$ compared to 7.7 $mmol.l^{-1}$) and during maximal exercise (17.1 $mmol.l^{-1}$ compared to 10.0 $mmol.l^{-1}$).

Bergstrom, Guarnieri and Hultman (1971) examined lactate levels in blood and muscle during heavy exercise lasting 20 minutes. Blood lactate levels increased throughout the work period, with the highest values being recorded at the end of exercise (12 $mmol.l^{-1}$). Muscle lactates, on the other hand, increased initially in the first five minutes and then remained constant (32 $mmol.l^{-1}$) or decreased slightly (20 $mmol.l^{-1}$) during the remainder of the exercise period. Similarly, Bergstrom et al. (1971) found that muscle lactate levels were approximately three times higher than blood lactate levels at all exercise intensities (12.3 $mmol.l^{-1}$ compared to 4.0 $mmol.l^{-1}$ respectively after five minutes of exrcise, and 13.8 $mmol.l^{-1}$ compared to 5.5 $mmol.l^{-1}$ respectively after 20 minutes of exercise).

In another study, Karlsson (1971) examined muscle and blood lactate levels during prolonged mild exercise (50% $VO_2$max.) and during severe exercise to exhaustion. Up to 50% to 60% $VO_2$max., no increases in muscle lactate occurred, but thereafter muscle lactate levels increased rapidly. Karlsson (1971) also examined muscle and blood lactate levels under three conditions of intense exercise :

I) Repeated maximum exercise bouts of 60 second duration resulted in maximum lactate concentrations from the end of the first exercise period. Repeated work bouts did not increase lactate levels further. Blood lactate levels, on the other hand, continued to increase during each rest period until they reached a level equal to the muscle lactate concentration. Karlsson (1971) concluded that the highest blood lactate concentrations measured following brief, exhaustive exercise reflected the muscle lactate concentrations "fairly well", and that therefore maximal blood lactate measurements were a useful indicator of peak muscle lactate concentrations.

II) During exercise at 50% $VO_2$max. which followed prolonged heavy exercise of two to four hours and five to seven hours duration, blood lactate levels were lower than they were during exercise that was not preceeded by such prolonged

exercise. Muscle lactate levels were the same, however, suggesting that prolonged exercise led to an increased utilisation of blood-borne lactate during subsequent exercise bouts.

III) During submaximal exercise, muscle and blood lactate concentrations showed a concentration gradient which increased as the workload increased, and equal concentrations only occurred in muscle and blood ten minutes after cessation of exercise. As also found by Diamant, Karlsson and Saltin (1964) and Agnevik et al. (1969), Karlsson (1971) showed that blood and muscle lactate levels continued to decrease asymptotically after ten minutes of rest, with levels taking more than 60 minutes to reach basal values.

The highest muscle lactate concentrations were observed at exhaustion after maximal exercise, and were approximately double the blood lactate concentrations measured simultaneously. In contrast, Bergstrom et al. (1971) found that muscle lactate levels were approximately three times higher than blood lactate levels, whereas Karlsson (1971) found a close relationship between the highest blood and muscle lactate levels measured immediately after the cessation of short-term, maximal exercise.

Karlsson (1971) also reported that muscle lactate levels at maximal exercise were higher in trained than in untrained subjects (23 $mmol.l^{-1}$ and 17 $mmol.l^{-1}$ respectively) and this was reflected by similar differences in blood lactate levels (15 $mmol.l^{-1}$ and 12 $mmol.l^{-1}$ respectively). At rest and up to 75% $VO_2max.$, there was no difference in muscle lactate levels in trained and untrained subjects, but during submaximal exercise lower blood lactate concentrations were found in trained subjects. Although Karlsson (1971) does not discuss these findings further, the lower blood lactate levels observed in the trained compared to the untrained subjects, in the face of equal muscle lactate concentrations, would suggest an increased rate of lactate oxidation in tissues other than muscle. This finding is therefore compatible with that of Donovan and Brooks (1983) who showed that training did not influence the rate of lactate production by muscle but increased the rate of lactate oxidation by other tissues.

Karlsson, Nordesjo, Jorfeldt and Saltin (1972) examined the effect of a seven month training period on muscle and blood lactate concentrations during ten minutes of exercise at 85% $VO_2max.$, followed 15 minutes later by a five minute maximal test to exhaustion. Muscle lactate levels at 85% $VO_2max.$ decreased from 7 $mmol.l^{-1}$ to 3 $mmol.l^{-1}$ with training, but during maximal exercise no such training effect was observed.

After training, the rate of glycogen depletion during submaximal exercise was reduced, indicating a lower glycolytic rate which would account for the lower muscle lactate levels. No such relationship was observed with maximal exercise and muscle lactate levels were in fact higher after training, indicating an increased tolerance for high muscle lactate levels as also shown by Karlsson et al. (1972) and Robinson et al. (1973).

Knuttgen and Saltin (1972) examined changes in blood and muscle lactate levels during exercise at intensities ranging from mild (15% $VO_2$max.) to heavy (90% $VO_2$max.). Little or no change occurred in muscle and blood lactate levels up to 60% $VO_2$max., but at 75% and 90% $VO_2$max. large increases occurred which were proportional to the exercise intensity. Muscle lactate concentrations were consistently two to three times higher than blood lactate levels and these researchers concluded that this was due to a slow diffusion of lactate from muscle to blood.

Sahlin, Harris, Nylind and Hultman (1976) examined pH changes in relation to lactate levels in both muscle and blood after dynamic exercise. Lactate levels in muscle were two to three times higher than blood concentrations immediately after exercise, as also observed by Knuttgen and Saltin (1972). After eight minutes of recovery, blood and muscle concentrations were the same but, contrary to previous findings (Diamant et al,

1964; Agnevik et al, 1969; Karlsson, 1971), Sahlin et al. (1976) observed that thereafter muscle lactate levels were in fact lower than blood lactate levels.

Tesch, Daniels and Sharp (1982) studied muscle lactate concentrations in subjects exercising on an incremental cycle test, consisting of 30 watt increases every four minutes up to a previously determined lactate turnpoint at 65% $VO_2max$.. At this level, muscle lactate concentrations averaged 7 $mmol.kg^{-1}$ wet weight, whereas blood lactate levels immediately before cessation of exercise were 3 $mmol.l^{-1}$ and continued to rise to 3.5 $mmol.l^{-1}$ one minute after the cessation of exercise.

Muscle lactate levels after exercise were not significantly related to blood lactate levels. However, there was a positive relationship between muscle lactate levels and the degree to which blood lactate levels rose immediately after exercise. Only a small increase in blood lactate concentrations occurred in subjects with low post-exercise muscle lactate levels, whilst a much larger increase occurred in subjects with high post-exercise muscle lactate concentrations. These results indicate that higher muscle lactate levels favour increased lactate efflux, with the increase in exercise to post-exercise blood lactate levels indicating an increased release from muscle after exercise. Tesch et al. (1982) concluded that blood lactate

concentrations during submaximal steady-state exercise could not predict muscle lactate levels because of large individual variations in the muscle to blood lactate gradients.

Jacobs and Kaiser (1982) examined the relationship between muscle and blood lactate levels during an incremental cycle test to exhaustion involving 50 watt increments every four minutes. Muscle and blood lactate levels increased exponentially as exercise intensity increased, and at an intensity calculated to result in a blood lactate level of 4 $mmol.l^{-1}$, muscle lactate levels were just above 8 $mmol.l^{-1}$. At exhaustion, muscle lactate levels were again double the blood lactate concentrations (20 $mmol.kg^{-1}$ wet weight compared to 9 $mmol.l^{-1}$). Jacobs and Kaiser (1982) concluded that there was a relationship between blood and muscle lactate levels at the 4 $mmol.l^{-1}$ threshold, and suggest that blood lactate concentrations do in fact reflect muscle lactate concentrations at exercise intensities close to that specific threshold.

Although no significant correlation between muscle and blood lactate levels above the 4 $mmol.l^{-1}$ threshold was evident, the muscle to blood ratio increased markedly at this intensity. Jacobs and Kaiser (1982) suggested that this indicated that lactate release was maximal at blood lactate concentrations of up to 4 $mmol.l^{-1}$.

In the final relevant study, Hughson et al. (1982) showed that muscle lactate levels increase linearly with increasing exercise intensity during progressive exercise even below the blood lactate turnpoint and do not show a sudden "turnpoint".

In summary, research concerning the relationship between muscle and blood lactate levels during exercise can be categorised as follows :

I) Those who conclude that no specific relationship exists. Karlsson (1970) found that while muscle lactate levels were higher than blood lactate levels at rest, during submaximal exercise and during maximal exercise, these results did not show a clear relationship between blood and muscle lactate levels.

Tesch et al. (1982) showed a positive relationship between muscle lactate levels and the exercise to post-exercise blood lactate differences, but concluded that levels in individual subjects were not significantly correlated.

Diamant et al. (1964) and Agnevik et al. (1969) found that muscle lactate levels were higher than blood lactate levels after exercise, but they did not examine the possibility of any specific relationship between the two.

II) Those who found a relationship.

Karlsson and Saltin (1970), Karlsson (1970), and Karlsson et al. (1972) all showed that peak blood lactate levels reflected muscle lactate concentrations "fairly well" after maximal exercise. Sahlin et al. (1976) extended this relationship by concluding that muscle lactate concentrations were two to three times greater than blood lactate concentrations measured simultaneously after maximal exercise. Bergstrom et al. (1971), Karlsson (1970), Knuttgen and Saltin (1972) and Jacobs and Kaiser (1982) all found that muscle lactate concentrations were consistently two to three times higher than blood lactate concentrations during prolonged submaximal exercise.

It would seem then, that although no definite relationship has been established between muscle and blood lactate concentrations, muscle lactate levels are consistently higher than blood lactate levels, placing doubt on the validity of using blood lactate measurements as indicative of actual muscle lactate concentrations. However, since most researchers consistently reported muscle lactate levels two to three times higher than blood levels, blood lactate levels do provide an indirect estimate of muscle lactate levels, although they should not be used to calculate accurately absolute muscle lactate concentrations.

## B PRACTICAL RELEVANCE OF A LACTATE TURNPOINT.

The lactate turnpoint, like the $VO_2max.$, is frequently used as an indication of an individual's ability to perform dynamic exercise, and of his present state of fitness. A delayed lactate turnpoint indicates an ability to exercise at a higher intensity before blood lactate levels start to rise. Since increases in blood and muscle lactate levels are associated with fatigue in short-duration, high-intensity exercise, the higher the work intensity at which blood lactate levels start to rise, the greater that athlete's "fitness" and the greater his ability to resist fatigue during that type of exercise.

Farrell, Wilmore, Coyle, Billing and Costill (1979) tested a group of long distance runners running on a treadmill at speeds and times similar to those they achieved during races at distances ranging from 10 - 42.2 km. They found a significant relationship between racing performance at all distances and the speed at which blood lactate levels began to accumulate, the lactate turnpoint, regardless of the competitive abilities of the runner. They suggested that especially during the 42.2 km. marathon, runners maintain an average velocity which is only slightly above the running velocity at the lactate turnpoint, but not severe enough to cause blood lactate levels to rise continuously.

Sjodin and Jacobs (1981) also found a strong relationship between marathon-running performance and the lactate turnpoint. The ability to perform prolonged exercise was closely related to both the running velocity at the lactate turnpoint, and to the ability to run at a pace close to that velocity during the race.

Thus it would appear that marathon runners are able to pace themselves to maintain an average speed which is close to that at which their lactate turnpoint occurs. It follows then that the lactate turnpoint may be an important predictor not only of general running fitness (Wyndham et al, 1969; see figure 13), but also of potential performance in running races. For this reason, it is clear that further research to define the nature of the lactate turnpoint is warranted.

## 2.5 SUMMARY OF THE LITERATURE REVIEW.

Blood lactate levels remain stable at low exercise intensities, but rise as a result of an imbalance in the rates of production and uptake of lactate, with this rise being affected by both the intensity and the duration of exercise. As the exercise intensity increases, or exercise becomes prolonged, so the equilibrium between lactate production and uptake is altered. During high intensity exercise a workload is reached at which the rate of lactate production exceeds its rate of oxidation, resulting in a continuous accumulation of blood lactate.

Blood lactate levels are also influenced by the following factors :

1) Training : trained athletes have lower blood lactate levels than do untrained athletes working at the same percentage $VO_2$max., with the turnpoint in trained athletes occurring at higher work intensities (Saltin et al, 1976; Denis et al, 1982).

2) Diet : the greater the pre-exercise glycogen stores, the greater the potential for lactate production. During exercise, subjects on a high carbohydrate diet have higher blood lactate levels than they do when exercising at the same intensity on a mixed diet or on a fat/protein diet

(Bergstrom et al, 1967; Ivy et al, 1981).

3) Skeletal muscle fibre-type : the different metabolic profiles of fast-twitch and slow-twitch muscle fibres result in slow-twitch fibres producing less lactate than do the fast-twitch fibres (Essen and Haggmark, 1975; Tesch et al, 1978). Consequently, athletes with muscles comprising predominantly slow-twitch fibres will not only have lower blood lactate levels at the same work intensities than athletes with predominantly fast-twitch muscle fibres (Tesch, 1980), but their blood lactate turnpoints will also occur at higher exercise intensities (Ivy et al, 1980; Sjodin and Jacobs, 1981).

It appears that muscle lactate production results from either or both of two processes :

1) Muscle anaerobiosis : In favour of the theory that lactate is produced as a result of tissue hypoxia are the results of Lundin and Strom (1947) and Linnarson et al. (1974) who showed tha blood lactate levels were increased when subjects exercised while breathing air containing low oxygen percentages. Against these results are the observations that the mild arterial hypoxemia that occurs during severe exercise is not sufficient to cause a major limitation in

the oxygen supply to the muscles (Dempsey et al, 1975; Dempsey et al, 1982).

Further evidence against anaerobiosis is that lactate is produced under conditions of steady-state oxygen uptake (Thomas et al, 1965), and that blood lactate levels remain elevated but constant during prolonged submaximal exercise (Nagle et al, 1970; Scheen et al, 1981). If anaerobiosis was the sole cause of muscle lactate production, blood lactate levels would continue rising for the duration of exercise instead of remaining constant.

2) Glycolytic overflow : The same arguments that contradict the theory of anaerobic production of lactate during exercise may be used to support the theory that lactate is produced because the oxidative capacity of the mitochondria is exceeded, resulting in an imbalance between the rates of pyruvate production (from glycolysis) and its' oxidation by the mitochondria in the Krebs cycle. For example, lactate is released from muscle even in the presence of high venous oxygen tensions (Jobsis, 1963; Keul et al, 1967), whereas, conversely, low oxygen tensions are not necessarily accompanied by elevated blood lactate levels (Doll et al, 1968; Dempsey et al, 1975).

In support of these conclusions, Mazzeo et al. (1982) reported lactate production and oxidation under conditions of constant oxygen uptake, while Jones and Ehrsam (1982) concluded that muscles could not be hypoxic if exercise could be maintained for prolonged periods with lactate levels remaining elevated but constant.

Considering the above arguments, my own conclusions are that blood lactate levels remain low during low intensity exercise because any lactate produced is being oxidised and taken up either by slow-twitch fibres or by the heart and liver, for example. As the exercise intensity increases, so the rate of production of lactate increases in accordance with the increased rate of pyruvate production from glycolysis. Up to a certain exercise intensity, (around a blood lactate level of 4 $mmol.l^{-1}$), this increased rate of production is matched by an increased rate of lactate uptake by other tissues. But beyond this exercise intensity lactate production exceeds lactate uptake so that blood lactate levels continue to rise.

It seems, therefore, that whereas glycolytic overflow is primarily responsible for lactate production at low exercise intensities, at workloads close to or exceeding 100% $VO_2max.$, tissue anaerobiosis may contribute to the rapid increases in blood lactate levels, but direct evidence of this possibility is lacking.

# CHAPTER THREE

## RESEARCH AIMS, MATERIALS AND METHODS.

The literature review indicates that there are three main questions involving the production of lactate during exercise :

1) What is the biochemical basis for increased lactate production during exercise? Is it caused by tissue anaerobiosis or is it due to glycolytic overflow?

2) What is the significance of the 2 $mmol.l^{-1}$ and the 4 $mmol.l^{-1}$ blood lactate concentrations, and why do blood lactate levels show specific patterns during exercise at these intensities?

3) Is there a relationship between blood lactate levels measured during progressive exercise and those measured during prolonged, constant intensity exercise?

In accordance with these aims, three different studies were conducted :

A) A comparison of blood lactate levels measured at 30 second intervals during progressive exercise to exhaustion, with blood lactate levels measured at the same intervals but during six minutes' exercise at a constant, pre-selected intensity.

B) A comparison of blood lactate levels measured during progressive exercise under normal and neutral pH conditions obtained with a bicarbonate infusion.

C) A comparison of blood lactate levels measured during progressive exercise before and after beta-receptor antagonism with propranolol.

The rationale for these studies was to determine whether the rise in blood lactate levels during exercise could be manipulated by continuous exercise, by a bicarbonate infusion or by beta-receptor antagonism .

The aim was to manipulate muscle lactate production by interventions aimed at both ends of the glycolytic pathway; first, by attempting to increase lactate release from the muscle by increasing the amount of buffer available, since Hirsch et al. (1972) showed that lactate diffuses out of the muscle cells more readily when buffer supplies are adequate. Second, by reducing the rate of muscle glycogenolysis by beta-receptor antagonism. Changes in the lactate turnpoint produced by either of these techniques would support the view that increased rates of muscle lactate production during exercise are more likely due to glycolytic overflow than to tissue hypoxia.

In addition, six-minute exercise periods were used in order to compare the lactate turnpoint measured during short-term, progressive exercise with that measured during continuous exercise. To date, the lactate turnpoint has not been determined during constant intensity exercise at a pre-selected intensity, and our aim was to see whether there is only a single blood lactate turnpoint, as indicated by a progressive protocol, or whether numerous such turnpoints could be identified. The occurrence of numerous turnpoints would also tend to support the theory of glycolytic overflow since, if anaerobiosis was responsible for the lactate increases, blood lactate levels would continue to rise and not remain constant at any exercise intensity.

## 3.1 A COMPARISON OF BLOOD LACTATE LEVELS MEASURED DURING PROGRESSIVE EXERCISE WITH BLOOD LACTATE LEVELS MEASURED DURING SIX MINUTES EXERCISE AT A CONSTANT INTENSITY.

Six runners of varying fitness levels performed a progressive treadmill test, starting at a speed of 8km $h^{-1}$ and zero inclination with the speed increasing by 0.5km.$h^{-1}$ every 30 seconds until voluntary exhaustion.

The subjects warmed up at 8km.$h^{-1}$ for five minutes while the right hand was heated with a hairdryer to "arterialise" the venous blood in the forearm. After an initial five minute warm-up, the treadmill was stopped and an indwelling catheter (20 gauge Jelco IV Catheter Placement Unit) was placed into a forearm vein. A length of polythene tubing was attached to the catheter at one end and, at the other end to the silastic tubing passing through a Varioperpex peristaltic pump (EYELA Micro Tube pump, MP-3). In this way blood was pumped from the vein and collected into pre-prepared 5ml. test-tubes containing 2mls. ice cold 0.3M perchloric acid (PCA) for subsequent lactate determination.

Before the tubing was attached to the catheter, the total internal volume of the tubing was measured and the pump rate adjusted so that blood leaving the vein would take precisely 60

seconds before it reached the test-tube. Heparinised saline was recirculated through the tubing for five minutes before the study to prevent blood clotting in the tubing during collection.

During the test, approximately 1ml. of blood was collected into test-tubes every 30 seconds and for a further five minutes after exercise had stopped. The test-tubes were prepared before each test and contained 2ml. ice-cold 0.3M perchloric acid (PCA). The test-tubes were then numbered and weighed on a Sartorius (type 1412) scale.

After each sample had been collected, the test-tube contents were mixed thoroughly on a Whirlimix and then stored on ice until the completion of the test. These samples were then centrifuged at 2000rpm in a Beckman centrifuge (model TJ6) for ten minutes and reweighed to calculate the amount of blood collected in each tube. To convert the change in weight to a blood volume, a specific gravity of 1.06 was assumed for blood. The supernatant was then poured off into correspondingly numbered test-tubes and frozen until the assay could be completed according to the method of Bergmeyer, 1974.

Glass tubes were then made up using three blanks and two standards as follows:

| | Standard | Blank | Test |
|---|---|---|---|
| Hydralazine buffer | 1.0 ml | 1.0 ml | 1.0 ml |
| NAD | 0.1 ml | 0.1 ml | 0.1 ml |
| PCA | - | 0.1 ml | - |
| LDH | 0.01 ml | 0.01 ml | 0.01 ml |
| Supernatant | - | - | 0.1 ml |
| Standard | 0.1 ml | - | - |

The solutions were then mixed on a vortex mixer (Fissons BP 931263) and kept at room temperature for 30 minutes.

The absorption at 340 nm was then read on the Beckman spectrophotometer (Model 35) which was zeroed against distilled water.

To calculate the blood lactate concentration in $mmol.l^{-1}$, the following calculation was used :

$$\frac{\text{Total volume in the test-tube}}{\text{Volume of supernatant}} \times \frac{\text{Vol. of PCA + blood}}{\text{Vol of blood}} \times \frac{1}{6.22}$$

where 6.22 is the millimolar extinction coefficient of NADH.

Blood lactate concentrations were then plotted for each 30 second interval to obtain a lactate accumulation curve (figure

1). The lactate turnpoint, identified as an abrupt increase in blood lactate levels (0.26 mmol.$l^{-1}$ change), was obtained visually on each curve (figure 2). Orr et al (1982) have shown that this visual method of turnpoint determination is as effective as determining the turnpoint using a computer algorithm.

Having established the running velocity at the lactate turnpoint, subjects returned to the laboratory seven to ten days later and exercised continuously for six minutes at speeds just above and just below the turnpoint. The normal warm-up procedure was again followed, then subjects started exercising at 8 km.$h^{-1}$ following the normal protocol of increasing the speed by 0.5 km.$h^{-1}$ every 30 seconds until the desired speed was reached. This speed was then maintained for six minutes whereafter the speed was increased by 0.5 km.$h^{-1}$ for a further six minutes. A final six minutes' exercise was performed at a treadmill speed another 0.5 km.$h^{-1}$ higher. During the test which lasted up to 25 minutes, blood lactate samples were collected continuously at 30 second intervals.

This same procedure was done twice more at weekly intervals, starting with six minutes at the exercise speed reached in the previous test, and concluding after the athlete had run two more workloads.

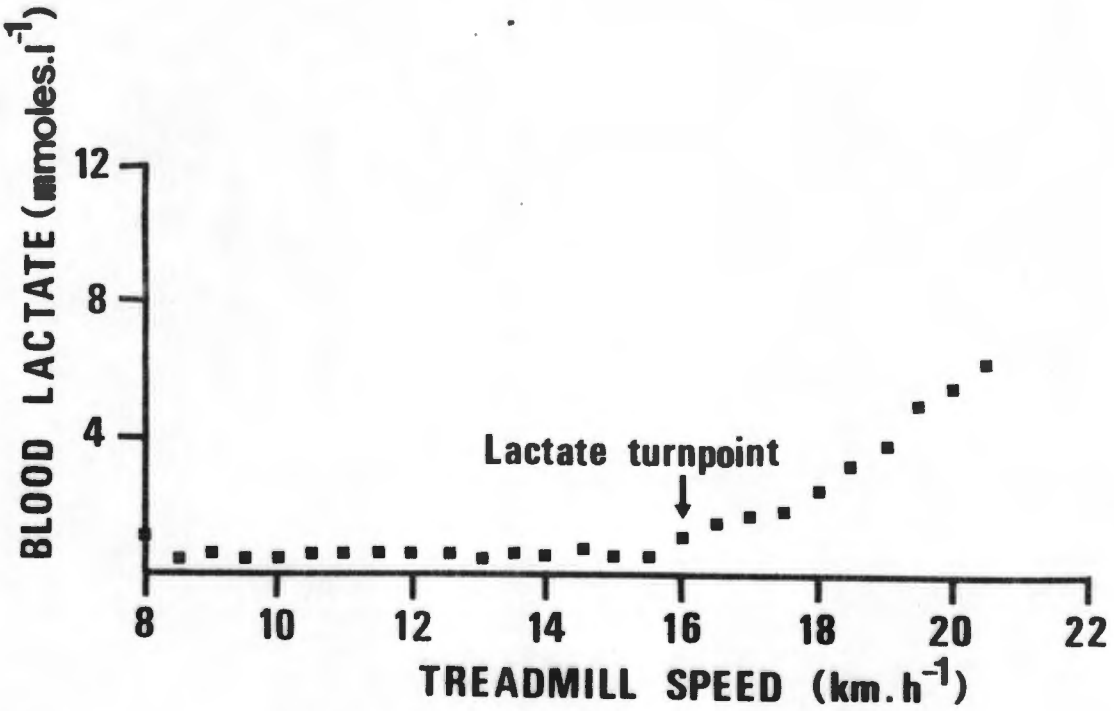



FIGURE 1

Blood lactate levels were plotted at 30 second intervals to establish a blood lactate accumulation curve for each individual during a progressive exercise test (subject TN). The lactate turnpoint was considered to occur at the running speed that caused the blood lactate level to increase abruptly from the starting concentration.

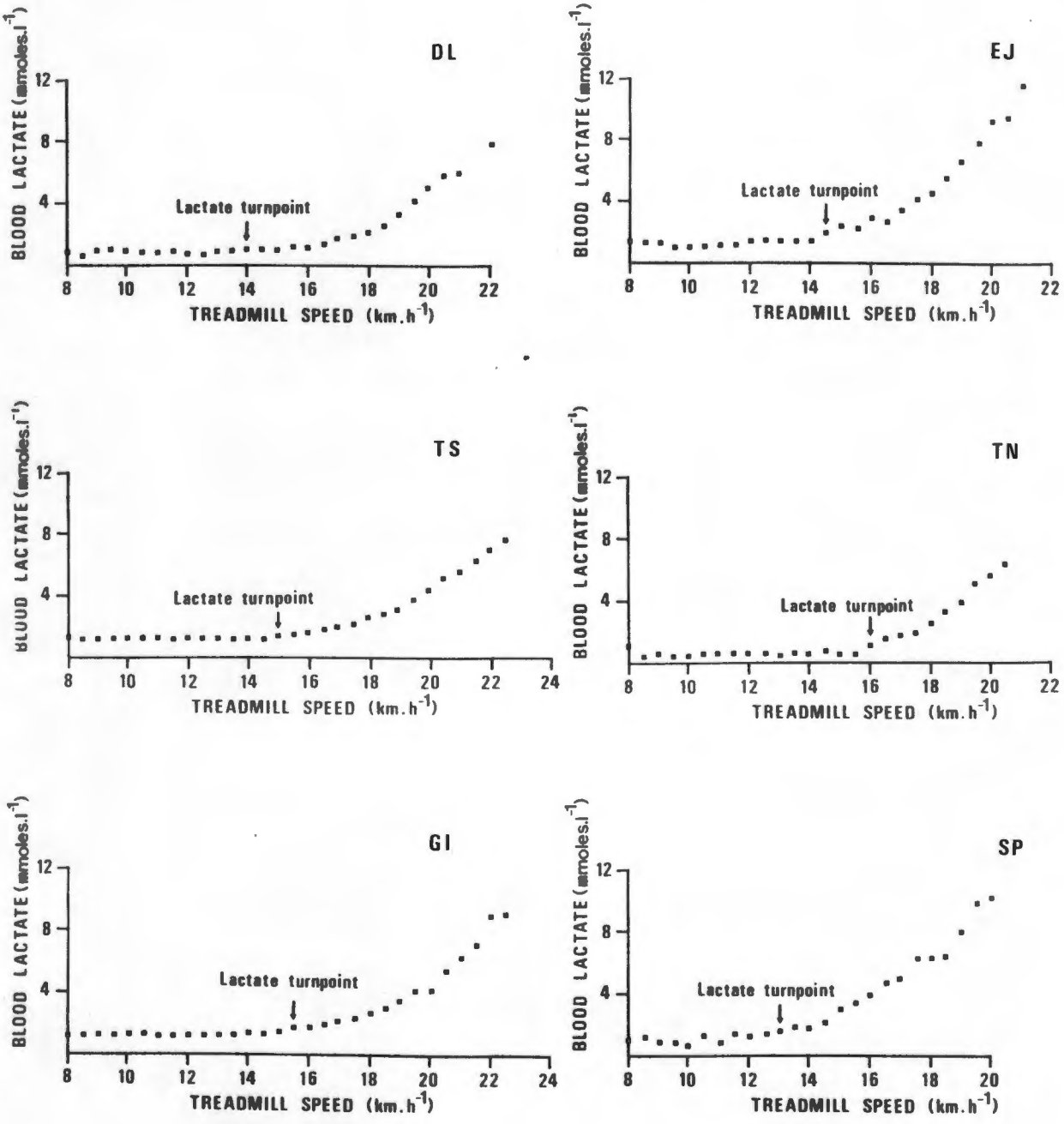



FIGURE 2

The blood lactate turnpoint was established visually for each subject using values obtained during the progressive incremental test to exhaustion. The turnpoint was considered to occur at the running speed that caused the blood lactate level to increase abruptly from the starting concentration.

In total, three running speeds below and four speeds above the lactate turnpoint were studied, as well as six minutes' exercise at the turnpoint itself. Blood lactate concentrations at each 30 second interval were then plotted for each six minute period.

## 3.2 A COMPARISON OF BLOOD LACTATE LEVELS UNDER ACIDEMIC AND NEUTRAL pH CONDITIONS OBTAINED BY A BICARBONATE INFUSION.

Following a 15 minute rest period, 4 trained runners and 2 untrained subjects exercised incrementally on a Monark cycle ergometer, starting at zero watts and increasing by 16.4 watts (100 $kpm.min^{-1}$) every minute until voluntary exhaustion, defined as the point where the subject was no longer able to maintain a pedalling rate of 50 rpm. Tests were performed in the afternoon, with subjects having ingested only fluids since breakfast.

As in the previous study, arterialised venous blood samples were drawn by in-dwelling cannula from a warmed hand vein, the success of the arterialisation being evidenced by blood $PO_2$ levels above 8 kPa. Blood samples were taken at rest, at the end of every second workload up to 163.5 watts (1000 $kpm.min^{-1}$), and thereafter at the end of every workload from 180 watts (1100 $kpm.min^{-1}$) until the end of the test. 1 ml of blood was pipetted into perchloracetic acid (as in the previous study) for subsequent spinning and plasma lactate assay. The remainder of each sample was used to measure blood gas tensions and pH using an ABL2 automatic blood gas analyser (Radiometer, Copenhagen), whose calibration was checked at the beginning and the end of the experiment using quality control solutions from the

manufacturers.

Blood bicarbonate was calculated from pH and $PCO_2$ using the Henderson-Hasselbalch relationship:

$$pH = pKa + \log_{10} \frac{[HCO_3]}{[0.031 \times PCO_2]}$$

(West, 1981).

Inspired ventilation was measured using a Parkinson-Cowan CD4 dry gas meter yielding an electrical output via a potentiometer. The gas meter was placed on the inspiration port of a one-way mouthpiece valve (Hans-Rudolph). Expired gas was directed from the mouthpiece into a baffled, six litre mixing chamber and sampled to obtain the fractional concentrations of oxygen and carbon dioxide using an S3A Applied Electro-chemistry oxygen analyser and a Gould-Godart Capnograph respectively. Oxygen intake ($VO_2$) was calculated at each workload using standard formulae (N.L. Jones et al., 1975).

A week later, subjects were re-tested using the same protocol, but on this occasion a 500 mmolar solution (4.2%) of sodium bicarbonate was infused intravenously via a cannula situated in the arm not being used for blood sampling. The objective of the infusion was to maintain the subject's pH and bicarbonate levels

at resting values throughout the test. No bicarbonate was infused during the initial workloads, with the infusion commencing at the workload during which a fall in blood bicarbonate first occurred in the control test. The amount of bicarbonate infused in any given minute was calculated from the fall in blood bicarbonate seen over that minute during the initial test. This mmol fall in bicarbonate was multiplied by one third of the subject's body weight in kilograms, making the assumption that bicarbonate is distributed in extra-cellular body water, accounting for approximately one third of body weight. In practice, the infusion commenced approximately two thirds of the way through the test in most subjects, and thereafter the infusion rate increased progressively until the end of the test when the infusion was stopped.

The amount infused therefore depended on the severity of the metabolic acidosis developed by each subject, and varied from a total of 135 to 365 mmol., mean 247 mmol.

## 3.3 A COMPARISON OF BLOOD LACTATE LEVELS BEFORE AND AFTER BETA-RECEPTOR BLOCKADE WITH PROPRANOLOL.

Four well trained marathon runners and two untrained subjects participated in this study. Two maximal progressive treadmill tests were conducted along the same lines described for the progressive versus the six-minute exercise tests. After a five minute warm-up and placement of the intravenous catheter, subjects started exercising at 8 $km.h^{-1}$ with the speed increasing 0.5 $km.h^{-1}$ every 30 seconds up to voluntary exhaustion. Blood samples were taken every 30 seconds as described earlier.

In the second maximal test conducted a week later, subjects ingested two, 40 milligram tablets of propranolol one hour before the test. A medical history was obtained for each subject prior to the propranolol test, with specific reference to asthma, diabetes or cardiovascular disease. Exactly the same procedure was followed in the treatment as in the non-treatment test.

In both tests, three electrocardiographic leads attached to disposable electrodes were used to record heart rate on an AI Life Trace (model 12). Heart rate was then recorded off the display every 30 seconds throughout the exercise period and for three minutes post-exercise.

## 3.4 STATISTICAL METHODS

In all the studies, non-parametric statistical tests were conducted in view of the small sample sizes. With only six points for comparison, normal distribution cannot be shown, as required for parametric statistics (Miller, 1982).

In the prolonged, constant intensity exercise test versus the progressive exercise test, the Wilcoxon matched-pairs signed ranks test was used to establish the point where blood lactate levels became statistically significant. Blood lactate levels obtained during the progressive test were compared with those obtained in the last 30 seconds of each six minute work period to ensure that steady-state levels had been reached.

The Wilcoxon matched-pairs signed ranks test was again used in the six-minute test in order to compare values obtained in the last 30 seconds of each test with those measured in the first 30 seconds.

In the bicarbonate infusion test, the most consistent means for data comparison between subjects who achieved different maximal workloads was the percentage $VO_2max$. It has been noted that, at very high workloads, $VO_2$ levels off, and may in fact

decrease slightly between the penultimate and final workloads. In this study, this occurred in 2 instances only - once during a control test, and once, on a different subject, during the infusion test. These differences in $VO_2$ were 0.2% and 2.0% respectively. For the purpose of statistical analysis, I therefore ignored the data that was collected after this "levelling off" occurred, and used only those values up to the true, $VO_2$max. It may be argued, however, that since values at 100% $VO_2$ max. are different from those measured at maximal exercise, they may affect my conclusions - for this reason, values obtained at maximal exercise, as well as those obtained at $VO_2$ max., are also presented for examination in Appendices III, IV and V.

Resting values and values obtained at true 100% $VO_2$ max. (as opposed to maximal exercise) were plotted, and a mean and standard deviation obtained. Since the $VO_2$ values between these two points varied in relation to the workload and were not the same for any individual in the pre- and post-infusion tests, it became necessary to use a method of interpolation in order to facilitate statistical analyses. For this purpose, fixed points of 20%, 40%, 50%, 60%, 70%, 80% and 90% were selected; linear regression between points either side of each of these percentages resulted in interpolated values which were then used for statistical analysis (see Appendices III, IV and V).

The differences between the infusion and the control conditions were compared using a Friedman Analysis of Variance, and if overall significance was established, the exact point was located using the Wilcoxon matched-pairs signed ranks test.

In the beta-antagonism study, statistically significant differences were determined using the Wilcoxon matched-pairs signed ranks test.

All results quoted in the text, tables and graphs refer to mean and standard deviation.

# CHAPTER FOUR

# EXPERIMENTAL RESULTS

## 4.1 A COMPARISON OF BLOOD LACTATE LEVELS DURING SIX-MINUTE, CONSTANT INTENSITY EXERCISE WITH THOSE MEASURED DURING PROGRESSIVE EXERCISE.

Six male subjects of average age 26.0 ± 5.4 years, average height 179.5 ± 5.9 centimetres, and average weight 74.8 ± 3.0 kilograms were tested.

Initially the blood lactate turnpoint was established visually in the progressive exercise test, and identified by an abrupt increase in the blood lactate concentrations (figure 2). This increase (0.26 ± 0.15 $mmol.l^{-1}$) occurred at an average treadmill speed of 15.75 $km\ h^{-1}$, and at a blood lactate level of 1.49 ± 0.34 $mmol.l^{-1}$. After their individual turnpoints had been established, subjects then exercised for six minutes each at three intensities below the turnpoint (14.25 $km.h^{-1}$, 14.75 $km.h^{-1}$ and 15.25 $km.h^{-1}$), at the turnpoint itself,and at four intensities above the turnpoint (16.25 $km.h^{-1}$ to 17.75 $km.h^{-1}$) with blood lactate levels being measured every 30 seconds (figure 3).

Visual inspection of the steady-state values showed that the lactate turnpoint, also identified by an average increase of 0.26 $mmol.l^{-1}$, occurred one workload earlier than in the progressive test i.e. at a speed of 15.25 $km.h^{-1}$ and a blood

## TABLE I

A comparison of blood lactate levels measured during progressive exercise with those measured during six minutes' exercise at a constant intensity.

| SUBJ. | AGE (YRS) | HT. (CMS) | WT. (KGS) | | BLOOD LACTATE LEVELS ($mmol.l^{-1}$). T-3 | T-2 | T-1 | T | T+1 | T+2 | T+3 | T+4 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GI | 32 | 170 | 72 | P | 1.40 | 1.37 | 1.41 | 1.70 | 1.77 | 1.94 | 2.13 | 2.40 |
| | | | | S | 1.71 | 1.75 | 2.05 | 2.91 | 2.87 | 3.20 | 4.77 | 5.67 |
| EJ | 25 | 186 | 74 | P | 1.45 | 1.52 | 1.80 | 1.98 | 2.65 | 3.00 | 2.90 | 3.00 |
| | | | | S | 1.97 | 2.08 | 2.41 | 2.89 | 4.70 | 5.90 | 7.98 | 10.7 |
| DL | 23 | 175 | 75 | P | 0.93 | 0.94 | 1.05 | 1.18 | 1.20 | 1.22 | 1.41 | 1.85 |
| | | | | S | 0.94 | 0.96 | 1.13 | 1.42 | 1.89 | 2.55 | 3.92 | 5.06 |
| TN | 33 | 183 | 80 | P | 0.73 | 0.52 | 0.57 | 1.09 | 1.41 | 1.17 | 1.84 | 1.52 |
| | | | | S | 0.94 | 1.12 | 1.09 | 1.40 | 1.99 | 3.35 | 5.80 | 8.33 |
| SP | 19 | 181 | 76 | P | 1.39 | 1.38 | 1.32 | 1.64 | 1.86 | 1.89 | 2.12 | 3.07 |
| | | | | S | 1.82 | 1.75 | 2.51 | 3.29 | 3.90 | 5.35 | 6.70 | 8.61 |
| TS | 24 | 182 | 72 | P | 1.13 | 1.21 | 1.19 | 1.33 | 1.50 | 1.58 | 1.70 | 1.87 |
| | | | | S | 0.82 | 0.99 | 1.01 | 1.23 | 1.42 | 1.59 | 4.41 | 6.15 |
| MEAN | 26 | 179.5 | 75 | P | 1.17 | 1.16 | 1.22 | 1.49 | 1.73 | 1.80 | 2.02 | 2.45 |
| SD | 5.4 | 5.9 | 3.0 | | 0.29 | 0.37 | 0.40 | 0.34 | 0.51 | 0.67 | 0.51 | 0.53 |
| MEAN | | | | S | 1.37 | 1.44 | 1.70 | 2.19 | 2.80 | 3.66 | 5.60 | 7.42 |
| SD | | | | | 0.52 | 0.48 | 0.70 | 0.93 | 1.28 | 1.66 | 1.51 | 2.15 |
| Statistical significance | | | | | NS | NS | NS | NS | NS | S | S | S |

KEY : "P" indicates results obtained during the progressive test; "S" indicates those results obtained during the six minute exercise test.
NS indicates no statistically significant differences; S indicates a statistical significance of $p<0.05$.
"T" indicates the blood lactate turnpoint obtained at a treadmill speed of 15.75 $km.h^{-1}$; the values either side of "T" indicate the number of workloads above or below the turnpoint, where one workload is 0.5 $km.h^{-1}$.
Therefore : "T-3" = 14.25 $km.h^{-1}$
"T-2" = 14.75 $km.h^{-1}$
"T-1" = 15.25 $km.h^{-1}$
"T+1" = 16.25 $km.h^{-1}$
"T+2" = 16.75 $km.h^{-1}$
"T+3" = 17.25 $km.h^{-1}$

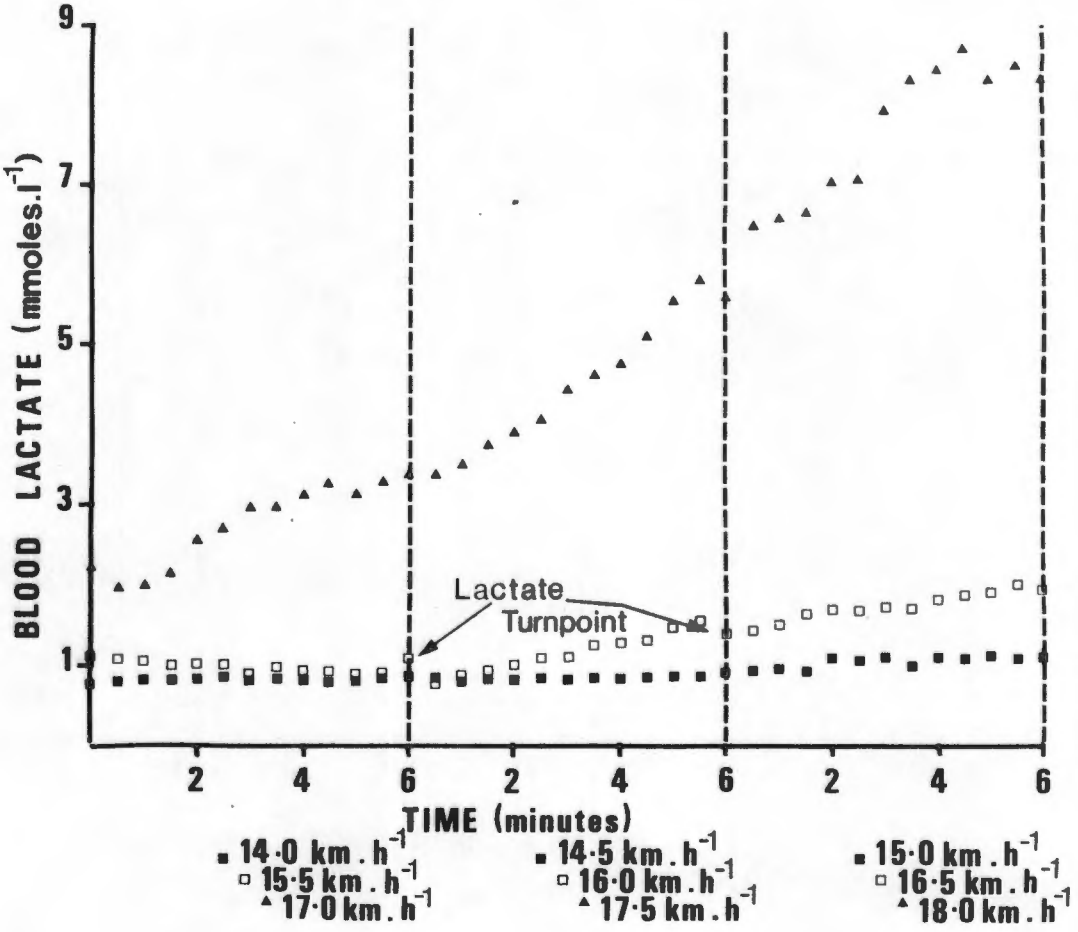



FIGURE 3

Blood lactate levels were measured at 30 second intervals during each six-minute exercise period of constant-intensity exercise (subject TN).

lactate level of 1.70 ± 0.70 mmol.$l^{-1}$ (figure 4).

Considering the progressive and six-minutes' exercise lactate curves individually (figure 4), lactate levels at "T - 3" (treadmill speed of 14.25 km.$h^{-1}$ and lactate levels of 1.37 mmol.$l^{-1}$) were used as basal concentrations for comparison with values measured at the other work levels. During the progressive test, blood lactate concentrations at the turnpoint "T" (treadmill speed of 15.75 km.$h^{-1}$ and lactate levels of 1.49 mmol.$l^{-1}$) were significantly different from basal values ($p<0.05$), whereas during the six-minute test this significance became manifest at "T - 1" (treadmill speed of 15.25 km.$h^{-1}$ and lactate levels of 1.70 mmol.$l^{-1}$). This shift to the left in the lactate turnpoint supports the visual evidence that the lactate turnpoint occurred 0.5 km.$h^{-1}$ earlier in the continuous intensity test than in the progressive test.

Blood lactate levels measured during the progressive test were then compared with those observed during the last 30 seconds of each six minute period in the constant intensity study. Although the shape of the curves appeared on visual inspection (figure 4) to be different from the "T - 1" workload, this difference only became statistically significant at the "T + 2" intensity, at which speed blood lactate levels during the progressive test were 1.80 ± 0.67 mmol.$l^{-1}$, compared to 3.66 ± 1.66 mmol.$l^{-1}$

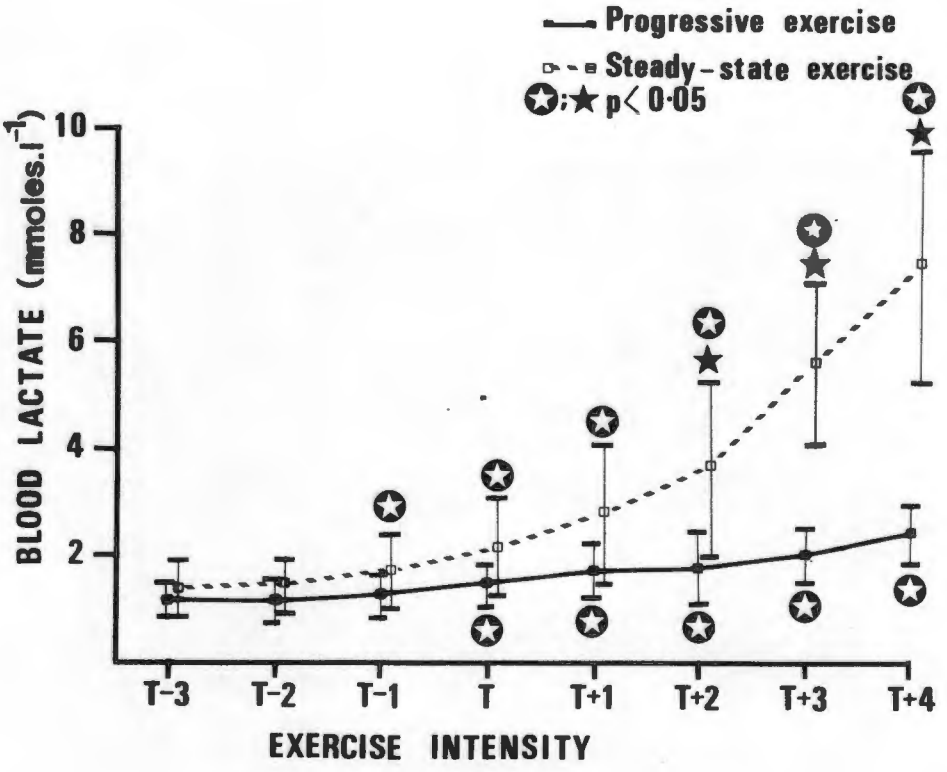



FIGURE 4

The blood lactate turnpoint occurred at an average speed of 15.75 km.h$^{-1}$ ("T") in the progressive test, and at an average speed of 15.25 km.h$^{-1}$ ("T - 1") in the six-minute test.

The solid star (★) indicates the treadmill speed at which blood lactate levels measured during the six-minute test were significantly different from those measured in the progressive test.

The open star within the dark circle (✪) indicates blood lactate levels which are higher than basal "T-3" levels. In the six-minute exercise test blood lactate levels were elevated at "T-1" whereas in the progressive test, these differences only become significant at the visually-identified lactate turnpoint ("T"). Thus the lactate turnpoint shifted to a lower workload during constant-intensity exercise.

in the six-minute test (figure 4).

Average blood lactate levels measured during the six-minute test were plotted after one, three and six minutes of exercise at the different running speeds (figure 5). At all running speeds, blood lactate concentrations increased in the first three minutes but thereafter either remained constant or continued to increase, depending on the exercise intensity. At all intensities, up to and including the lactate turnpoint, blood lactate levels remained constant during the last three minutes of each workload. Beyond the turnpoint, however, blood lactate levels continued to rise throughout the exercise period, rising more markedly as the exercise became more strenuous. For example, at "T + 1" (16.25 $km.h^{-1}$), blood lactate levels only increased by 0.1 $mmol.l^{-1}$ during the last three minutes of exercise, whereas they increased by 0.82 $mmol.l^{-1}$ at "T + 4" (17.75 $km.h^{-1}$). This increase during the last three minutes became significant at "T + 3" (17.25 $km.h^{-1}$ - figure 5).

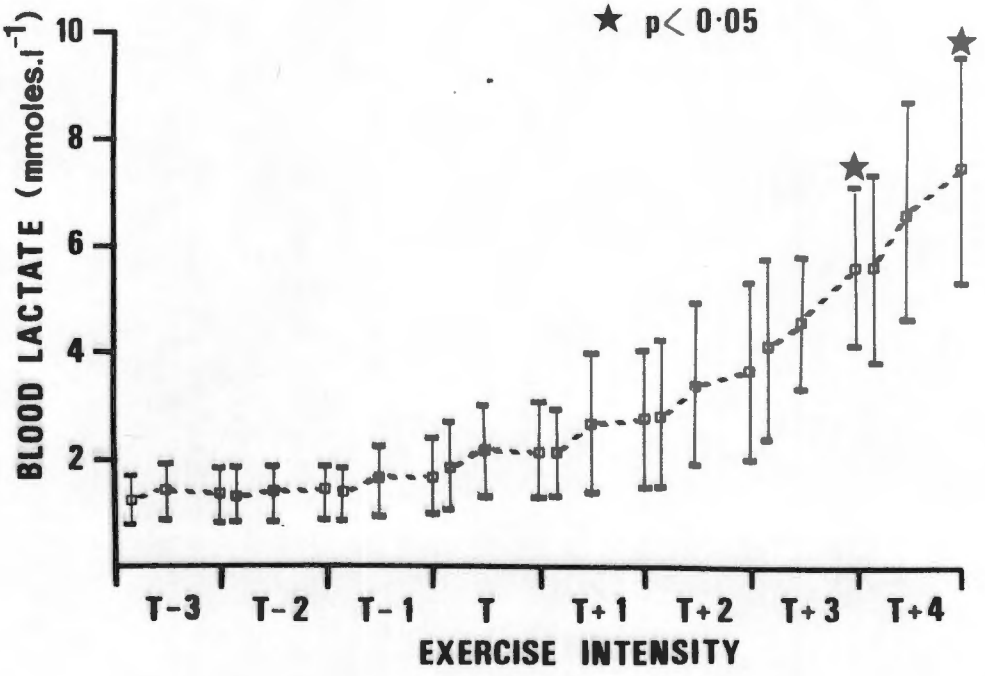



FIGURE 5

Blood lactate levels measured during the six minute protocol were plotted at one, three and six minute intervals in order to examine the trend of blood lactate accumulation during workloads above and below the lactate turnpoint ("T").

## 4.2 A COMPARISON OF BLOOD LACTATE LEVELS UNDER ACIDEMIC AND NEUTRAL pH CONDITIONS OBTAINED BY A BICARBONATE INFUSION.

Six male subjects of average age 28.7 ± 5.5 years, average height 178.8 ± 8.0 centimetres, and average weight 76.3 ± 7.5 kilograms were tested (table II). Average maximum oxygen uptake was 53.9 ± 9.5 mls.kg$^{-1}$.min$^{-1}$., reached at an average maximum workload of 291.6 ± 43.1 watts.

pH, blood lactate and blood bicarbonate levels were measured every two minutes up to a workload of 163.5 watts, and thereafter every minute. All other variables were measured every minute.

Figure 6 shows that pH under control conditions remained constant up to 50% $VO_2$max. (7.36 ± 0.01) and thereafter decreased sharply over the remainder of the exercise period, reaching a value of 7.27 ± 0.03 at 100% $VO_2$max. In the infusion test, pH remained constant throughout the test (7.38 ± 0.02), even increasing slightly towards the end of the test (7.42 ± 0.02 at 90% $VO_2$max.). pH values were significantly different at 70%, 80%, and 90% $VO_2$max. ($p<0.05$), but not at 100% $VO_2$max. However this probably resulted from a single extremely low pH level recorded in one of the subjects during the infusion condition.

## TABLE II

Subject data obtained in connection with bicycle ergometer tests used to compare blood lactate levels under acidemic and neutral pH conditions obtained by a bicarbonate infusion.

| SUBJECT | AGE (YRS) | HEIGHT (CMS) | WEIGHT (KGS) | $VO_2$ MAX. (ml/kg/min) | WORKLOAD MAX (Watts) |
|---|---|---|---|---|---|
| GI | 32 | 170 | 72 | 58.69 | 294.3 |
| EJ | 25 | 186 | 74 | 53.20 | 294.3 |
| GL | 26 | 170 | 68 | 67.10 | 359.7 |
| SM | 35 | 188 | 78 | 40.42 | 245.3 |
| TN | 33 | 183 | 80 | 57.68 | 310.7 |
| WN | 21 | 175 | 88 | 46.16 | 245.3 |
| MEAN | 28.7 | 178.8 | 76.7 | 53.88 | 291.6 |
| SD | 5.47 | 8.0 | 7.0 | 9.52 | 43.1 |

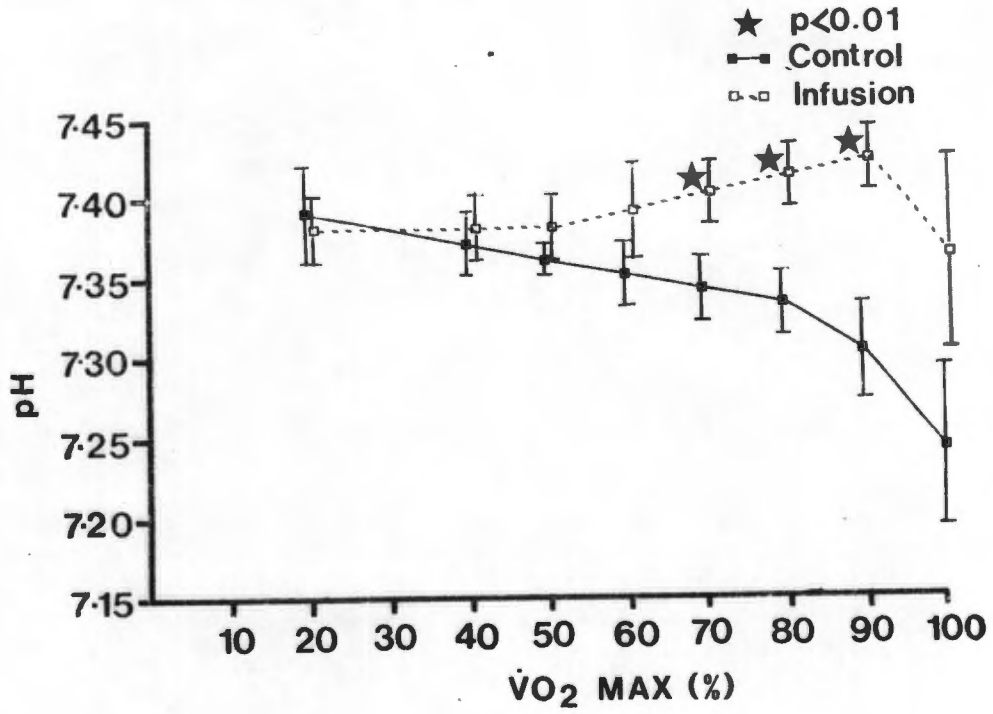



FIGURE 6

pH levels decreased significantly during the control test, but stayed relatively constant, even increasing slightly, during the bicarbonate infusion.

Blood bicarbonate levels also remained constant up to 50% $VO_2$max. in both the control and infusion tests (26.60 ± 1.10 mmol.$l^{-1}$ and 26.22 ± 2.18 mmol.$l^{-1}$ respectively), but thereafter decreased in the control test to 18.86 ± 1.98 mmol.$l^{-1}$ and stayed constant in the infusion test (27.36 ± 2.41 mmol.$l^{-1}$ at 100% $VO_2$max.), even increasing slightly towards the end of the test (see figure 7). Bicarbonate levels were significantly different from 70% $VO_2$max. to 100% $VO_2$max. ($p<0.05$).

The fact that both pH and bicarbonate levels remained constant in the infusion test indicates that the intention to maintain a neutral pH in each subject was successful.

Blood lactate levels increased non-linearly as the exercise intensity increased in both the control and the infusion tests, and there was no difference between the two conditions (figure 8). Blood lactate levels at 100% $VO_2$ max. were higher in the infusion test than in the control test (10.99 ± 1.13 and 9.19 ± 1.13 mmol.$l^{-1}$ respectively), but since results were only obtained for both tests in 3 subjects, statistical analyses could not be conducted (a minimum of six subjects are required for the Wilcoxon matched-pairs signed-ranks test). Even when results obtained at maximal exercise (as opposed to 100% $VO_2$ max.) are compared in the pre- and post-infusion states,

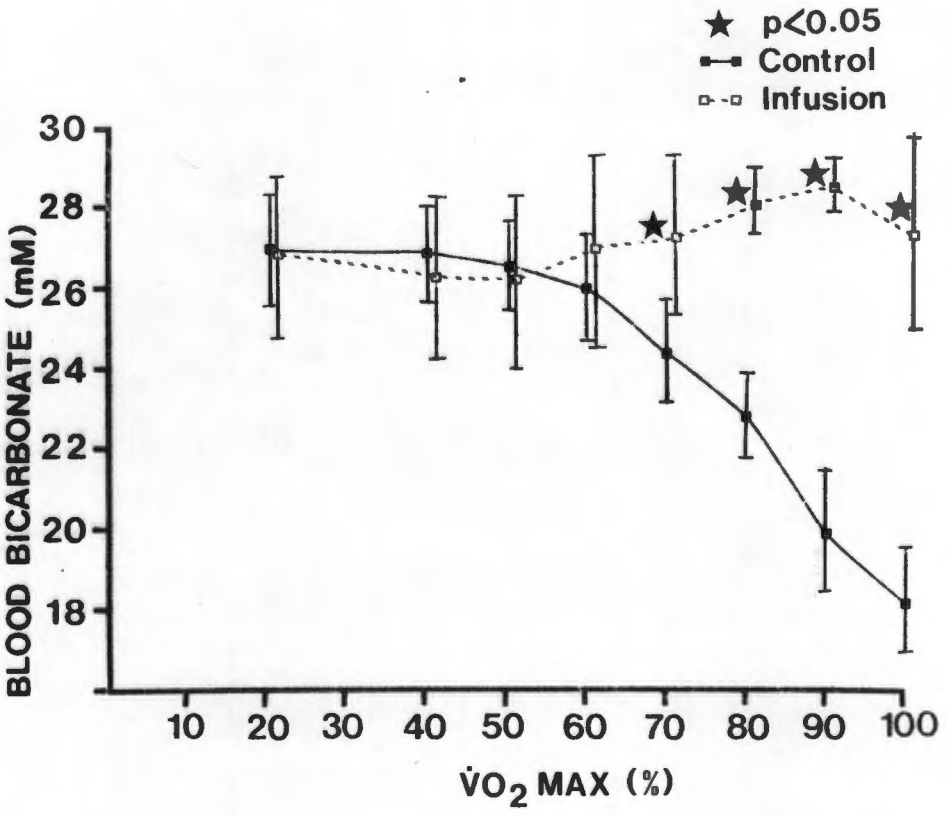



FIGURE 7

Blood bicarbonate levels decreased during the control exercise, but remained constant or increased slightly during the infusion test. This finding indicates that the infusion successfully maintained blood bicarbonate concentrations at near resting levels.

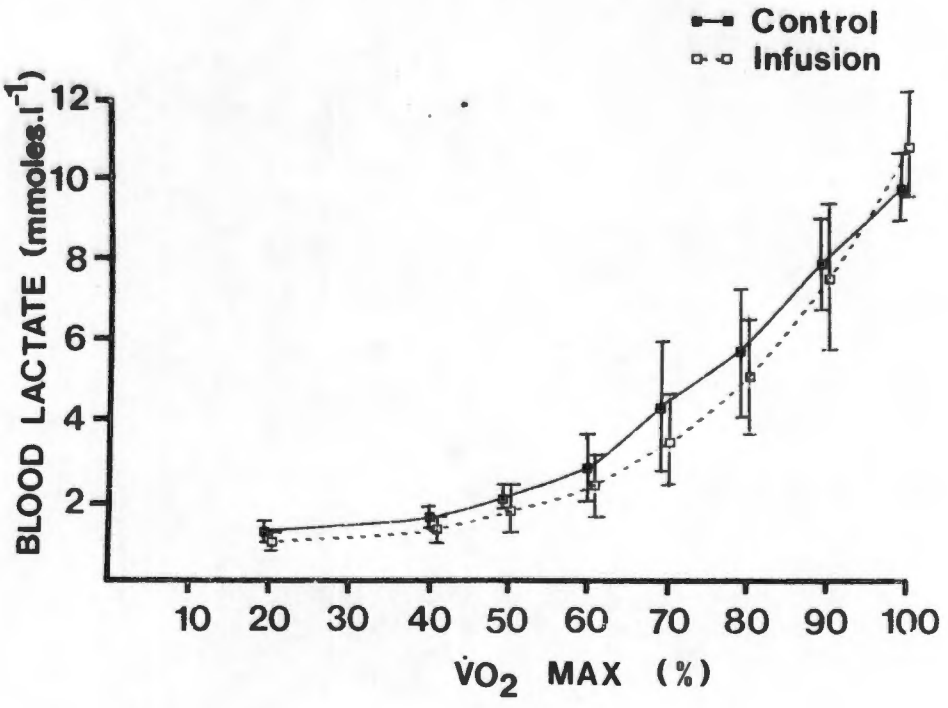



FIGURE 8

Although blood lactate levels during the infusion test are lower than during the control study at all exercise intensities except at 100% $\dot{V}O_2$ max., these differences were not statistically significant.

statistical significance could not be established due to insufficient. However, the trend was for blood lactate levels following bicarbonate infusion to be higher than those measured under control conditions and further studies will be essential in order to determine any significant changes.

The lactate turnpoint, obtained visually, occurred at 49.6% $VO_2$max. in the control test, and at 51.5% $VO_2$max. in the infusion test ($p > 0.1$), (see figure 9), but this was to be expected since the bicarbonate infusion only commenced at the time of the turnpoint, as calculated in the control test. Between the lactate turnpoint and 90% $VO_2$ max., there was no difference ($p > 0.05$) in the blood lactate values.

Appendices III, IV and V contain the full individual data for these experiments.

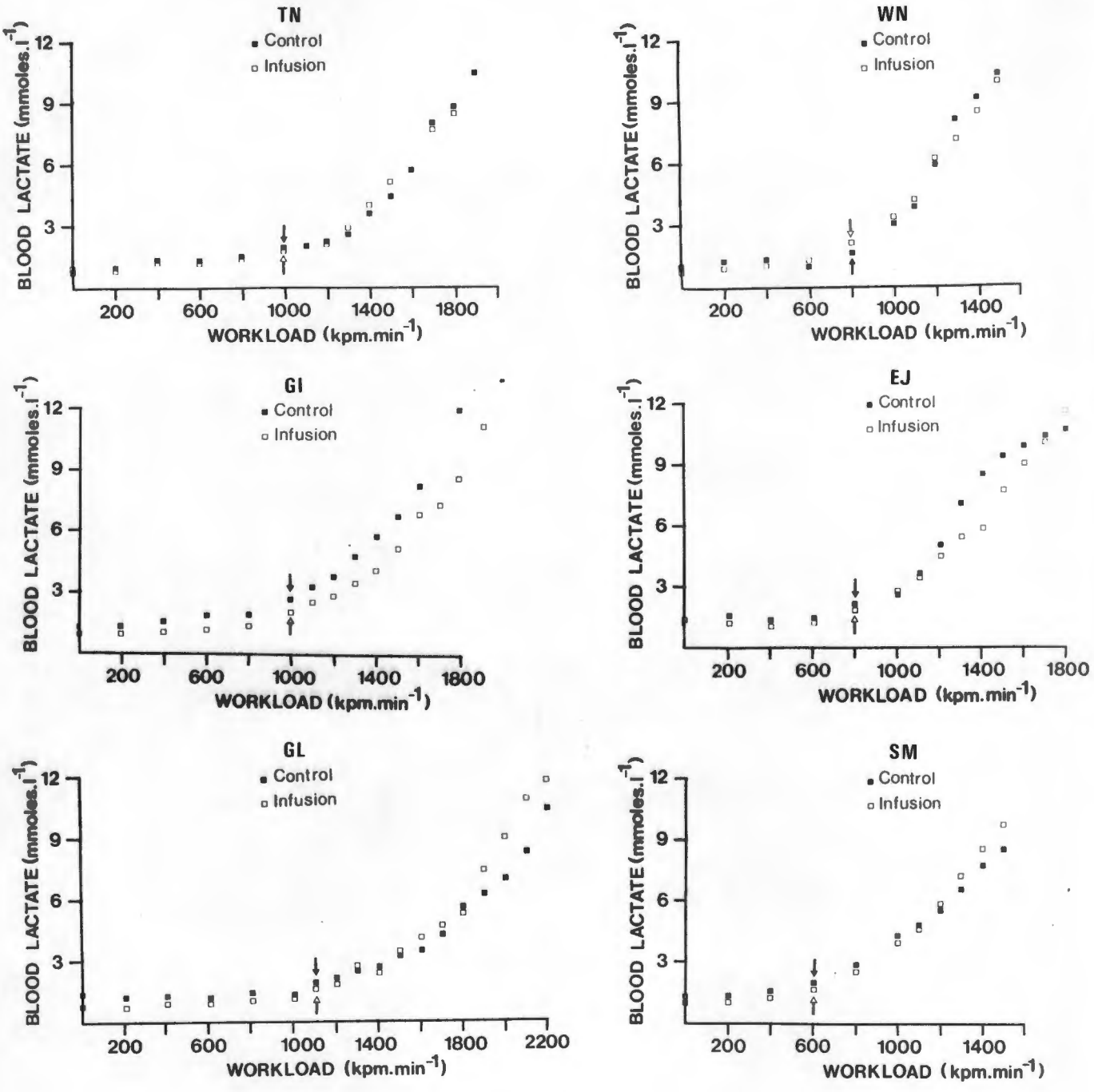



FIGURE 9

Blood lactate levels increased non-linearly in both the control and the infusion tests. Although peak plasma lactate values appeared to be higher following the alkaline infusion, these differences could not be statistically proved due to the small sample size.

## 4.3 A COMPARISON OF BLOOD LACTATE LEVELS BEFORE AND AFTER BETA-RECEPTOR ANTAGONISM WITH PROPRANOLOL.

Six trained athletes of average age 27.2 ± 4.8 years, average height 170 ± 9.2 cms., and average weight 64.7 ± 8.1 kgs participated in this study which involved a progressive test to exhaustion (as with the progressive test described in the six-minute versus progressive exercise test). The progressive test was repeated one week later following the ingestion of 80 mg. propranolol.

Exercising heart rates were significantly lower after propranolol ingestion ($p<0.001$), with these differences becoming manifest from a speed of 8.5 km $h^{-1}$ to the end of the test (figure 10). Mean maximal heart rate after beta-blockade (141.8 ± 12.45 beats per minute) was 76.3% of the maximal heart rate observed under normal exercising conditions (185.8 ± 5.23 beats per minute).

The maximum speed reached after propranolol ingestion (17.8 ± 1.99 $km.h^{-1}$) was 92% of the maximum speed reached in the initial, non-treatment test (19.3 ± 2.3 $km.h^{-1}$), indicating that running speed was not markedly affected even though the heart rate was significantly reduced. Even though running speed was not significantly altered, all subjects reported more severe

## TABLE III

A comparison of blood lactate levels before and after beta-receptor antagonism with propranolol.

| SUBJ. | AGE (YRS) | HT. (CMS) | WT. (KGS) | MAX. HEART RATE (bpm) | | MAX. BLOOD LACTATE (mmol/l) | | MAX. SPEED (km/h) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | C | I | C | I | C | I |
| AB | 36 | 179 | 64 | 185 | 132 | 9.33 | 4.73 | 22.5 | 21.0 |
| CG | 26 | 172 | 73 | 192 | 142 | 9.14 | 8.24 | 18.5 | 17.5 |
| IL | 27 | 163 | 66 | 199 | 163 | 12.18 | 6.56 | 21.5 | 19.5 |
| CV | 28 | 165 | 64 | 210 | 142 | 9.84 | 4.96 | 19.5 | 16.5 |
| EV | 23 | 182 | 71 | 189 | 127 | 8.90 | 4.91 | 17.0 | 16.5 |
| WW | 23 | 159 | 50 | 182 | 145 | 5.00 | 4.88 | 17.0 | 16.0 |
| MEAN | 27.2 | 170 | 64.7 | 192.8 | 141.8 | 9.10 | 5.70 | 19.3 | 17.8 |
| SD | 4.8 | 9.2 | 8.1 | 10.3 | 12.4 | 2.30 | 1.40 | 2.3 | 2.0 |

KEY : "C" indicate results obtained in the control progressive exercise test, while "I" indicates those obtained during the beta-antagonistic study.

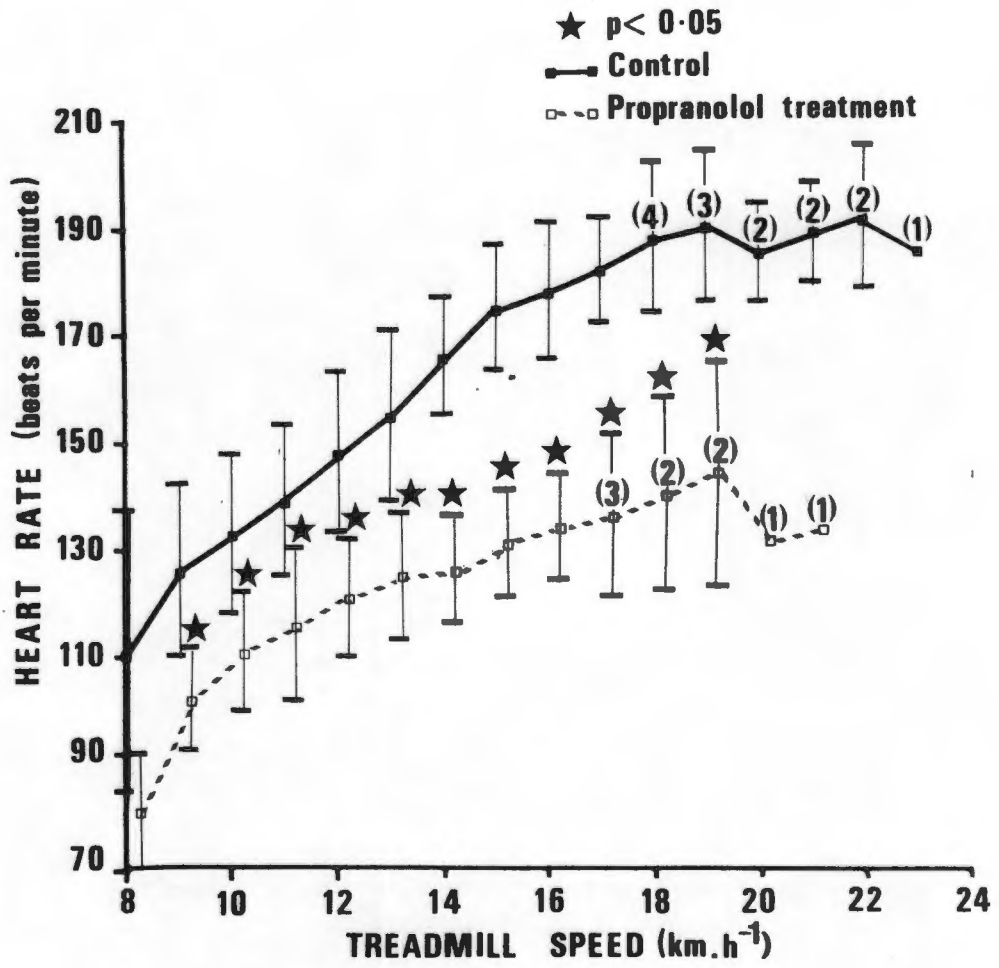



FIGURE 10

Heart rates during exercise following propranolol ingestion were significantly lower than under normal exercising conditions at all running speeds above 8 $km.h^{-1}$.

feelings of exhaustion during exercise following propranolol ingestion.

Maximum blood lactate concentrations after beta-blockade (5.71 ± 1.41 $mmol.l^{-1}$) were significantly different ($p<0.05$) from those measured under normal exercising conditions (9.07 ± 2.32 $mmol.l^{-1}$ - table III). However, since blood lactate levels are affected by the exercise intensity reached, it would be unreasonable to compare maximum levels when they occurred at different exercise intensities. For this reason, mean maximum blood lactate levels measured at the same speed before and after propranolol ingestion were compared: no statistical differences were found, but in 3 subjects the blood lactate levels were lower on propranolol (figure 11).

The blood lactate turnpoint occurred 1 $km.h^{-1}$ (two workloads) later after propranolol ingestion, occurring at an average treadmill speed of 12.7 $km.h^{-1}$ in the control test as compared to 13.7 $km.h^{-1}$ in the propranolol test (figure 12). Although the lactate turnpoint occurred at a faster treadmill speed following propranolol ingestion, the absolute turnpoint concentrations remained the same at 2.09 ± 0.43 $mmol.l^{-1}$ and 2.04 $mmol.l^{-1}$ in the control and propranolol tests respectively.

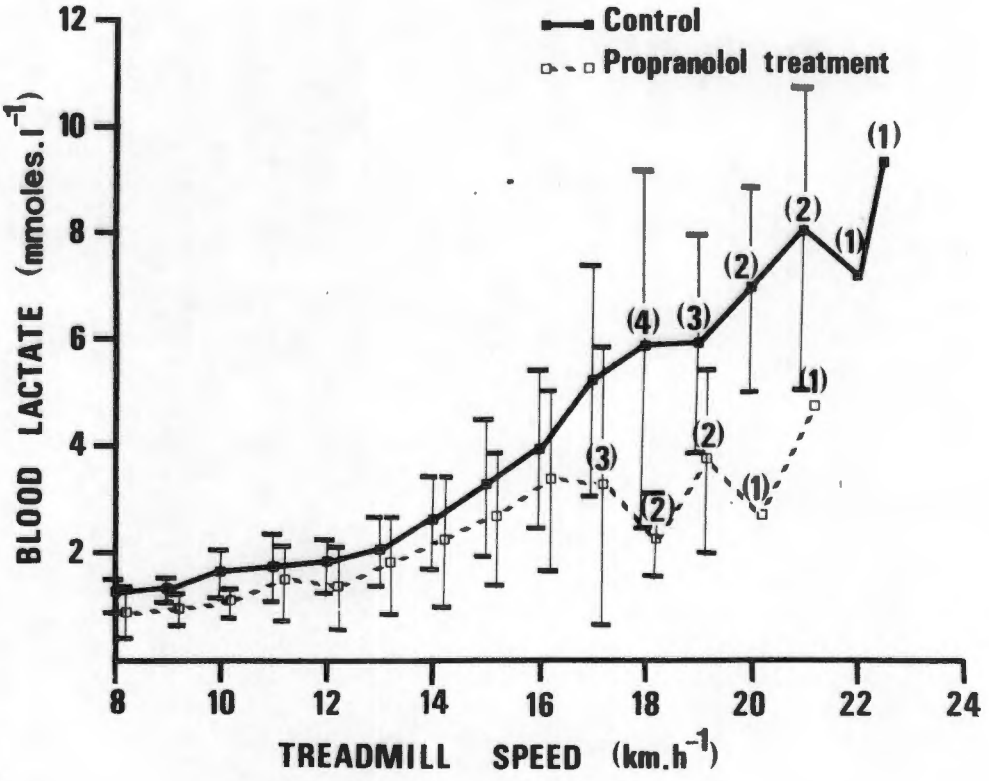



FIGURE 11

Blood lactate levels were significantly reduced by propranolol ingestion.

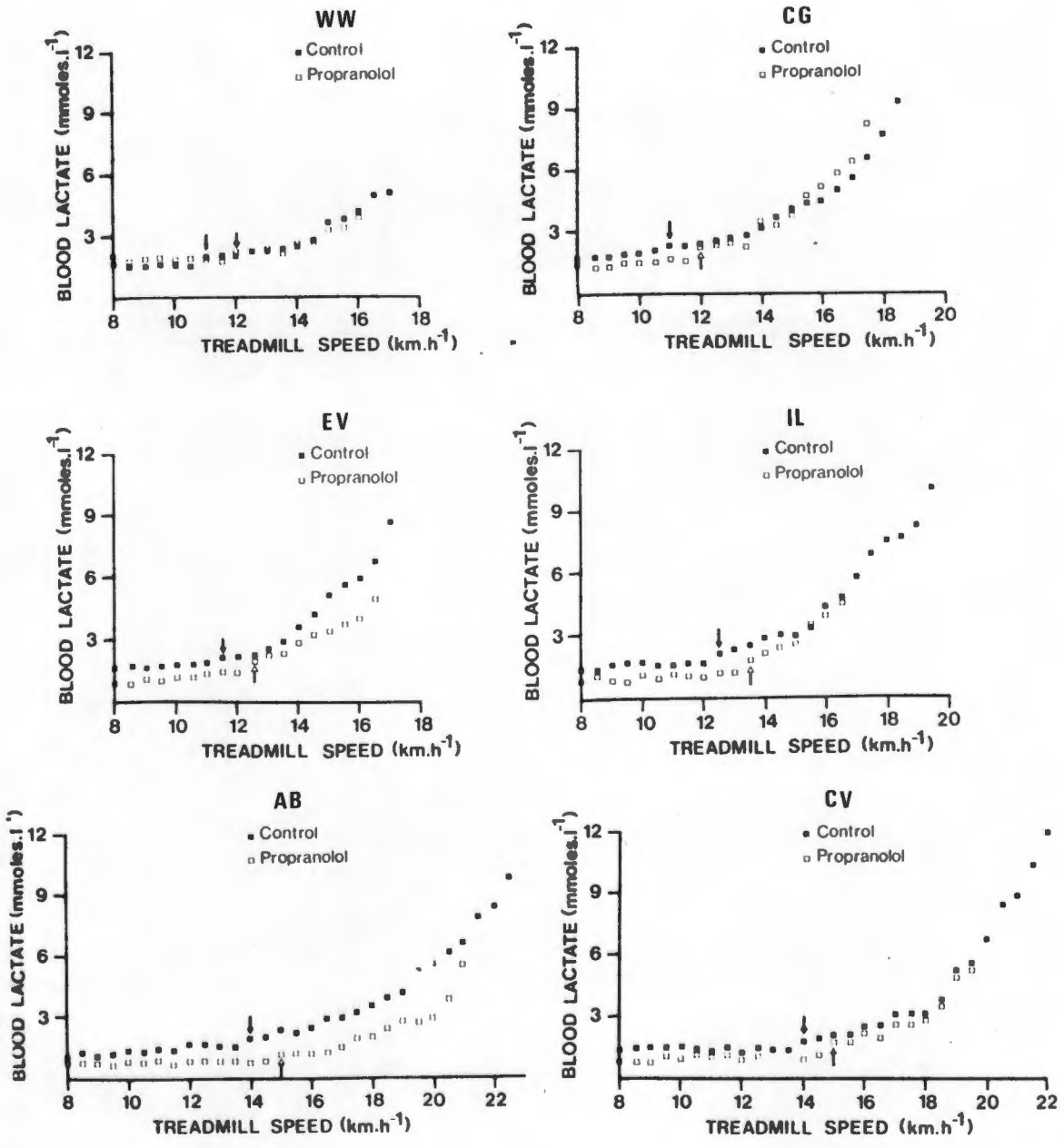



FIGURE 12

The blood lactate turnpoint occurred at the same blood lactate concentrations (2 mmol.$l^{-1}$) in the control and beta-receptor antagonistic studies, but the lactate turnpoint occurred two workloads later in the beta-antagonism study.

# CHAPTER FIVE

# DISCUSSION

## 5.1 A COMPARISON OF BLOOD LACTATE LEVELS MEASURED DURING SIX-MINUTE, CONSTANT INTENSITY EXERCISE WITH THOSE MEASURED DURING PROGRESSIVE EXERCISE.

In this study, blood lactate levels were measured every 30 seconds during a progressive test to exhaustion to determine the initial blood lactate turnpoint. Blood lactate levels were then compared to those measured at 30 second intervals during steady-state exercise at various intensities near the lactate turnpoint obtained in the progressive test.

During progressive exercise blood lactate levels rose gradually from the start of exercise, but increased abruptly at a certain exercise intensity in such a way that the lactate turnpoint could be determined. The occurrence of this turnpoint suggests that muscle lactate production at exercise intensities at and beyond the lactate turnpoint exceeds the rate of lactate oxidation (figure 1) (Donovan and Brooks, 1983). However, since the workload in a progressive test is continually increasing, the increased rate of lactate production might in fact be matched by increased rates of oxidation, at least at some workloads beyond the lactate turnpoint, were the exercise to be continued for a longer period of time at a constant workload. This evidence is supported by the fact that blood lactate levels stayed constant during continuous, constant intensity exercise,

even at exercise intensities beyond the lactate turnpoint.

Our aim, therefore, was to determine whether blood lactate levels continue to rise at exercise intensities above the lactate turnpoint, or whether levels remained steady during these constant-intensity, six minute exercise periods. A continuous increase at intensities beyond the lactate turnpoint would suggest that the lactate turnpoint reflects the point where an increased rate of muscle production and release of lactate into the blood not met by equivalent increases in the lactate oxidation rate in other tissues (Donovan and Brooks, 1983). Conceivably, rising levels of blood lactate during steady-state exercise could indicate muscle anaerobiosis.

On the other hand, lactate levels which initially rose but then remained constant, albeit at higher blood levels, would indicate that the increased rate of muscle lactate production was balanced by an increased rate of lactate utilisation by other tissues. This, in turn, would suggest that muscle anaerobiosis was not the cause of the increased rate of muscle lactate production, as anaerobiosis would be expected to stimulate glycolysis maximally causing blood lactate to continue rising inexorably during exercise.

Furthermore, this finding would call into question the belief

that there is a single lactate turnpoint (Owles, 1930; Wyndham et al, 1962; Mader et al, 1976), but rather a range of workloads at which an increased rate of lactate production by muscle is balanced by an increased rate of utilisation by other tissues. This would be compatible with the findings of Wells et al. (1957), Davis and Gass (1979) and Skinner and McLellan (1980) that various lactate turnpoints can be identified during exercise.

Our studies provided two major findings. Firstly, that blood lactate levels rose at lower workloads in the steady-state tests than during the progressive test. Secondly, that the blood lactate levels during the six minute protocols did indeed remain constant, albeit elevated, at workloads beyond the "turnpoint" established during the progressive test. This latter result indicates that the rate of lactate utilisation matched production for up to two workloads beyond the "lactate turnpoint." These two points will now be discussed in detail.

Hughson and Green (1982) also found that the lactate turnpoint occurred earlier during prolonged exercise than during progressive exercise, and speculated that this resulted from different rates of either muscle lactate production, lactate efflux from muscle or lactate uptake by non-exercising fibres. Our finding that the lactate turnpoint occurred one workload

earlier in the steady-state exercise test than during the progressive test, and that blood lactate levels during the steady-state test were also higher than those during the progressive test at the same exercise intensities, confirm the work of Hughson and Green (1982).

The single most obvious cause of these results is the time factor, in which case one, if not all, of the causes proposed by Hughson and Green (1982) may be responsible for the differences which occurred in blood lactate levels during progressive and steady-state exercise.

Considering lactate production first, if as seems likely, the same amount of lactate is produced per unit time at the same exercise intensity in both exercise tests, the fact that a steady-state exercise test lasts twelve times longer than does the same exercise intensity during the progressive test, would lead to a proportionally greater lactate production.

Furthermore, fatigue results in an increased recruitment of Type IIb glycolytic muscle fibres (Tesch, 1978). Since these fibres have a greater capacity to produce lactate than do the slow-twitch fibres which are recruited during lower exercise intensities, the rate of lactate production will increase disproportionately at higher work intensities.

Hughson and Green (1982) also suggested that the rates of lactate efflux from muscle may affect blood lactate levels during progressive and steady-state exercise. The majority of researchers who have examined muscle and blood lactate levels during both steady-state and progressive exercise protocols have shown that muscle lactate levels are usually two to three times higher than blood lactate levels at the same exercise intensities, with these concentrations only becoming similar about 30 minutes after the cessation of exercise (Diamant et al, 1964; Agnevik et al, 1969; Bergstrom et al, 1971; Karlsson et al, 1972; Sahlin et al, 1976; and Jacobs and Kaiser, 1982). Karlsson (1971) suggested that these differences occur as a result of a diffusion barrier which impedes the efflux of lactate from muscle. This diffusion barrier may therefore also contribute to the higher blood lactate levels measured during steady-state exercise, with the time factor again becoming important; the longer exercise period facilitates muscle lactate efflux, causing blood lactate levels to be higher.

Another explanation for the higher blood lactate levels during the steady-state test would relate to the rates of lactate oxidation by other tissues.

Contrary to popular theory, Donovan and Brooks (1983) found that there were no differences in the rates of lactate production

between trained and untrained rats so that the lower blood lactate levels after training were due to increased rates of lactate clearance from blood in the trained rats. They suggest that tissues such as the heart and liver which oxidise lactate, may have a limited capacity for blood lactate utilisation so that once their combined lactate oxidation rate has been exceeded, blood lactate levels will begin to rise. Their findings also predict that training increases the rate of lactate utilisation by these tissues.

Since steady-state exercise results in the earlier elevation of blood lactate levels (figure 4), this limiting rate must be reached earlier during the steady-state than during a progressive test. However, the finding that blood lactate levels achieved a new but higher constant blood level for a further two workloads above the lactate turnpoint presumably indicates that lactate utilisation was able to increase during these intermediate workloads. At workloads beyond "T+3", the rate of lactate utilisation was unable to keep up with the increased rate of production so that blood lactate levels continued to rise.

It seems likely, then, that the higher blood lactate levels and the earlier lactate turnpoint recorded in the steady-state test is due to a combination of the factors initially proposed by

Hughson and Green (1982), that is increased rates of lactate production due to the longer exercise duration, increased rates of lactate efflux due to the greater time for diffusion, and possibly an increased rate of lactate production due to recruitment of Type IIb glycolytic fibres as fatigue increased during the longer exercise duration. Since all of these factors are closely related to the amount of time spent exercising at each exercise intensity, the absolute blood lactate levels recorded during exercise are therefore critically dependent on worktime. Consequently, it is essential for researchers to establish, and state clearly, their particular protocol selected for the measurement of the "lactate turnpoint", and to justify the use of this specific test according to their proposed aims.

This is particularly important when use is made of specific blood lactate concentrations, for example 2 $mmol.l^{-1}$ or 4 $mmol.l^{-1}$ (Mader et al, 1976), for the determination of lactate turnpoints. Our results showed an initial turnpoint in the steady-state test at "T-1", with blood lactate levels of 1.70 $\pm$ 0.70 $mmol.l^{-1}$, close to the 2 $mmol.l^{-1}$ concentration considered by Mader et al. (1976) to indicate the transition between aerobic and anaerobic metabolism. At higher workloads, although blood lactate levels continued to increase, they remained constant for the last three minutes of each workload up to the "T+2" workload, at which exercise intensity, blood

lactate levels of 3.66 ± 1.66 mmol.$l^{-1}$ indicate, as suggested by Mader et al. (1976), a second threshold at around 4 mmol.$l^{-1}$ beyond which blood lactate levels continued to increase throughout the exercise period. The fact that blood lactate levels during this intermediate period ("T-1" to "T+2") increased for the first three minutes of exercise but remained constant thereafter indicates that a balance must have been reached between rates of lactate production and of lactate utilisation. The continual, unchecked rise in blood lactate levels which occurred beyond the 4 mmol.$l^{-1}$ concentration indicate what can be called a true lactate turnpoint at which the rate of lactate production was no longer matched by an increased rate of lactate utilisation.

Kindermann et al. (1979) also considered that blood lactate levels of 2 mmol.$l^{-1}$ indicated the upper limit of exclusively aerobic metabolism, with blood lactate concentrations of 4 mmol.$l^{-1}$ indicating the point beyond which metabolism was exclusively anaerobic. However, as indicated above, the use of a specific blood lactate concentration to indicate a specific turnpoint will be greatly affected by the exercise duration, and therefore the exercise testing protocol is again of prime consideration when using a specific "turnpoint" concentration. It must be remembered that the longer the duration of the exercise period, the earlier these blood lactate concentrations

will be reached, possibly leading to the establishment of artificially early turnpoints (figure 4).

With regard to steady-state exercise at low intensity, Bang (1936) found that during such exercise, lactate levels initially increased for the first five minutes of exercise before decreasing. During steady-state exercise we found that lactate levels increased in the first three minutes and then decreased only at the lowest exercise intensity ("T - 3") from 1.43 $mmol.l^{-1}$ to 1.37 $mmol.l^{-1}$ after six minutes. This decrease suggests that muscle glycolysis was initially overstimulated at the start of exercise so that the rate of lactate production exceeded that of oxidation causing blood lactate levels to rise. Thereafter the rate of oxidation exceeded that of production causing blood lactate levels to fall.

Beyond this lowest intensity (14.25 $km.h^{-1}$) and up to the turnpoint speed at "T" (15.75 $km.h^{-1}$), lactate levels increased in the first three minutes, but thereafter remained constant up to the sixth minute of each exercise intensity. Similar results were found by Wasserman et al. (1967) and Saiki et al. (1967) who concluded that lactate levels increased and then remained constant at all exercise intensities. However, Nagle et al. (1970), Hermansen and Stensvold (1972) and Scheen et al. (1981) found that this increase followed by a

steady-state in blood lactate concentrations only occurred up to a certain exercise intensity, and that beyond this level lactate concentrations continued to increase throughout the exercise period.

Our results agree with these latter observations; lactate levels increased markedly in the first three minutes at each exercise intensity, and then either remained constant up to the turnpoint "T" (15.75 $km.h^{-1}$), or increased continuously throughout the exercise period at intensities above this treadmill speed (figure 5). This increase in blood lactate levels during the last three minutes of each workload became more marked as the exercise intensity increased, so that whereas the increase at "T + 1" (16.25 $km.h^{-1}$) was only 0.10 $mmol.l^{-1}$, the increase at "T + 4" (17.75 $km.h^{-1}$) was 0.82 $mmol.l^{-1}$. The minimal increases in blood lactate levels which occurred during exercise at "T+1" and "T+2" suggest that during these intermediate exercise intensities, a new balance between the rates of lactate production and oxidation is achieved. This finding is compatible with observations in marathon runners showing that such runners run their races with blood lactate levels above resting values (Farrell et al, 1979),but that these levels do not continue rising during the exercise. It appears then that six minutes' exercise at the higher workloads was either too short for a steady-state to be reached, or the intensity was too high to be

continued until a new steady-state could be reached. The latter possibility seems the more likely, particularly at the last two exercise levels ("T + 3" and "T + 4"), because the subjects were already becoming fatigued to the point that some experienced great difficulty in maintaining these exercise intensities over the required six minutes.

Valuable information would have been added to this study had expired gases been measured during the exercise tests. In this way, we would have been able to determine whether a steady oxygen uptake correlated to the steady blood lactate levels, and whether an increasing blood lactate concentration corresponded to a non-steady state in both ventilation and oxygen uptake. This would have allowed a more detailed examination of the relationship between the whole body oxygen consumption and blood lactate levels and would have allowed a closer examination of the theories of Fletcher and Hopkins (1907), Hill and Lupton (1923), Lundin and Strom (1947), Linnarsson et al. (1974) and Jorfeldt et al.(1978) who proposed that hypoxia causes blood lactate accumulation during exercise.

Contrary to early theories that lactate is only produced above a certain exercise intensity (Owles, 1930; Margaria et al, 1933), our results show that lactate is produced at all exercise levels (see figure 5), with production increasing markedly beyond a

certain exercise intensity. The fact that lactate is produced even at rest is shown by resting lactate levels of around 1 $mmol.l^{-1}$. This combined with the fact that lactate is produced even when the oxygen consumption remains constant (Whipp and Wasserman, 1969; Dempsey et al, 1975), contradict the "anaerobiosis" theory that lactate is produced as a result of inadequate oxygen supplies (Lundin and Strom, 1947; Asmussen et al, 1948), at least during submaximal steady-state exercise. On the other hand, lactate production cannot be due entirely to "glycolytic overflow" since, at rest at least, the mitochondrial capacity should be able to convert pyruvate via the citric acid cycle without lactate production.

Why then is lactate produced at low intensity exercise, and particularly at rest? Both the lungs and the red blood cells produce lactate at rest, which may account for the elevated resting blood lactate levels, but it is interesting to note that tissues which use lactate as a fuel (such as the slow-twitch fibres and the heart) do not utilise all this lactate so that resting lactate levels are maintained at zero. The reason for these elevated levels has been unexplored and unexplained, so one is only able to guess at possible causes for resting blood lactate levels being above zero.

Elevated lactate concentrations during exercise are more easily

explained. At the start of exercise, blood lactate levels increase rapidly in the first three minutes because there is an imbalance in the rate of mitochondrial ATP production; ATP levels fall, stimulating glycolysis. As the exercise period continues, however, lactate production becomes consistent with the exercise intensity, and concentrations over the next three minutes either decrease at low intensity exercise as lactate oxidation exceeds production, level off at intensities up to the initial lactate turnpoint (as determined by a progressive test) indicating that lactate production is balanced by lactate utilisation, or continue to increase at exercise intensities above the lactate turnpoint, indicating that the rate of lactate production exceeds that of its' utilisation.

As the exercise intensity increases, so the level at which the blood lactate concentrations become steady also increases. An increased uptake of lactate by other tissues such as the heart, the liver and non-exercising muscles occurs as blood lactate levels rise, thus facilitating the maintenance of a constant blood lactate level as long as the exercise intensity remains constant. As the exercise intensity increases beyond that which produces the initial lactate turnpoint, blood lactate levels continue to rise during the six minute exercise period, due both to stimulation of glycolysis and an increased recruitment of fast-twitch Type II fibres which have a greater capacity for

lactate production. At high exercise intensities this elevated rate of lactate production exceeds the maximum rate of lactate oxidation by other tissues (Donovan and Brooks, 1983), so that the rate of blood lactate accumulation now becomes more rapid.

In conclusion, it would appear that there is no single blood lactate turnpoint as such, since blood lactate levels increase at all exercise intensities. However, there is a specific exercise intensity beyond which this increase becomes more marked, and it is beyond this point that steady-state blood lactate levels are not reached within six minutes of exercise. It is possibly for this reason that marathon runners tend to run at, or just below, their "turnpoint" speeds (Sjodin and Jacobs, 1981), since blood lactate levels remain slightly elevated but constant, and do not continue to accumulate to a point where elevated levels cause fatigue due to the associated metabolic acidosis.

This exercise intensity was established as a range of intensities around that which produces the initial lactate turnpoint ("T") in the progressive test ("T").

## 5.2 A COMPARISON OF BLOOD LACTATE LEVELS UNDER ACIDEMIC AND NEUTRAL pH CONDITIONS OBTAINED BY A BICARBONATE INFUSION.

The aim of this study was to study a factor that might influence the rate of either muscle lactate production or the rate of lactate efflux from the exercising muscles into the blood.

Hydrogen ions may leave the muscle in exchange for sodium in the plasma (Aickin and Thomas, 1977) and, once in the blood, these ions combine with bicarbonate to form carbon dioxide and water. Turrell and Robinson (1942), Wasserman and McIlroy (1964) and Wasserman et al. (1967) have all shown that blood lactate levels increase at the same time that blood bicarbonate levels decrease, concluding from these results that the rise in blood lactate levels causes a depletion of plasma buffers.

According to Reybrouck, Heigenhauser and Faulkner (1975), lactate diffuses more readily out of the cell when combined with hydrogen ions, but Benade and Heisler (1978) found that the two are not necessarily so closely related.

Our results showed that an attempt to delay the lactate turnpoint using a bicarbonate infusion was unsuccessful, even though blood bicarbonate levels were maintained at resting concentrations throughout the exercise period. However since

bicarbonate was not given before blood lactate levels rose, but were instead infused at the lactate turnpoint, we could possibly not have expected the infusion to have any effect on the turnpoint itself, although blood lactate levels might have been reduced subsequently.

However, the results showed that there was no difference in the blood lactate levels before and after the bicarbonate infusion (figure 8). Blood lactate levels rose in the same way with and without the bicarbonate infusion, and were slightly, but not significantly, higher than the control values at the maximal exercise intensity.

One of the most interesting findings was that the blood pH remained constant after the infusion, even though blood lactate levels continued to rise, and it would appear, therefore, that the accumulation of blood lactate during exercise does not cause the acidosis. Sutton et al. (1981) came to the same conclusion using a similar exercise protocol.

In conclusion, we were unable to either prevent an exercise-induced increase in blood lactate levels, or cause a shift in the lactate turnpoint to a higher intensity by infusing bicarbonate. This would indicate that the rapidly diminishing bicarbonate concentrations observed during progressive exercise

are not the cause of blood lactate accumulation, even though they may appear to have a cause-and-effect relationship (Wasserman and McIlroy, 1964; Wasserman et al, 1967). The fact that blood lactate levels following a bicarbonate infusion tended to be higher than under control conditions suggests that lactate formation is not impeded by an alkaline environment, and that lactate diffusion from muscle into blood is enhanced by an increased blood bicarbonate concentration. Sutton et al. (1981) showed that muscle and blood lactate levels were higher under alkaline as opposed to acidic conditions which supports our results and indirectly supports the theory of glycolytic overflow.

Further studies to determine the effect of buffering on blood lactate levels should probably involve bicarbonate infusions during prolonged exercise at a constant intensity. Infusion should begin a short while before the occurrence of the calculated deficiency to allow for a longer diffusion period, with the same variables that were studied during the progressive test being examined during a prolonged, constant intensity test. Maintenance of resting blood bicarbonate levels during steady-state exercise may facilitate hydrogen ion buffering, thereby successfully reducing blood lactate levels and delaying the blood lactate turnpoint.

## 5.3 A COMPARISON OF BLOOD LACTATE LEVELS BEFORE AND AFTER BETA-RECEPTOR ANTAGONISM WITH PROPRANOLOL.

It has been suggested that beta-blockade inhibits glycolysis (Cronin, 1967), although more recent research shows that beta-receptor antagonism may have little effect on glycolytic rate and subsequently on lactate production (Twentyman et al, 1981; Uusitupa et al, 1982). Our aim in this study was to determine whether beta-receptor antagonism with propranolol would influence the lactate turnpoint identified during progressive exercise. Beta-receptor blockade also causes a reduced exercising heart rate (Twentyman et al, 1981; Uusitupa et al, 1982; Petersen et al, 1983) and an increased peripheral resistance caused by inhibition of vasodilation in the exercising muscles, thereby limiting the blood flow (Goodman and Gilman, 1975).

Our results showed that heart-rate was significantly reduced during exercise following propranolol ingestion (figure 11), showing that beta-receptor antagonism was successfully achieved by the ingestion of 80mg. propranolol one hour before exercise.

The reduced heart rate response to exercise may have resulted in an inadequate supply and removal of substrates to and from the exercising muscles, compounded by the relative vasoconstriction

within the muscles which would further have limited the blood flow. This may have explained the more severe feelings of exhaustion experienced by the subjects after propranolol ingestion, and, almost certainly, is one of the major factors which reduced their maximal exercise tolerance (figure 12). None of the subjects were able to reach the same maximum speed obtained during the normal progressive test after taking propranolol, and this finding is also commonly documented in similar pre- and post-beta blockade studies (Twentyman et al, 1981; Lehman et al, 1982; Folgering et al, 1982).

Besides the cardiovascular effects of propranolol, beta-receptor antagonism may also affect the catecholamine-initiated responses to exercise by preventing intracellular cyclic AMP accumulation. Under normal exercising conditions, circulating catecholamine levels increase, stimulating an increased heart rate, increased rates of glycogenolysis, thereby increasing the potential for lactate production, and increased lipolysis. By preventing these changes, beta-receptor antagonism should decrease substrate availability within the exercising muscles and, coupled with an increased peripheral resistance and potentially reduced muscle blood flow, would explain the significant reduction in maximal exercising ability.

Whether or not beta-blockade alters lactate production during

exercise is a currently uncertain; if blood flow to the exercising muscles is reduced by beta-blockade, this would suggest that the oxygen supply would become inadequate and, according to the theory of "anaerobiosis", blood lactate levels would be higher during exercise. On the other hand, a reduced glycolytic rate resulting from catecholamine inhibition should result in lower blood lactate levels.

Recent research does not favour either of these theories, however, with some researchers showing lower blood lactate levels after beta-blockade (Frisk-Holmberg et al, 1979; Folgering et al, 1982; Juhlin-Dannfelt et al, 1982), while others found blood lactate levels to be higher following beta-blockade (Twentyman et al, 1982; Petersen et al, 1983). It is interesting to note that both Frisk-Holmberg et al. (1979) and Juhlin-Dannfelt (1982) found that, although blood lactate levels were lower after beta-blockade, muscle lactate levels remained unchanged both at rest and during exercise. They suggest that while beta-blockade does not markedly affect glycogenolysis, it may create some "translocation hindrance" which prevents muscle lactate from diffusing out into the blood.

Our results agree with those of Frisk-Holmberg et al. (1979), Folgering et al. (1982), Lehmann et al. (1982) and Juhlin-Dannfelt et al. (1982) in that blood lactate levels were

lower after beta-receptor antagonism than those measured during the control test (see figure 11).

On the basis of these results, one could conclude either that beta-blockade restricts glycolysis, resulting in a decreased production of lactate, or that it reduces lactate efflux from the cell. Support for the former interpretation was the finding that the blood lactate turnpoint occurred two workloads later following beta-blockade, but occurred at the same absolute blood lactate concentration (2 $mmol.l^{-1}$). The rate of glycolysis may therefore have been temporarily slowed by beta-antagonism, and this ability to successfully shift the lactate turnpoint strongly suggests that anaerobiosis is not the cause of the initial rise in blood lactate levels during exercise. Although the lactate turnpoint was successfully delayed by beta-antagonism, this was of no practical advantage since it resulted in a reduced exercise tolerance for reasons that are presently unclear.

Confirmation of the postulate that the lower blood lactate levels during exercise after beta-blockade were due to an inhibition of glycolysis would require measurement of muscle lactate levels. Unfortunately, these levels were not measured in our study, and this is certainly an important factor to consider in future research. Although it would not be practical

to perform numerous biopsies for muscle lactate measurement during the progressive test, it would certainly be valuable if muscle lactate measurements could be taken at rest immediately prior to the test, at the lactate turnpoint, and immediately after the completion of exercise both before and after beta-blockade.

## OVERALL DISCUSSION

The following graph (figure 13) provides a schematic representation of my interpretation of how the rates of lactate production and oxidation increase during exercise in relation to the oxygen consumption.

Oxygen uptake increases linearly during progressive exercise from a resting level of around 250 mls.min$^{-1}$. to a maximum of about 4 l.min$^{-1}$, thereafter levelling off to remain constant regardless of whether the exercise intensity continues to increase or not (Strauss, 1979; Berger, 1982). Blood lactate levels remain low (around 1 mmol.l$^{-1}$) up to an intensity of 40% to 50% $VO_2$max., and then increase abruptly (2 mmol.l$^{-1}$) and continue to rise steeply as the exercise intensity becomes more severe.

Considering lactate oxidation in relation to blood lactate changes, it appears that there is a resting rate of lactate oxidation which successfully balances the increased rate of muscle lactate production up to about 50% $VO_2$max., resulting in the maintenance of stable blood lactate levels (Donovan and Brooks, 1983). Beyond this level, steady-state exercise at increasing exercise intensities results in step-wise increases in blood lactate levels which cause an elevated oxidative rate

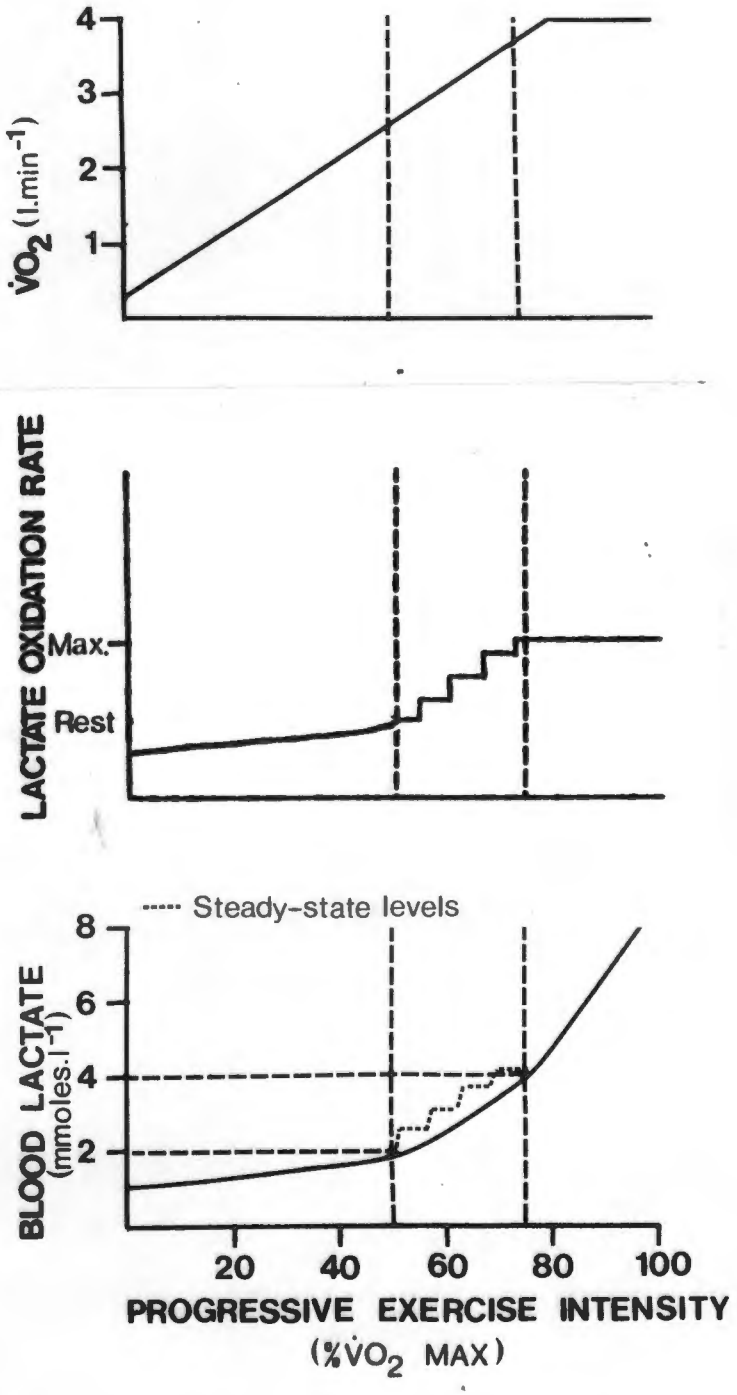



FIGURE 13

A schematic representation of lactate production and oxidation in relation to oxygen uptake during progressive exercise. The dotted line (•••••••) in the lactate graph indicates what could be expected to happen to blood lactate levels if the exercise was maintained for six minutes at those intensities.

so that, although elevated, steady-state blood lactate levels are again achieved. At exercise intensities above 75% $VO_2max.$, however, it appears that the maximum oxidative rate is exceeded. Lactate production therefore exceeds lactate uptake and blood lactate levels will continue to rise even during steady-state exercise.

The conclusion, therefore, is that the initial lactate turnpoint obtained during a progressive exercise test results from glycolytic overflow. Decreased ATP levels accompanied by increased ADP and AMP levels stimulate glycolysis, with an increased rate of production of pyruvate, hydrogen ions. The high avidity of lactate dehydrogenase for these substrates ensures that lactate is produced when these substrates accumulate. Up to blood lactate levels of around 2 $mmol.l^{-1}$, the increased rate of lactate production due to glycolytic overflow is balanced by an increased rate of oxidation, but once the blood lactate levels reach 4 $mmol.l^{-1}$, the rates of lactate production and oxidation become unbalanced, resulting in continually increasing blood lactate levels. It is unlikely, however, that even this second turnpoint is caused by anaerobiosis, since subjects are still able to exercise for prolonged period at these exercise intensities (Wasserman et al, 1967; Saiki et al, 1967).

# CHAPTER SIX

# OVERALL SUMMARY AND CONCLUSIONS

The findings of this study allow the following conclusions to be made :

1) Multiple blood lactate turnpoints exist.

Whereas a single turnpoint can be identified during a progressive test involving workload increments every 30 seconds, exercise for six minutes at intensities around the turnpoint show that blood lactate levels increase for the first three minutes with each increase in intensity, and then remain constant over the remainder of the exercise period. This results in the occurrence of multiple turnpoints at exercise intensities which correspond to blood lactate levels of between 2 $mmol.l^{-1}$ and 4 $mmol.l^{-1}$.

2) Lactate release into the blood may be facilitated by metabolic alkalosis, is evidenced by the tendency for blood lactate levels during a bicarbonate infusion to be higher than those found under control conditions.

3) The lactate turnpoint, identified by an abrupt increase in blood lactate levels measured during a progressive exercise test, can be manipulated by interventions such as beta-receptor antagonism.

4) Anaerobiosis is an unlikely explanation for the initial lactate turnpoint which occurs during progressive exercise. The theory of glycolytic overflow is favoured by the constant blood lactate levels which occurred during prolonged, constant intensity exercise, even at intensities above the blood lactate turnpoint.

The ability to manipulate experimentally the lactate turnpoint provides evidence against the theory that lactate production during exercise is due to anaerobiosis. That blood lactate levels remained constant even during prolonged exercise at intensities above the lactate turnpoint provides further evidence for this conclusion.

The occurrence of multiple turnpoints also favours the theory that lactate production occurs as a result of glycolytic overflow; the elevated rate of glycolysis which occurs with increased exercise intensity results in increased blood lactate levels. Up to a lactate concentration of 4 $mmol.l^{-1}$ this increased rate of production is matched by an increased rate of lactate uptake, resulting in the maintenance of constant, albeit elevated, blood lactate levels.

Future research to confirm these findings and conclusions should include muscle biopsies to measure muscle lactate, ATP, ADP and

AMP levels as well as those of the glycolytic intermediates at exercise intensities corresponding to the various lactate turnpoints. In this way information pertaining to conditions within the exercising muscle could be compared with blood lactate levels, while the levels of adenine nucleotides and glycolytic intermediates would indicate rates of glycolytic activity at these exercise intensities. Anaerobiosis would be expected to cause persistent falls in muscle ATP levels during continuous exercise.

# APPENDICES

# APPENDIX I

## "LACTIC ACID" OR LACTATE?

Although many of the early researchers refer to the accumulation of "lactic acid" during exercise, more recent research refers to "lactate" so that these terms are often used interchangeably. However, the term "lactic acid" is physiologically incorrect, and it is for this reason that in this thesis, the term "lactic acid" will always appear in inverted commas, or will be replaced by the term "lactate".

The term "lactic acid" is incorrect in that both pyruvic and lactic acids have a $pK_a$ of less than 4.0, and are therefore fully ionised at physiological pH values of around 7.4 (Hultman and Sahlin, 1980).

# APPENDIX II

## THE OXYGEN DEBT

During recovery from exercise, although the energy demand decreases, the oxygen consumption continues at a relatively high level for a period of time, depending on the duration and intensity of the preceding exercise bout (see figure II). This additional oxygen which is taken in over and above the normal resting requirements is referred to as the "oxygen debt" (Hill and Lupton, 1923).

Originally Hill and Lupton (1923) theorised that the oxygen debt was responsible for the conversion of "lactic acid", produced during exercise, back to glycogen. Subsequently, however, it has ben shown that an oxygen debt of up to three litres can be incurred without causing elevated blood lactate levels (Margaria et al, 1933), and for this reason two components of the oxygen debt have been proposed :

1) The alactacid component, which is attributed to the restoration of high energy phosphate and to the resupply of myoglobin and haemoglobin stores.

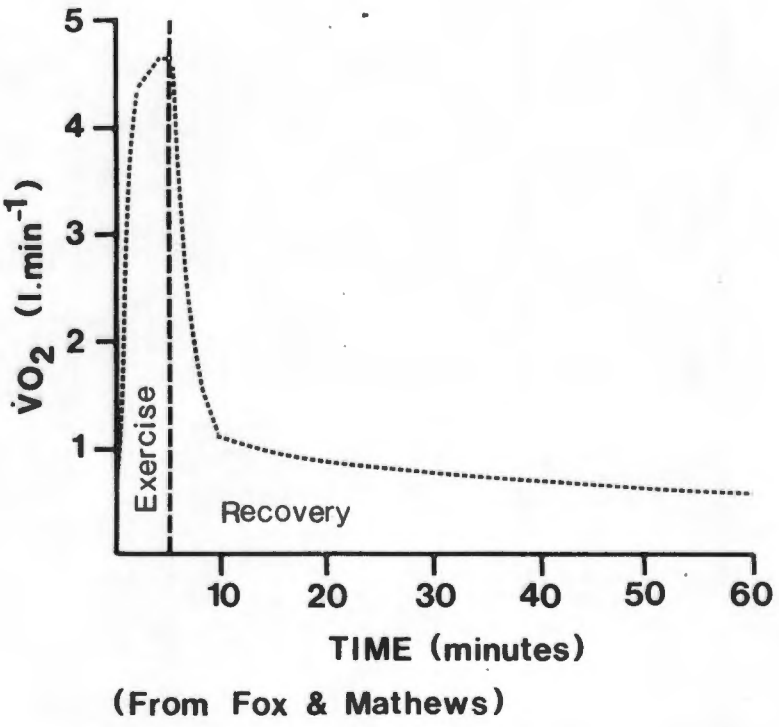



FIGURE II

The oxygen debt refers to the amount of oxygen consumed during recovery in excess of the normal resting requirements (± 250 mls.min$^{-1}$). The rapid component illustrates the repayment of the alactacid oxygen debt, while the slower component ilustrates the repayment of the lactacid oxygen debt.

2) The lactacid component which is attributed to the oxidation of lactate.

## APPENDIX III

Values obtained for pH during the control and bicarbonate infusion cycle ergometer tests at maximal exercise, at 100% $VO_2$ max. and at submaximal levels of exertion derived by interpolation.

| SUBJECT | PER CENT $VO_2$MAX. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 20 | 40 | 50 | 60 | 70 | 80 | 90 | 100 | MAX.EX. |
| CONTROL | | | | | | | | | |
| TN | 7.39 | 7.38 | 7.36 | 7.36 | 7.36 | 7.35 | 7.29 | 7.23 | 7.23 |
| WN | 7.44 | 7.39 | 7.38 | 7.37 | 7.36 | 7.35 | 7.35 | 7.26 | 7.26 |
| SM | 7.40 | 7.39 | 7.37 | 7.36 | 7.35 | 7.33 | 7.32 | 7.28 | 7.28 |
| GI | 7.39 | 7.37 | 7.36 | 7.34 | 7.34 | 7.33 | 7.25 | 7.15 | 7.16 |
| EJ | 7.35 | 7.35 | 7.34 | 7.31 | 7.30 | 7.29 | 7.25 | - | - |
| GL | 7.39 | 7.38 | 7.37 | 7.37 | 7.36 | 7.35 | 7.32 | 7.28 | 7.28 |
| MEAN | 7.39 | 7.37 | 7.36 | 7.35 | 7.34 | 7.33 | 7.30 | 7.27 | 7.25 |
| SD | 0.03 | 0.02 | 0.01 | 0.02 | 0.02 | 0.02 | 0.03 | 0.03 | 0.06 |
| INFUSION | | | | | | | | | |
| TN | 7.38 | 7.36 | 7.37 | 7.36 | 7.37 | 7.40 | 7.40 | 7.34 | 7.34 |
| WN | 7.38 | 7.37 | 7.36 | 7.37 | 7.39 | 7.44 | 7.45 | 7.43 | 7.43 |
| SM | 7.42 | 7.41 | 7.40 | 7.40 | 7.38 | 7.40 | 7.42 | 7.40 | 7.40 |
| GI | 7.39 | 7.38 | 7.41 | 7.43 | 7.43 | 7.41 | 7.40 | 7.25 | 7.25 |
| EJ | 7.36 | 7.37 | 7.38 | 7.40 | 7.42 | 7.42 | 7.40 | 7.37 | 7.37 |
| GL | 7.38 | 7.37 | 7.36 | 7.37 | 7.40 | 7.41 | 7.43 | 7.37 | 7.31 |
| MEAN | 7.38 | 7.38 | 7.38 | 7.39 | 7.40 | 7.41 | 7.42 | 7.36 | 7.35 |
| SD | 0.02 | 0.02 | 0.02 | 0.03 | 0.02 | 0.02 | 0.02 | 0.06 | 0.06 |

## APPENDIX IV

Values obtained for the blood lactate levels measured during the control and bicarbonate infusion cycle ergometer tests ($mmol.l^{-1}$) at maximal exercise, at $VO_2$ max. and at submaximal levels of exertion (derived by interpolation).

| SUBJECT | PER CENT $VO_2$MAX. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 20 | 40 | 50 | 60 | 70 | 80 | 90 | 100 | MAX.EX |
| CONTROL | | | | | | | | | |
| TN | 0.87 | 1.34 | 1.69 | 1.85 | 2.70 | 3.66 | 7.87 | 10.29 | 10.29 |
| WN | 1.10 | 1.52 | 1.94 | 2.28 | 3.56 | 4.88 | 6.70 | 8.00 | 8.00 |
| SM | 1.18 | 1.82 | 2.41 | 3.52 | 4.52 | 6.21 | 7.29 | 8.47 | 8.47 |
| GI | 1.30 | 1.84 | 2.02 | 2.87 | 3.44 | 5.15 | 7.84 | -- | 12.05 |
| EJ | 1.56 | 1.65 | 2.30 | 4.05 | 7.34 | 8.38 | 9.96 | -- | -- |
| GL | 1.00 | 1.32 | 1.62 | 2.23 | 4.05 | 5.37 | 7.27 | 10.01 | 10.01 |
| MEAN | 1.17 | 1.59 | 2.00 | 2.80 | 4.27 | 5.61 | 7.82 | 9.19 | 9.76 |
| SD | 0.24 | 0.23 | 0.32 | 0.85 | 1.62 | 1.59 | 1.13 | 1.13 | 1.61 |
| INFUSION | | | | | | | | | |
| TN | 0.93 | 1.05 | 1.22 | 1.41 | 1.96 | 2.94 | 4.85 | -- | -- |
| WN | 0.87 | 1.53 | 2.1 | 3.43 | 4.74 | 6.71 | 8.80 | 10.63 | 10.63 |
| SM | 1.17 | 1.27 | 1.92 | 2.27 | 3.95 | 4.80 | 6.63 | 9.43 | 9.43 |
| GI | 0.82 | 1.05 | 1.58 | 2.18 | 2.58 | 4.70 | 6.96 | 12.59 | 12.59 |
| EJ | 1.20 | 1.65 | 2.42 | 3.42 | 4.65 | 6.62 | 10.12 | 11.54 | 11.54 |
| GL | 0.65 | 0.95 | 1.00 | 1.49 | 2.73 | 4.41 | 7.66 | 10.75 | 11.13 |
| MEAN | 0.94 | 1.25 | 1.71 | 2.37 | 3.43 | 5.03 | 7.50 | 10.99 | 11.06 |
| SD | 0.21 | 0.33 | 0.55 | 0.78 | 1.17 | 1.43 | 1.82 | 1.17 | 1.16 |

## APPENDIX V

Values obtained for the blood bicarbonate levels measured during the control and bicarbonate infusion cycle ergometer tests ($mmol.l^{-1}$) at maximal exercise, at 100% $VO_2$ max. and at submaximal levels of exertion (derived by interpolation).

| SUBJECT | PER CENT $VO_2$MAX. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 20 | 40 | 50 | 60 | 70 | 80 | 90 | 100 | MAX.EX |
| CONTROL | | | | | | | | | |
| TN | 24.69 | 24.48 | 24.77 | 24.64 | 23.49 | 22.94 | 17.70 | 16.06 | 16.06 |
| WN | 26.03 | 27.54 | 27.44 | 26.80 | 25.11 | 23.09 | 20.97 | 21.37 | 21.37 |
| SM | 27.44 | 26.74 | 26.16 | 25.18 | 24.49 | 22.03 | 21.04 | 19.62 | 19.62 |
| GI | 27.88 | 27.12 | 27.48 | 28.02 | 26.07 | 23.51 | 20.14 | 17.99 | 15.31 |
| EJ | 27.47 | 27.05 | 26.20 | 24.77 | 22.44 | 21.25 | 18.47 | - | - |
| GL | 28.36 | 27.94 | 27.55 | 26.29 | 24.89 | 24.16 | 21.19 | 19.27 | 19.27 |
| MEAN | 26.98 | 26.81 | 26.60 | 25.95 | 24.41 | 22.83 | 19.92 | 18.86 | 18.27 |
| SD | 1.37 | 1.22 | 1.10 | 1.33 | 1.28 | 1.04 | 1.49 | 1.98 | 2.29 |
| INFUSION | | | | | | | | | |
| TN | 24.54 | 23.53 | 22.58 | 22.84 | .08 | 26.95 | 27.48 | 23.33 | 23.33 |
| WN | 26.22 | 25.80 | 25.8 | 26.33 | 26.54 | 28.14 | 28.72 | 28.80 | 28.80 |
| SM | 28.55 | 28.17 | 27.69 | 27.18 | 26.65 | 28.40 | 28.19 | 27.11 | 27.11 |
| GI | 24.56 | 24.62 | 25.59 | 29.28 | 29.65 | 27.76 | 29.46 | 27.16 | 27.16 |
| EJ | 27.99 | 26.45 | 28.31 | 29.23 | 28.40 | 29.25 | 28.84 | 27.18 | 27.18 |
| GL | 29.05 | 28.70 | 27.84 | 26.65 | 28.67 | 28.46 | 28.70 | 30,61 | 29.95 |
| MEAN | 26.82 | 26.21 | 26.22 | 26.90 | 27.33 | 28.16 | 28.57 | 27.36 | 27.26 |
| SD | 2.00 | 2.00 | 2.18 | 2.37 | 2.00 | 0.77 | 0.67 | 2.41 | 2.24 |

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