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MARATHON RUNNING:
THE PHYSIOLOGICAL AND PATHOLOGICAL EFFECTS,
WITH PARTICULAR REFERENCE TO
RENAL FUNCTION AND FLUID SHIFTS

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TO DAWN

DECLARATION

I, Robert Anthony Irving, 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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ABBREVIATIONS

ADH	Anti-diuretic hormone
ANP	Atrial natriuretic peptide
AP	Serum alkaline phosphatase activity
AST	Serum aspartate transaminase activity
CK	Serum creatine kinase activity
Cl^-	Chloride
cm	Centimetre
COD	Calcium oxalate dihydrate
COM	Calcium oxalate monohydrate
CRP	Serum C-reactive protein
ECF	Extracellular fluid
GFR	Glomerular filtration rate
Hb	Haemoglobin
Hct	Haematocrit
ICF	Intracellular fluid
ISF	Interstitial fluid
Iu	International unit
kg	Kilogram
km	Kilometre
LDH	Serum lactate dehydrogenase activity
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
mL	Millilitre
mmol	Millimole
nm	Nanometre

PAH	P-aminohippuric acid
PRA	Plasma renin activity
PV	Plasma volume
RBC	Red blood cell
RPF	Renal plasma flow
ug	Microgram
uL	Microlitre
VO_2max	Maximal oxygen uptake

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ABSTRACT

Marathon running can induce acute renal failure and hyponatraemia and may be associated with the formation of renal stones. The pathogenesis of these conditions is uncertain and the physiological response with regard to renal function and fluid shifts has not been clearly defined, particularly during the recovery days after marathon running.

In this thesis, eight marathon races were studied and daily blood and 24 hour urine samples were collected. The following were measured or calculated: urine output, creatinine, osmolal, free water and renal $beta_2$-microglobulin clearances as well as total protein, sodium, potassium, urea and creatinine excretion rates. Changes in total serum contents of sodium, chloride, albumin, total protein and uric acid, and in plasma volume and mean cell volume, were calculated. Plasma C-reactive protein concentrations, aspartate transaminase, lactate dehydrogenase and creatine kinase activities were also measured.

Urine samples from runners who participated in a further 2 marathons were subjected to particle counting, while deposited crystals were examined with a scanning electron mircroscope and X-ray powder diffraction. Eight runners who

developed hyponatraemia after an 88km marathon were studied during recovery, for fluid and sodium balance and renal function.

The principal finding was that contrary to traditional belief, renal function as measured by urine output, creatinine, osmolal and free-water clearance, urea and creatinine excretion and production is generally well maintained. Plasma volume was maintained during a 56km marathon due to intravascular protein and sodium influxes, while a decreased urine sodium excretion occurred for at least 24 hours after the race.

Urine $beta_2$-microglobulin excretion and plasma $beta_2$-microglobulin concentration increased but renal tubular impairment was not generally found.

During the post-race days there was an increase in creatinine clearance as well as a plasma volume expansion (of up to 12.5%) due to an intravascular influx of albumin (17g on Day 1) and an increased plasma content of sodium.

Two of the total of 27 runners studied developed temporary renal tubular dysfunction; one was clearly related to an inadequate fluid intake.

The crystalluria found in runners was identical to that of recurrent stone formers. Crystalline particles were mainly calcium oxalate dihydrate with crystal aggregation and numerous crystals in the 15-40 um diameter range. Thus runners are at risk of stone formation.

Finally, it was shown that the hyponatraemia of exercise was caused by fluid overload (between 1.2 and 5.9L), with only moderate sodium loss. The subjects' plasma volumes were markedly decreased (up to 24%). During the recovery period both creatinine clearance and urine output were elevated.

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INTRODUCTION

The popularity of long-distance running has increased dramatically in recent years throughout the world. In 1899, the Boston (Massachussets) 42.2 km Marathon footrace attracted 17 entrants (Williams and Arnold 1899); today the same race has approximately 9 000 official and an equal number of unofficial entrants (Adner 1988). The first South African Comrades 90 km ultramarathon in 1922 had 38 competitors (Alexander 1986); in 1989 more than 13 000 participated.

During recent years there has been a concomitant increase in the performance of the average runner. In 1970 only 812 runners throughout the United States of America completed a 42,2 km marathon within 3 hours. Five years later 887 competitors accomplished this feat during a single race (Maron and Horvath 1978).

Although the vast majority of runners usually complete these races with no more serious ill-effects than blisters and delayed onset muscle soreness, acute renal failure (Bar-Sela et al 1979; Dancaster et al 1969; MacSearraigh et al 1979; Schrier et al 1967; Stewart and Posen 1980) and heat stroke have been recorded (Nicholson and Somerville 1978); the latter was the probable cause of death of the Portuguese runner, Lazaro in the 1912 Olympic Marathon in Stockholm.

More recently the increased popularity of ultramarathon running has resulted in hyponatraemia becoming an increasing cause of hospitalization with several near-fatal incidents (Frizzel et al 1986; Noakes et al 1985; 1990; Young et al 1987). The pathogenesis of this condition is unclear with two conflicting theories currently proposed (Hiller et al 1986; Noakes et al 1985; 1990), while the treatment of the condition is also controversial (Arieff 1986; Narins 1986; Sterns et al 1986; Swales 1987).

A further cause for concern is the possible relationship of long distance running and an increased risk of urolithiasis (Milvy et al 1981). The incidence of urolithiasis was found to be 5 times greater in male runners under 45 years compared to controls and 3 times greater than controls in runners aged 45-64.

Despite these potentially serious medical complications and the large volume of research that has been undertaken (Maron and Horvath 1978), a review of the literature shows that the renal response to the stress of long distance running has been incompletely investigated. This is particularly true of renal function during the recovery period after marathon running and of the nature and frequency of any pathological changes induced by marathon running.

This thesis is the result of seven years of research into aspects of renal function in marathon and ultra-marathon runners. Subjects were studied before and after 8 long-distance running events. These races were the following:

1. The 1982 42,2km Kellerprinz Marathon (Cape Town, South Africa)
2. The 1983 56km Two Oceans Marathon (Cape Town, South Africa)
3. The 1983 201 mile Twenty Four Hour Relay (Cape Town, South Africa)
4. The 1984 90km Comrades Marathon (Durban, South Africa)
5. The 1984 42,2km Kellerprinz Marathon (Cape Town, South Africa)
6. The 1985 90km Comrades Marathon (Durban, South Africa)
7. The 1986 56km Two Oceans Marathon (Cape Town, South Africa)
8. The 1988 88km Comrades Marathon (Durban, South Africa)

The results of these studies are described in 2 sections:

Section 1: The physiological response to marathon running with special reference to renal function and plasma volume changes.

Section 2: Pathological renal functional responses to marathon running. This section comprises 3 parts. In the first, details of 2 runners who showed transient renal tubular dysfunction during marathon running are reported and compared with other runners who ran in the same races but

who showed a normal renal response to running. In the second, similarities between renal crystal excretion in idiopathic renal stone formers and marathon runners were investigated. In the third, renal functiona and fluid homeostasis were evaluated during recovery from the hyponatraemia of exercise. Eight runners who developed hyponatraemia after the 1988 88 km Comrades Marathon were studied.

Parts of this thesis have already been published, or are in press:

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Irving RA, Noakes TD, Irving GA, Van Zyl-Smit R. The immediate and delayed effects of marathon running on renal function. J Urol 1986; 136: 1176-1180.

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CHAPTER 1

LITERATURE REVIEW

The kidney plays the central role in maintaining the body's internal environment (Selkurt 1976). It does so by altering the amount of water and various solutes excreted in the urine, thus regulating the water content and salt balance of the body. The effects of exercise on kidney function have been incompletely studied (Poortmans 1984).

As a background to the research work undertaken for this thesis, aspects of kidney function and fluid balance are reviewed, not only under resting conditions, but also in response to the stress of exercise and more specifically, that of marathon running. This review is divided into two parts. In the first, the normal physiological response of the kidney during exercise is reviewed; in the second, the pathological response to marathon running with specific reference to acute renal failure, renal stone disease and hyponatraemia is described.

PART 1: THE PHYSIOLOGICAL RESPONSE TO EXERCISE

1.1. RENAL CIRCULATION

1.1.1. Introduction

In the the fully grown adult at rest, the kidneys receive 1200 - 1300 ml of blood per minute or just under 25% of the cardiac output of a 63 kg adult. Renal blood flow can be altered by renal vasoconstriction or vasodilation (Ganong 1977) and can be measured by both direct (utilizing flow probes of various types) and indirect methods (using the Fick principle). The Fick principle states that the amount of a substance taken up by an organ per unit of time is equal to the arterial concentration of the substance, minus the venous concentration, times the blood flow. As the kidney filters plasma, the renal plasma flow (RPF) has commonly been measured by infusing para-aminohippuric acid (PAH) or iodopyracet (Diodrast) and determining the urine and plasma concentrations. These substances are utilized because they have a high extraction ratio. For example 90% of the PAH in arterial blood is removed in a single circulation through the kidney (Ganong 1977, Moran Campbell et al 1984).

1.1.2. The effect of exercise

During maximal exercise, cardiac output can increase five- to six-fold (Selkurt 1976). Most of this increased blood flow is directed to the active skeletal muscles. In addition there is re-distribution of blood flow away from the inactive tissue so that splanchnic and renal plasma flow is reduced. The renal plasma flow can decrease from 1200 to 250 mL/min (Anderson 1968). Numerous studies have shown that the decrease in RPF is inversely related to the intensity of the exercise (Aurell et al 1967; Barclay et al 1947; Castenfors 1967; Chapman et al 1948; Grimby 1965; White and Rolf 1948). Pre-exercise hyper- hydration alters this effect of exercise on RPF only slightly (Castenfors 1967) although dehydration (equal to a 4-8% decrease in body weight) accentuates this reduction during moderate exercise (Smith et al 1952).

This progressive decrease in RPF with increasing exercise intensity can be explained by progressive vasoconstriction of renal arterioles (Sanders et al 1976) possibly controlled by a combination of increased sympathetic nervous system activity causing vasoconstriction of both the afferent and efferent glomerular arterioles and the release of adrenaline from the adrenal medulla (Poortmans 1984).

1.1.3. The effect of marathon running

Marathon runners compete at between 65-90% of their maximal oxygen uptake (VO_2 max.) depending on their state of training (Costill 1970; Costill and Fox 1969; Maron et al 1976). It is likely that at this exercise intensity, a reduction in RPF should occur. Neviackas and Bauer (1981), however, reported a normal RPF after marathon running, but their study took place only 6 hours after the race and after the subjects had been rehydrated. The authors assumed but could not verify that, prior to rehydration and during exercise, there had been a decreased effective RPF. A similar assumption was made by Refsum and Stromme (1974, 1975, 1977) after long-distance cross-country ski-racing. They based this assumption on an exercise-induced decrease in urine flow, a fall in urine-to-serum osmolality ratio as well as an extrapolation of findings during short-term intensive exercise (Refsum and Stromme 1975, 1977).

1.2. THE GLOMERULAR FILTRATION RATE (GFR)

1.2.1. Introduction

The glomerular filtration rate in an average-sized man is approximately 125 ml/min while values in women are 10% lower even after correction for their smaller surface areas (Ganong 1977). The GFR is calculated from the renal plasma

clearance in which the rate at which a substance is excreted in the urine is the product of its urinary concentration and the volume of urine produced per minute divided by the plasma concentration. Factors governing filtration across glomerular capillaries are: the size of the capillary bed; capillary permeability which is normally 50 times greater than that of the capillaries in skeletal muscle, and the hydrostatic and osmotic pressure gradients across the capillary wall.

Inulin, a polymer of fructose is frequently used to measure GFR as it is almost 100% freely filtered (filtrate/filtrand is approximately 0.96). However, endogenous creatinine can also be used despite the fact that some creatinine is secreted by the renal tubules and some may be reabsorbed (Moran Campbell et al 1984). Values for GFR measured with creatinine clearance agree well with GFR values measured with inulin partially because although there is tubular secretion of creatinine, this is compensated for by an elevated plasma measurement due to a non-specific chromagen when this is measured in plasma by colorimetric analysis (the Jaffe reaction) (Ganong 1977; Selkurt 1976).

1.2.2. The effect of exercise on GFR

During light exercise there is little change in GFR (Aurell et al 1967; Grimby 1965; White and Rolf 1948). However

during heavy exercise there are moderate decreases in inulin and creatinine clearances (Barclay et al 1947; Grimby 1965; Refsum and Stromme 1975, 1977; White and Rolfe 1948) with the clearances being inversely related to the severity of the exercise (Kachadorian and Johnson 1970).

On the other hand, Castenfors (1967) noted a maximal decrease of 32% in inulin clearance after light exercise and no further decrease at higher exercise intensities. Inulin clearance returns to normal within one hour of stopping exercise; increasing the level of hydration prior to exercise can lessen the exercise-related fall in inulin clearance (Castenfors 1967). Conversely, when compared with well-hydrated controls, dehydrated subjects show a more marked decrease in GFR during exercise (Smith et al 1952).

The reduction in GFR is always less than the decrease in RPF (Castenfors 1967; Grimby 1965) owing to an associated increase in the filtration fraction (FF) which can increase from 0.20 to 0.45 (Castenfors 1967). The explanation for this is likely to be a constriction of both the afferent and efferent glomerular arterioles with a greater constriction of the latter (Poortmans 1977).

1.2.3. The effect of marathon running

There are few references to measurements of GFR in marathon runners but Neviackas and Bauer (1981) showed that inulin and creatinine clearance decreased by 50% in 3 runners during warm weather marathons, but were unchanged during a cold weather race. However these measurements were first made only 6 hours after each race. Both inulin and creatinine clearances were normal one week later. Dancaster and Whereat (1971) measured creatinine clearances in 6 runners, 2-3 weeks after a 86km race. Three of these runners had elevated blood urea concentrations after the race (> 50mg/100mL), but only one (a competitor who collapsed at the end of the race) had a reduced creatinine clearance (79 mL/min). Five months later the creatinine clearance of that runner was 99 mL/min. An intravenous pyelogram performed on this runner 3 weeks after the race showed a small diverticulum in the upper calyx of the left kidney and slight delay in drainage from that kidney. No other abnormalities were noted.

1.3. URINE OUTPUT

1.3.1. Introduction

A glomerular filtration rate of 125 ml/min means that 180 litres of fluid are filtered through the glomerulus each day, which is equivalent to four times the total body water. However normal urine volume is about one litre per day, and thus 99% or more of this filtrate is reabsorbed. Depending on homeostatic requirements the urine can be concentrated, in which case water is retained in excess of solute, or diluted, in which case water is lost in excess of solute.

Many substances are actively transported out of the fluid in the proximal tubules and water moves passively out of the tubules along the osmotic gradient. Approximately 75% of the filtered solute and water are removed by the end of the proximal tubules. A further 5% is reabsorbed in the loops of Henle and the remainder in the distal tubules and collecting ducts (Burg and Stoner 1964). The latter depends on the presence of the posterior pituitary hormone, arginine vasopressin or anti-diuretic hormone (ADH) which increases the permeability of the epithelium of the collecting ducts to water. When ADH is secreted, small volumes of concentrated urine are excreted, and when ADH activity is absent, large volumes of urine are excreted. In the presence of ADH, 99.7% of filtered water can be reabsorbed

and the urine osmolality can be 1400 mosmol/L (almost 5 times the concentration of plasma). When ADH is absent, the urine osmolality can be as low as 30 mosmol/L and urine output can exceed 16 ml/min (Selkurt 1976).

1.3.2. The effect of exercise

In general, exercise exerts an anti-diuretic effect (Castenfors 1967; Refsum and Stromme 1975; Wesson 1960; White and Rolf 1948) usually varying directly with the severity of exercise (Castenfors 1967). Even hyperhydration sufficient to cause urine flow rates of 7-17 mL/min, does not prevent this decrease (Poortmans 1984). The response can vary however (Wesson 1960) and light exercise may even increase urine output (Kachadorian and Johnson 1970).

Factors affecting the rate of urine output during exercise are the GFR, the rate of tubular reabsorption of water, tubular secretion of solutes and circulating ADH concentrations. ADH is thought to be an important, if not a primary factor in electrolyte and fluid regulation in exercise (Castenfors 1967; Poortmans 1984). Hyperosmolality is the primary stimulus for ADH secretion, and volume depletion the second (Baylis and Heath 1977; Convertino et al 1981; Goldberg 1981; Kimura et al 1976; Robertson 1974; Robertson and Athar 1976). In addition there are other stimuli for the release of ADH such as pain, anxiety and

hypoxia. A linear correlation between serum ADH concentration and work intensity has been demonstrated (Convertino et al 1981; Wade and Claybaugh 1980). When urine output falls below 1ml/min, there is a correlation between the decrease in urine flow and in GFR (Castenfors 1967; Kachadorian and Johnson 1970; Refsum and Stromme 1974, 1975; Smith et al 1952) probably because the free-water reabsorption induced by ADH secretion is maximal so that the rate of urine flow is affected principally by changes in the filtered load (Poortmans 1977).

1.3.3. The effect of marathon running

Although several studies have examined urine samples after marathon running (Boileau et al 1980; Pugh et al 1967; Siegal et al 1979), urine output during marathon running has not been adequately studied. Dancaster and Whereat (1971) examined urine specimens from 53 competitors voided immediately after an 86 km ultramarathon. Volumes were measured in 8 runners who passed a mean of 100 mL (range 0-440 mL) during the race . The times these runners recorded during the race were not given, but the race took up to 11 hours to complete.

After a 29km average daily run which was part of a 20 day road race, a decrease in urine flow rate from 1.2 to 0.8 mL/min has been reported (Wade et al 1985).

1.4. URINE SODIUM EXCRETION

1.4.1. Introduction

Sodium is the most abundant cation in the extracellular fluid and sodium salts account for over 90% of the osmotically active solutes in plasma and interstitial fluid. Sodium is therefore a major determinant of extracellular fluid volume.

Although sodium is filtered through the glomerulus in large quantities, about 99% of this filtered sodium is reabsorbed by active transportation mainly out of the proximal tubules but also from the distal tubules and collecting ducts.

Urine sodium excretion is affected by changes in the amount of sodium filtered, which can be altered by changes in the GFR, as well as the amount reabsorbed in the tubules. Factors affecting the latter include the oncotic and hydrostatic pressures in the peritubular capillaries, the renin-angiotensin-aldosterone system (Davis and Freeman 1976), the rate of tubular secretion of hydrogen and potassium ions (Moran Campbell et al 1984), and possibly other factors such as atrial natriuretic peptide (ANP) (Anderson et al 1986; Laragh 1985).

1.4.2. The effect of exercise

A post-exercise decrease in sodium excretion has been reported by several authors particularly after severe exercise (Aurell et al 1967; Castenfors 1967; Grimby 1965; Refsum and Stromme 1975). This decrease may amount to 50% of the pre-exercise value and does not correlate with the GFR, indicating increased tubular reabsorption of sodium (Castenfors 1967; Castenfors 1978).

Several factors can be responsible for the increase in renal tubular reabsorption during exercise. These are renal sympathetic nerve activity, an increased filtration fraction, an increased plasma ADH concentration and an increased plasma adlosterone concentration.

Sodium re-absorption and potassium excretion in the renal tubules are under the control of aldosterone, the serum concentration of which increases during exercise (Kosunen and Pakarinen 1976; Newmark et al 1976; Wade et al 1981). This in turn is a response to activation of the renin-angiotensin-aldosterone cascade system. A major mechanism for renin release during exercise is probably sympathetic nerve activity stimulating the renal juxtaglomerular cells (Convertino et al 1981; Davis and Freeman 1976; Donald 1979; Kotchen et al 1971). Exercise has been shown to increase plasma renin activity (PRA) (Aurell and Vikgren 1971; Convertino et al 1980, 1981; Kotchen et al 1971; Kosunen and Pakarinen 1976; Wade and Claybaugh 1980). This increase is linearly correlated to work intensity (Convertino et al 1981; Kotchen et al 1971; Wade and Claybaugh 1980) and can be prevented during supine exercise by 3 days of salt-loading (Aurell and Vikgren 1971).

A decreased urine sodium excretion occurs soon after the onset of exercise, however, before the minimum period required for plasma aldosterone concentration to increase

(Castenfors 1967) and renal sympathetic nerve activity may be of importance in sodium reabsorption in the initial phases of exercise (Zambraski 1990).

1.4.3. The effect of marathon running

Long distance running is associated with elevated serum norepinephrine and epinephrine concentrations, (Maron et al 1975) and also increased plasma aldosterone concentrations (Newmark et al 1976).

Urinary sodium/potassium ratios were measured in individual samples 24 and 56 hours after a 56km race (Dickson et al 1982). This ratio was lowest immediately after the race. A reduction in urine sodium concentration was found 30 minutes after a 42,2 km race (Viru and Korge 1971).

Urine sodium excretion was also decreased 12 hours after 28km/day runs and this renal retention of sodium was continued for up to 12 hours (Wade et al 1981).

1.5. URINE POTASSIUM EXCRETION

1.5.1. Introduction

Potassium is also filtered through the glomerulus, but most is actively re-absorbed in the proximal tubules. Potassium

can, however, also be secreted by the distal tubular cells (Giebisch and Windhager 1964), depending on the electrical potential gradient across the tubules. Potassium excretion is also affected by intracellular alkalosis. Potassium depletion on the other hand causes an intracellular acidosis which decreases potassium secretion.

1.5.2. The effect of exercise

Exercise has no consistent effect on urine potassium excretion (Castenfors 1967; Kachadorian 1972) although the excretion rate can triple after heavy exercise (Castenfors 1967).

1.5.3. The effect of marathon running

Viru and Korge (1971) studied urine potassium excretion in 14 subjects before and after a 42.2 km race. The urine potassium concentration was significantly increased in all except 2 runners, both of whom finished the race in an exhausted condition and with mild hypokalaemia. It was assumed that the low plasma potassium concentrations was a factor in the fatigue experienced by these runners.

1.6. URINE PROTEIN EXCRETION

1.6.1. Introduction

During normal daily activity human subjects excrete 40-80 mg of protein (Boyce et al 1954; Poortmans and Van Kerchove 1962). Fifty percent of these proteins are derived from the plasma (Berggard 1970; Poortmans 1969), which are selectively filtered mainly through the glomerulus in proportion to their plasma concentration, their molecular weight and to the transcapillary hydraulic and colloid osmotic pressures (Brenner et al 1976; Lambert et al 1970), as well as the molecular charge (Brenner et al 1978). Schultz and Heremans (1966) have postulated that 360 mg each of high and low molecular weight protein are filtered through the glomerulus every day. Consequently most of the filtered protein is reabsorbed in the proximal tubules (Flynn and Platt 1968; Poortmans and Jeanloz 1968; Schultz and Heremans 1966).

1.6.2. The effect of exercise

It has long been recognized that excess proteins are found in the urine after exercise (Collier 1907). The proteinuria is often associated with an increased incidence of granular and hyaline casts and increased numbers of red blood cells (Alyea and Boone 1957; Alyea et al 1958; Boileau et al 1980;

Blacklock 1977; Bozovic et al 1967; Bailey et al 1976; Siegel et al 1979). The term "athletic pseudonephritis" has been proposed to describe this phenomenon (Gardner 1956).

Post-exercise proteinuria does not seem to be related to trauma (Alyea and Boone 1957; Alyea et al. 1958) but is related to the type of exercise with runners excreting more protein than cyclists, swimmers and rowers (Poortmans et al 1982). There are also large individual variations (Castenfors et al. 1967) and some genetic factors must be involved (Liljefors et al 1969).

The protein excretion rate shows a positive correlation with the intensity of exercise (Delforge et al 1969; Kachadorian and Johnson 1970; Poortmans and Labilloy 1988). After exhaustive cycle exercise both urinary total protein and albumin excretion require approximately 4 hours to return to resting values (Poortmans et al 1989).

A comparison can also be drawn between this normal physiological response to exercise and the proteinuria found in renal damage. The latter can be differentiated into (i) a proteinuria associated with increased glomerular permeability (a glomerular proteinuria), and (ii) the proteinuria associated with renal tubular disorders, the decreased reabsorption of low molecular weight proteins of plasma origin (a tubular proteinuria) (Butler and Flynn

1958; Creeth et al 1963; Flynn and Platt 1968; Maack 1975; Peterson et al 1969).

The majority of the increased proteins excreted after exercise are of plasma origin (Poortmans and Van Kerchove 1962), and it has been shown that plasma proteins represent 82% of the total proteins found in urine after exercise compared with only 57% under resting conditions (Poortmans and Jeanloz 1968).

After short-term intensive exercise, both impaired renal tubular reabsorption and enhanced glomerular permeability (Poortmans 1972; Poortmans et al 1988; Poortmans and Vancalk 1978) have been reported. The proteinuria induced by this type of exercise is of a mixed glomerular/tubular type (Poortmans 1984; Poortmans et al 1988).

1.6.3. The effect of marathon running

Poortmans and Jeanloz (1967) collected urine samples from 20 athletes within an hour of completing a 42 km marathon (the 1966 Boston Marathon). Compared with urine samples collected over a 48 hour period from 6 controls, there was a 50-fold increase in the excretion rate of plasma proteins. These comprised 57% of the total protein content in the urines from the resting controls and 82% of the total protein content in the urines from the marathon runners.

The authors considered that the mechanisms of physiological proteinuria differ from those of pathological proteinuria as their is preferential tubular reabsorption of certain proteins.

Poortmans and Haralambie (1979) studied alterations in total plasma protein content and ten individual plasma protein concentrations in blood and urine of 11 runners prior to, immediately after and 1 day after a 100km race. The race induced a moderate increase in glomerular permeability without any significant change in the tubular reabsorption process. This finding is in contrast to the studies of short-term exhaustive exercise previously discussed in which the post-exercise proteinuria is of a mixed glomerular-tubular type, with the former predominating (Poortmans and Vancalk 1978; Poortmans et al 1988).

FLUID SHIFTS WITH EXERCISE

1.7. PLASMA VOLUME CHANGES

1.7.1. Introduction

Depending on body fat content, fifty to seventy percent of the body mass is water. This water exists in one of two compartments - the intracellular fluid (ICF) and the extracellular fluid (ECF). The ECF may be further

subdivided into the interstitial fluid, lymph and the plasma. The volume of the latter approximates 5% of the body weight or roughly 3500 ml in a 70 kg man.

The factors controlling fluid shifts between the different compartments were originally described by Starling (1895-1896) and Landis (1927). The major factors are transcapillary hydrostatic pressure, capillary surface area (Kjellmer 1964; Sjogaard and Saltin 1982), transcapillary colloid osmotic pressure, interstitial fluid pressure (Mohsenin and Gonzalez 1984) and plasma and interstitial osmolality (De Lanne et al 1959; Lundvall 1972; Lundvall et al 1972; Greenleaf 1979).

1.7.2. The effect of exercise

A study of the literature shows that the response of plasma volume to exercise varies and can increase or decrease. The comment has been made that 'disagreements abound' (Senay 1979). These differences, however, can be explained by factors such as hydration state, state of training, heat acclimation, type and duration of exercise, sex, age (Senay 1979) as well as posture in the exercise and pre-exercise control position (Diaz et al 1979, Eisenberg 1963; Hagan et al 1978; Hagan et al 1980; Thompson et al 1928). The subject is reviewed in detail by Senay and Pivarnik (1985).

Short term exercise in moderate environmental conditions, whether on a cycle ergometer (Costill et al 1974; Convertino et al 1981; Kaltreider and Meneely 1940), or on a treadmill (Kilburn 1966; Galbo et al 1975, 1976; Wilkerson et al 1977) causes a reduction in plasma volume. There is a positive correlation with the intensity of exercise on the cycle ergometer (Costill et al 1974; Convertino et al 1981) but not with treadmill exercise (Senay et al 1980; Wilkerson et al 1977).

Over a longer period of time (> 30 min) cycle ergometer exercise induces a decrease in plasma volume, the greater part of which occurs within the first 5 to 10 minutes (Ekblom 1970; Harrison et al 1975; Van Beaumont et al 1981). The same initial decrease also occurs with treadmill exercise (Galbo et al 1975; 1976;), but after a further period of exercise the plasma volume is restored to near the resting values (Edwards and Harrison 1983; Galbo et al 1975, 1976; Pivarnik et al 1984).

Plasma volume expansion has been reported after longer duration exercise such as 8-9 hours of hill walking (Pugh 1969 a,b), 7 days (Williams et al 1979) and 4 days of hill walking (Leiper et al 1988; Milledge et al 1982), and after a 90 km ski race (Refsum et al 1973). During the recovery stage (1 hour) after an 85 km ski race a 11% increase in plasma volume has been recorded although the plasma volume

had decreased by approximately 5% at the end of the race (Astrand and Saltin 1964).

1.7.3. The effect of marathon running

The effect of marathon running on internal body fluid dynamics has not been adequately studied (Senay and Pivarnik 1985). Plasma volume decreases of up to 13% have been recorded (Costill and Fink 1974; Costill 1977; Maughan et al 1985; Myhre et al 1982, 1985; Wells et al 1982) with one runner showing a 27% decrease in plasma volume (Myhre et al 1982). The majority of this decrease may occur shortly after the onset of exercise (Costill and Fink 1974; Costill 1977; Myhre et al 1985).

However Costill (1972) reported that despite a 7% decrease in mean body weight, there was a mean reduction in plasma volume of only 2% after marathon running. Others have reported only minimal decreases in plasma volume during and after marathon running (Maron et al 1975). Still others have reported plasma volume changes after a marathon ranging from an increase of 11% to a decrease of 25% (Maughan et al 1989).

Increasing the distance raced does not make the plasma volume changes more predictable. After a 100km race, Poortmans and Haralambie (1979) found that plasma volume was

maintained. Similarly Dancaster and Whereat (1971) measured only a moderate increase in haematocrit in most of their subjects competing in a 86 km road race. In 2 runners haematocrit was unchanged after exercise and in 6 out of the 27, it was actually lower. Haemolysis was not considered to play a role, but was not measured

During the recovery period after marathon running, a plasma volume increase has been recorded (Maron et al 1977; Kolka et al 1978) possibly due to an increased plasma sodium content (Maron et al 1977).

1.8. FACTORS INFLUENCING PLASMA VOLUME

In the upright posture the plasma volume is relatively constant after 35 minutes of standing (Hagan et al 1978). Once exercise begins there is an increase in capillary hydrostatic pressure (Hagan et al 1978; Pollack and Wood 1949), but the major determinant of plasma volume loss is increased muscle tissue osmolality (Lundvall 1972; Lundvall et al 1972; McMurray 1983) and changes in plasma colloid and crystalloid osmotic pressures (Greenleaf et al 1977; Mohsenin and Gonzalez 1984; Senay and Pivarnik 1985), as well as increased interstitial fluid pressure (Kohsenin and Gonzalez 1984).

1.8.1. The movement of colloids into and out of the intravascular compartment

1.8.1.1. Introduction

Plasma proteins are usually divided into the albumin, globulin and fibrinogen fractions. Because albumin does not diffuse freely through intact vascular endothelium it provides the critical colloid or oncotic pressure that helps to regulate passage of water and diffusable solutes through the capillaries.

1.8.1.2. The effect of exercise

At one time the belief was held (Adolph et al 1947) that only water and crystalloids leave or enter the vascular space but this has long since been disproved (Senay 1970, 1972). It is now known that protein translocation can occur with changes in the plasma content of certain proteins (Costill et al 1970; Costill and Fink 1974; Melin et al 1980; Pivarnik et al 1984; Poortmans and Haralambie 1979; Senay and Kok 1977; Sawka et al 1984; Van Beaumont et al 1972). An increase in plasma protein content during exercise forms an osmotic base for retention of water (and sodium) within the vascular space (Senay 1979) and the exercise-induced protein influx can be increased with training (Freund et al 1987).

The source of the proteins can be lymph flow (Harrison et al 1975; Olszewski et al 1977; Senay 1970, 1972) or a release from damaged tissue (Haralambie 1969, 1970).

1.8.1.3. The effect of marathon running

An influx of plasma protein into the vascular compartment has been noted after marathon running (Maron et al 1975; Maughan et al 1985; Myhre et al 1982; Poortmans and Haralambie 1979; Wells et al 1982; Whiting et al 1984). However other workers have reported that this influx does not occur (Myhre et al 1985) and the situation is therefore unclear.

1.8.2. The movement of crystalloids into and out of the intravascular compartment

1.8.2.1. Introduction

The ionic constituents of plasma maintain the osmolality and pH of blood within physiological limits. The most important inorganic cation is sodium which is usually present at a concentration of between 135 and 145 mmol/L (Castleman and McNeely 1974; Young 1975). Other cations found in smaller amounts in plasma are potassium, magnesium and calcium while the principal anion is chloride with an average

concentration of 104 mmol/L (Castleman and McNeely 1974; Young 1975). Other anions such as bicarbonate, phosphate, plasma proteins, sulphate and organic acids maintain ionic equilibrium. Plasma osmolality varies from 280-295 mmol/kg in different individuals (Young 1975).

1.8.2.2. The effect of exercise

After short-term exercise increased serum concentrations of sodium and potassium have been reported (Aurell et al 1967; Van Beaumont et al 1972; Castenfors 1965; Cullumbine and Koch 1949; Hultman and Bergstrom 1962; Kilburn 1966; Laurell and Pernow 1966). Plasma chloride concentrations also increase (Metivier 1968). These increases are considered by some to be solely due to haemoconcentration, while others consider them to be due to an influx from extravascular sources (De Lanne et al 1959; Metivier 1968). Van Beaumont et al (1973) have pointed out that conclusions regarding these changes should only be made on changes in total contents. These workers demonstrated a net decrease in total plasma and sodium chloride contents immediately after short-term maximal exercise. In the same study, total potassium contents increased immediately after exercise but subsequently fell significantly. This latter finding was confirmed by Costill (1977) who reported that in the early minutes of exercise potassium leaves the cell; this efflux causes a rise in plasma potassium concentrations. If

exercise continues, potassium appears to re-enter the active muscle cells.

1.8.2.3. The effect of marathon running

Disparate results have been reported after marathon running: no change in serum sodium concentrations were observed by Maron et al (1977) or Wells et al (1982), whereas Nelson et al (1989), Riley et al (1975) and Rose et al (1970) reported increased concentrations. Increased serum potassium concentrations have been recorded (Nelson et al 1989; Riley et al 1975; Rose et al (1970) whereas, after another race, serum potassium concentrations were unchanged (Wells et al 1982). Similarly serum chloride concentrations were increased after one marathon (Riley et al 1975) and unchanged after others (Nelson et al 1989; Rose et al 1970).

A similar variability was observed during ultramarathon running; although serum potassium concentrations were elevated (Dancaster and Whereat 1971; McKechnie et al 1967), serum sodium and chloride concentrations were unchanged.

1.9. THE RECOVERY PHASE AFTER MARATHON RUNNING

Only a few studies have investigated renal function during the recovery phase after marathon running and these have concentrated only on certain aspects of the renal response.

Some of these have been limited by insufficient subjects or have only dealt with certain post-race days. Furthermore, only single urine samples have frequently been analyzed, rather than more complete 24 hour samples.

Blake and Larrabee (1903) reported a reduced urinary urea concentration in 2 runners, 3 days after a marathon race. Riley et al (1975) studied blood biochemical parameters at 20-30 hours post-race in 5 runners, 4 of whom were unable to finish a marathon race. They found that whereas most blood constituents had returned to normal by 20-30 hours post-race, plasma lactate dehydrogenase, creatine kinase and aspartate aminotransferase activities all remained increased over pre-race values. Neviackas and Bauer (1981) measured creatinine and inulin clearances in 3 subjects one week after marathon races, by which time the clearances had returned to pre-race values after a marathon race run in cold weather. After warm weather marathons, the creatinine clearance was decreased in 2 out of 3 runners. Siegel et al (1975) studied single fresh urine samples for densitometry and microscopic analysis of spun sediments for 3 days after a marathon. Eighteen percent of the post-race samples showed haematuria which cleared within 48 hours. No other formed sediments such as casts were seen. Poortmans and Haralambie (1979) studied plasma and urine protein concentrations prior to, immediately after, and one day following a 100km marathon race. The concentrations of five

plasma proteins increased by 7-10% and lysozyme concentration increased by 40% immediately after the race, whereas plasma haptoglobin concentration decreased by 40% compared to pre-race levels. The latter two changes indicated a moderate haemolysis. Measurement of the renal clearance of the plasma proteins showed a moderate increase in glomerular permeability without any significant change in tubular re-absorption.

Dickson et al (1982) measured haematological parameters and urine sodium/potassium ratios after 56km and 160 km races. They showed that a post-race haemoconcentration was followed by haemodilution which was greatest 48 hours after a 160 km marathon. They considered that a post-race sodium retention was indicated by low urinary sodium/potassium ratios. Separate urine potassium and sodium concentrations were not, however, reported. Dancaster and Whereat (1971) studied creatinine clearance 2-3 weeks after an ultramarathon footrace and Maron et al (1977) measured blood biochemical constituents on the 10th day before and for 3 days following a 42.2 km marathon.

Apart from the above work, very little research has been done on renal function during the recovery days after marathon running.

Part 2: THE PATHOLOGICAL RESPONSE TO MARATHON RUNNING

2.1. ACUTE RENAL FAILURE

Acute renal failure associated with long distance running is well documented (Bar-Sela et al 1979; Dancaster et al 1969; MacSearraigh et al 1979; Stewart and Posen 1980). Various aetiological factors have been incriminated in this condition, including heat stroke (Nicholson and Somerville 1978), dehydration (Dancaster et al 1969; MacSearraigh et al 1979) particularly when aggravated by vomiting or diarrhoea, and viral infections (Bar-Sela et al 1979). The role of analgaesic and non-steroidal anti-inflammatory agents in the genesis of running-induced renal failure has not been documented.

Renal biopsies have shown that the renal failure is due to acute tubular necrosis (MacSearraigh et al 1979) and the immediate cause is considered to be exertional rhabdomyolysis (Bar-Sela et al 1979; Dancaster et al 1969; MacSearraigh et al 1979) with the release of nephrotoxic myoglobin. Rhabdomyolysis has also been incriminated as the cause of the nephropathy associated with heat stress and other forms of exercise (Schrier et al 1967; Vertel and Knochel 1967).

Running frequently induces skeletal muscle damage. The pathological nature of this damage has been investigated with electron microscopy (Warhol et al 1985). Lesions that have been identified include intra- and extra-cellular oedema with endothelial injury, myofibrillar lysis, dilation and disruption of the T-tubular system and focal mitochondrial degeneration without evidence of inflammatory infiltrates. These findings are considered to reflect reversible cell injury and not necrosis. Previous observations of muscle fibre necrosis with interstitial haemorrhage and inflammatory cell infiltrate (Hikida et al 1983) are possibly related to the trauma of the muscle biopsy technique (Warhol et al 1985).

Muscle damage may also be shown by increases in serum myoglobin concentrations (Demos et al 1974; Ono 1953; Olerud et al 1975; Hansen et al 1982; Thomas and Motley 1984) and possibly the increase in plasma enzyme activities (Kielbloch et al 1979); Rose et al 1970; Riley et al 1975; Noakes 1987; Noakes and Carter 1976, 1982; Siegel et al 1981, 1983). The extent of the rise in plasma enzyme activity has been related to the exercise duration (Berg and Haralambie 1978; Gardner et al 1964; Noakes 1987; Schmidt and Schmidt 1969) and varies according to the fitness of the subjects (Ahlborg and Brohult 1967; Hansen et al 1982; Hunter and Critz 1971; Magazink et al 1974; Noakes and Carter 1982; Nuttal and Jones 1968; Shapiro et al 1973). There is also a wide

degree of variability between individuals which cannot be correlated with differences in running ability, intensity of exercise or fitness levels (Noakes 1987).

The increase in serum creatine kinase (CK) activity after exercise also depends on gender; women as well as having lower serum CK activities at rest (Griffiths 1966) show a lesser increase in response to marathon running (Noakes 1987; Shumate et al 1979).

Myoglobin released from skeletal muscle injury is considered the major direct cause of acute renal failure (Bywater and Beall 1941; Goldberg and Chakrabarti 1966; Hamilton et al 1972; Vertel and Knochel 1967). However hyperuricaemia and high intratubular urate concentrations may also be involved in the pathogenesis of renal failure (Klineberg et al 1975; Knochel et al 1974; Koffler et al 1976; MacSearraigh et al 1979; Warren et al 1975), particularly when blood lactate concentrations are elevated as lactate and urate are both actively secreted across the renal tubule by the same transport mechanism (Steel and Rieselbach 1975). An increase in blood lactate concentrations would therefore impair the secretion of urate (Warren et al 1975). However most cases of acute renal failure occur after prolonged exercise which does not cause blood lactate concentrations to be greatly increased.

2.2. RENAL STONE DISEASE AND MARATHON RUNNING

Marathon runners may be prone to renal stone formation. A survey conducted among entrants for the 1977 New York City 42,2 km Marathon showed that urinary stone formation in these athletes was 4-5 times greater than the matched population (Milvy et al 1981). The populations were not, however, matched for diet and normal fluid intake.

No studies have yet been undertaken to explain this finding. It is known that plasma calcium concentrations rise after both prolonged (Noakes and Carter 1982) and short-term maximal exercise (Cunningham et al 1985). Urine calcium concentrations were not, however, measured. Another study showed a significant rise in urine calcium excretion after exercise without a change in urine hydroxyproline concentrations (McDonald et al 1975). It was suggested that the increase in urine calcium excretion probably involved the maintenance of acid-base balance.

An increase in urine calcium excretion was also recorded in both marathon runners and cyclists by Cox (1987) who concluded that, as cycling is a non-weight bearing sport, these findings were probably not the result of stress-induced increases in bone turnover.

2.3. THE HYPONATRAEMIA OF EXERCISE

Hyponatraemia associated with a variety of diseases, is probably the most common electrolyte disorder seen in the general hospital population (Flear and Singh 1973; Arieff 1986; Anderson et al 1985; Chung et al 1986). Hyponatraemia frequently constitutes a medical emergency (Thomas et al 1979), and may lead to death or permanent neurologic damage (Arieff 1986, 1987; Arieff and Guisado 1976; Anastassiades et al 1983; Ashraf et al 1981; Helwig et al 1935). The treatment of this condition, however, remains controversial (Arieff 1986, 1987; Swales 1987; Narins 1986; Dubois and Arieff 1984; Norenberg 1984).

The hyponatraemia that is seen in the clinical setting has been classified into 3 categories (Goldberg 1981).

(i) hypotonic hyponatraemia associated with low body sodium content and a contracted extracellular fluid volume. It is due either to external sodium losses via renal or extra-renal routes (for example, the gastro-intestinal tract or via the skin after extensive burns) or by the intracorporeal accumulation of fluid pools (for example in pancreatitis, peritonitis, muscle trauma or ileus)

(ii) hypotonic hyponatraemia associated with normal body sodium content and an increased extracellular fluid (ECF) volume. This can be found with acute water intoxication or as a form of chronic hyponatraemia associated with an abnormality in the regulation of ADH secretion or sensitivity, or both, and

(iii) hypotonic hyponatraemia associated with increased body sodium stores and an expanded ECF volume. This usually occurs in the oedematous state, such as in congestive heart failure, cirrhosis of the liver, nephrotic syndrome or severe hypoproteinaemia. It is also found in patients with acute renal failure who have been both sodium and water overloaded.

Hyponatraemia of exercise was first reported after the 1981 90km Comrades Marathon (Noakes et al 1985). The condition has been reported with increasing frequency subsequently (Hiller et al 1985; Frizzel et al 1986; Johnson and Thompson 1987; Noakes et al 1990; Novak 1988) probably as a result of the increased number of participants in ultramarathon races (Thompson et al 1982). Although the condition may be relatively asymptomatic (Hiller et al 1985), it has been associated with altered mental states, seizures, pulmonary oedema and increased intracranial pressure (Noakes et al 1985; Young et al 1987; Nelson et al 1988; Frizzel et al 1986).

The mechanisms causing the hyponatraemia of exercise have not been identified; thus there is uncertainty of how it should be treated and prevented. Some authors believe that the hyponatraemia results from dehydration and is induced by large sweat sodium losses (Hiller et al 1986; Hiller et al 1987; Hiller 1988; O'Toole 1988). Others also consider that sweat sodium losses play a role, but feel that the primary cause is increased intake and retention of hypotonic fluids with lower sodium chloride content (Frizzel et al 1986). Yet others suggest the aetiology is voluntary hyperhydration with hypotonic solutions combined with moderate sweat sodium losses (Noakes et al 1985; 1990).

SUMMARY

This review indicates that the renal response to moderate or heavy exercise is considered to be a decreased renal plasma flow with a lesser decrease in glomerular filtration rate, owing to an associated increase in the filtration fraction. Urine output is usually decreased mainly as a result of secretion of an anti-diuretic hormone. However, when secretion of this hormone is maximal urine output is primarily affected by changes in the filtered load. Tubular reabsorption of sodium occurs after exercise leading to a decrease in urine sodium concentration. Although large increases in urine potassium excretion can occur after exercise, this is not a consistent response. Formed

elements and red blood cells can be present in the urine after exercise and a proteinuria usually occurs. Short-term exhaustive exercise can induce impaired renal tubular reabsorption as well as enhanced glomerular permeability, whereas only the latter occurs after longer-term exercise.

As regards exercise-induced changes in plasma constituents, there is usually a haemoconcentration commencing in the first ten minutes of exercise but longer-term exercise can induce a plasma volume expansion. Protein translocation often occurs and forms an osmotic base for retention of water (and sodium) within the vascular space.

This thesis looks specifically at areas where controversy exists and attempts to answer the following questions:

Do creatinine clearance, osmolal clearance and urine output decrease during the course of a marathon race? Does a decrease in the renal concentrating capacity occur as has been shown after long-distance ski-racing, and is a decrease in urine sodium excretion the usual response to marathon running? Does a hypokalaemia associated with a decreased urine potassium excretion occur in fatigued runners? Is the increase in plasma creatinine and urea concentrations previously recorded after marathon running due to reduced excretion or to increased production of these substances. Are there changes in the above parameters during the

recovery period following marathon running, and if so why? Can renal tubular dysfunction, as measured by an increased rate of renal $beta_2$-microglobulin clearance occur as a physiological response to marathon running as happens after short-term exhaustive exercise?

Why has a haemoconcentration been recorded after some marathon races and not others? Is there a translocation of crystalloids and colloids or is the major factor in the efflux of fluid merely the increase in transcapillary hydrostatic pressure as has been suggested by some authors? Is the increase in plasma volume previously reported a usual occurrence during the post-race days; does it occur after an ultramarathon, and why does it occur?

Finally when taking into consideration the many physiological changes that occur after marathon running can one interpret biochèmical tests in runners in the same way as in sedentary individuals ?

As regards the pathological response to marathon running the review shows that there are 3 areas of controversy. Firstly, the precise cause of acute renal failure in runners has not been determined. Secondly, are runners at risk for renal stone formation and, thirdly, is the hyponatraemia of exercise recorded after marathon running associated with dehydration and induced by large sweat losses, or is it

primarily caused by over hydration? If the cause is the latter, why is the condition not prevented by the normal counter-regulatory mechanisms activated by an excessive fluid intake ?

To answer these questions, daily blood and 24 hour urine samples were taken from runners who participated in 5 marathons. The following parameters were measured: plasma and urine osmolality, plasma and urine sodium, potassium, urea, creatinine and $beta_2$-microglobulin concentrations. Plasma C-reactive protein concentrations and renin activity and urine total protein concencentrations were also measured. During one marathon study, plasma volume was measured using Evans Blue while subsequent changes in plasma volume were calculated from changes in haemoglobin and haematocrit. Mean cell haemoglobin concentration, red, white cell and platelet counts were also measured, as well as serum aspartate, lactate dehydrogenase and creatinine kinase activities, and serum total protein, albumin, chloride and uric acid concentrations.

From the above measurements the following were calculated: urine flow rates, creatinine, osmolal and free-water clearances, urea and creatinine production rates, renal $beta_2$-microglobulin clearances and urine $beta_2$-microglobulin, total protein, sodium, potassium, urea and creatinine excretion rates. Changes in the total contents

of sodium, chloride, albumin, total protein and uric acid in plasma and serum were also calculated in addition to the changes in plasma volume and mean cell volume.

In addition, urine samples were also taken from runners who took part in a further 2 marathons and these were subjected to particle counting using a coulter counter while deposited crystals were examined using a scanning electron microscope and X-ray powder diffraction.

Finally, the fluid and sodium balance and renal function of 8 runners who collapsed with hyponatraemia after an 88km marathon were studied.

These studies have provided important answers to the questions raised above.

CHAPTER II

BIOCHEMICAL DETERMINATIONS

The following biochemical methods were used in the studies reported in Chapters 3 to 8. All sample analyses were carried out in duplicate or triplicate and a mean taken.

2.1. BLOOD AND URINE BIOCHEMICAL ANALYSES

2.1.1. PLASMA AND URINE ELECTROLYTE CONCENTRATIONS

Plasma and urine sodium and potassium concentrations were determined by flame photometry (Instrument Laboratory: model 543). Plasma and urine chloride concentrations were determined with a CM T10 Chloride Titrator.

2.1.2. PLASMA AND URINE CREATININE CONCENTRATIONS

Creatinine determinations were made by the Jaffe reaction (Cook 1975; Larsen 1972) measured on an IL 919 Spectrophotometer Analyzer (Instrument Laboratory, Milan, Italy). Most compounds which interfere in the Jaffe reaction react more slowly than the creatinine and the IL 919 reduces this interference by choice of the appropriate measurement time and by avoidance of protein precipitation. Results obtained for control sera are not

significantly different from those obtained from assays on aqueous solutions of creatinine (Instrument Laboratory, Operators Manual, 3rd Edition, 1978)

2.1.3. PLASMA AND URINE UREA CONCENTRATIONS

Plasma and urine urea concentrations were measured using a urease/glutamate dehydrogenase procedure (Instrument Laboratory, Operators Manual, 3rd Edition, 1978) and an IL 919 Analyzer (Instrument Laboratory, Milan, Italy).

2.1.4. PLASMA AND URINE OSMOLALITY

Osmolality was measured by depression of freezing point using an automatic osmometer (Osmotte A, Precision Instruments Inc., Newton, Massachusetts)

2.1.5. PLASMA RENIN ACTIVITY (PRA)

Plasma renin activity was determined by the radioimmunoassay of generated Angiotensin I using a gammacoat (^{125}I) PRA radioimmunoassay kit CA-553. In the study of the hyponatraemia of exercise (Chapter 8), PRA was measured using a radioenzyme assay (Biodata, Serono, Switzerland).

2.1.6. C-REACTIVE PROTEIN CONCENTRATION (CRP)

Plasma C-reactive protein concentration was measured by the Laurell Rocket Electrophoretic assay (Laurell 1966).

2.1.7. PLASMA AND URINE BETA$_2$-MICROGLOBULIN CONCENTRATIONS

Beta$_2$-microglobulin concentrations were measured by the Phadebas beta$_2$-micro-Radio-immunoassay test (Pharmacia Diagnostics, Uppsala, Sweden).

2.1.8. URINE TOTAL PROTEIN CONCENTRATIONS

After filtration of the urine samples, urine total protein concentrations were determined by precipitation with 10% trichloroacetic acid, together with a standard of known protein concentration. After mixing and centrifugation, the clear supernatant was discarded and the protein dissolved by addition of Biuret reagent. The concentration was read on a spectrophotometer at wavelength 540 nm with distilled water and Biuret as a blank.

2.1.9. HAEMATOCRIT

Haematocrit was determined in triplicate by the micro-haematocrit method immediately after collection of whole blood samples. An MSE Micro-haematocrit Centrifuge (Type

346) (MSE Scientific Instruments, Crawley, England) was used with the centrifuge operated at 11 500 rpm for 5 minutes. For the study of renal function and fluid homeostasis during recovery from the hyponatraemia of exercise (Chapter 8), haematocrit was measured using a Coulter Counter Model ZF.

2.1.10. RED AND WHITE BLOOD BLOOD CELL AND PLATELET COUNTS; HAEMOGLOBIN CONCENTRATIONS

These were determined using an Automated Coulter Counter Model S-Plus II (Coulter Electronics, Hialeah, FL). The principle was described by Coulter (1956). A suspension of blood cells is passed through an orifice together with an electric current and the impedance change induced by the size of the cell is measured. The Coulter Counter can also be used to count platelets as described by Mundschenk et al (1976). The leukocyte count and haemoglobin estimation requires the simultaneous destruction of erythrocytes and rapid conversion of haemoglobin to haemoglobin cyanide. The leukocyte nuclei are left intact by the lysing agent and electronically visible. A single-beam photometer is used for haemoglobin measurement.

2.1.11. SERUM TOTAL PROTEIN, ALBUMIN AND URIC ACID CONCENTRATIONS

All were determined using a Technicon SMAC II Auto Analyzer (Technicon, Tarrytown, NY). The measurements of serum total protein concentration is based on the method of Skeggs and Hochstrasser (1964) who automated the manual method of Weichselbaum (1946). The measurement of serum albumin concentration is based on the work of Daumas et al (1971) who automated the manual method of Rodkey (1965). Serum uric acid concentration is measured using immobilized urease (urate oxidase) as the reaction catalyst (Leon et al 1978).

2.1.12. SERUM ASPARTATE TRANSAMINASE (AST) AND LACTATE DEHYDROGENASE (LDH) ACTIVITIES

The activities of these enzymes were measured by standard techniques using a Technicon SMAC II Auto Analyzer (Technicon, Tarrytown, NY). The determination of LDH activity is based on the method of Wacker et al (1956), modified by Morgenstrom et al (1973) while the determination of AST activity is based on the method of Karmen et al (1955), modified by Henry et al (1960).

2.1.13. SERUM CREATINE KINASE (CK) ACTIVITY

Serum CK activity was determined using a kinetic UV method monitored at 340 nm with a Centrifichem 500 analyzer using a CK N-acetyl cysteine-activated test kit (Monotest: Boehringer Mannheim, Federal Republic of Germany).

2.1.14. PLASMA VOLUME

Plasma volume was determined from the volume distribution of the dye T-1824 (Gregerson 1944) with the proportional changes in plasma volume computed from haematocrit and haemoglobin measurements (For calculation see 2.4.2.).

2.1.15. SERUM WATER CONTENT

Serum water content was measured as the loss in mass of pre-weighed samples of serum (150ul) after heating to dryness (110-115^{o}C for 90 minutes).

2.1.16. SERUM FREE-FATTY ACID CONCENTRATION

Serum free-fatty acid concentrations were determined colorimetrically using a modification of the technique of Noma et al (1973).

2.1.18. SERUM ALDOSTERONE CONCENTRATION

Serum aldosterone concentration was determined using radioimmunoassay (Biodata, Serono, Switzerland).

2.2. **LABORATORY PERFORMANCE VARIABLES**

2.2.1. MAXIMUM OXYGEN UPTAKE

Maximal oxygen uptake (VO_2 max) was measured using a continuous horizontal testing protocol. The test began with a 5-minute warm-up and familiarization period at 8 km/hr on a Quinton air-cooled transformer-type BA-1 treadmill (Tiernay Electrical Motor Co., Seattle, USA). Following a 5-minute rest period the test was begun at 8 km/hr with speed increments of 0.5 km/hr every 30 secs until the subject voluntarily stopped the test.

2.2.2. OXYGEN COST AT RACE PACE

To determine the oxygen cost at race pace of the subjects paticipating in the 24 hour relay (Table 3.6.) the subjects ran on the treadmill for 6 minutes at the average pace they maintained during the race. Their oxygen consumption was measured according to the methods described in paragraph 2.2.1. Subjects used a model no. 2766 counterbalanced head support holding a model no. 2700 Rudolph valve (Hans Rudolph

Inc., Kansas City, Kansas, USA) which was placed in the mouth. A noseclip prevented nasal breathing. Air was expired through clear-bore 35 mm tubing into a 15 litre perspex mixing chamber with baffles. Expired air from the mixing chamber was continuously sampled through Drierite anhydrous $CASO_4$ (Vacumed Inc., Ventura, USA) to the pick-up heads of an Ametec oxygen analyzer model 242 B and a Beckman LB-2 medical gas analyzer model 240 M (Beckman Instruments Inc., Illinois, USA). The outputs from the analyzers were recorded on a Beckman respiratory recorder RR-2.

Both analyzers were calibrated before and after each test using gases of known composition according to the Haldane technique.

The race pace as a percentage of the VO_2 max was calculated as VO_2/VO_2 max x 100.

2.2.3. EXERCISING HEART RATES

Exercising heart rates were measured using 3 Medi-Trace pellet electrodes in the CM 5 position and recorded on a Life Trace Monitor (Albury Instruments Ltd., London, GB).

2.3. **URINE PARTICLE ANALYSES**

2.3.1. URINE PARTICLE SIZE DISTRIBUTION ANALYSIS

A Model TA II Coulter Counter with Population Accessory Unit and fitted with a 100 um diameter orifice was used for particle distribution analysis. Samples to be counted were pipetted into a double walled glass vessel of internal capacity 230 ml through which a low viscosity oil was pumped from a thermostatically controlled oil bath maintained at 37^{o}C. The instument was calibrated using Latex calibration beads (Coulter Electronics, Herdfordshire) of diameter 19.00 um suspended in azide free ISOTON II soluiton.

The pH of each urine sample was measured prior to filtering through a 74 um sieve in order to remove particles too large to be accomodated by the Coulter Counter. Thereafter, a 1 ml aliquot of filtered urine was pipetted into 150 ml of the ISOTON II electrolyte and subjected to a trial count. Further aliquots were added in those cases where the concentration of particles was not sufficiently high to yield a statistically reliable particle size distribution. All samples were continuously stirred. The instrument was set to allow 2 ml of the ISOTON/urine solution to be drawn through the aperture for each counting procedure. Each sample was counted 3 times.

The use of the Coulter Counter in the study of crystalluria is a well documented technique which has been used previously by several researchers (Adamthwaite 1983; Crassweller et al 1979; Robertson 1969; Robertson and Peacock 1972)

2.3.2. URINE CALCIUM CRYSTALS

Calcium crystals were determined in urine samples by selective complexation with EDTA according to the method described by Robertson (1969).

2.3.3. SCANNING ELECTRON MICROSCOPY (SEM) AND X-RAY POWDER DIFFRACTION (XRD)

Urine samples at 37^{o}C were centrifuged for 5 minutes using a Piccolo table-top low speed centrifuge operating at 2000 revs per minute. The deposited crystals were removed by repeated aspiration using a Pasteur pipette. Drop amounts were then filtered through a 0.2 um Nucleopore filter (GMBH Gottingen). The filter papers, with deposited crystals, were then pasted on aluminium stubs for scanning electron microscope analysis. These were coated with approximately 100 nm of carbon at a pressure of 1.3 mPa in a Balzer's vacuum coater equipped with a planetary sample rotator. Specimens tilted at 35^{o}C to the collector were examined using a Cambridge S180 Scanning Electron Microscope

operating at a nominal beam potential of 15 kV and beam current of 100 uA. Images were recorded on Ilford FP4 roll film. The scanning electron microscope was equipped with an energy dispersive X-ray analyzer system which was used for routine elemental analysis of the specimen.

2.4. CALCULATIONS

2.4.1. RENAL BETA$_2$-MICROGLOBULIN CLEARANCE

Renal beta$_2$-microglobulin clearance was calculated in ul/min using the formula:

$$\frac{\text{Urine concentration (ug/min) x Urine output (ml/min)}}{\text{Plasma concentration (ug/ml)}}$$

(Poortmans and Haralambie 1979)

2.4.2. PERCENT CHANGES IN PLASMA VOLUME

Percent changes (%) in PV were calculated as:

a) $$\% \triangle PV = \frac{Hbpre\ (100-Hctpost)}{Hbpost\ (100-Hctpre)} \times 100$$

(Strauss et al 1951)

where pre stands for the pre-race sample, post the post race sample and Hb for haemoglobin concentration and Hct for haematocrit

For the study on the runners who collapsed with hyponatraemia (Chapter 8) the proportional changes in plasma volume were calculated from the equation:

$$b) \quad \% \triangle PV = \frac{100}{100 \times Hctpre} \times 100 \frac{(Hctpre - Hctpost)}{Hctpost} \%$$

(van Beaumont et al 1973)

2.4.3. PERCENTAGE CHANGES IN MEAN CELL VOLUME

Percentage changes in Mean Cell Volume (% $\triangle$ MCV) were calculated from Mean Cell Haemoglobin Concentration (MCHC) changes.

$$\% \triangle MCV = 100 \frac{[MCHCpre - MCHCpost]}{MCHCpre}$$

(Costill and Fink 1974)

with MCHC calculated by dividing Hb by Hct. The factor 0.96 was used to correct the Hct value for trapped plasma.

2.4.4. CHANGES IN TOTAL CONTENTS OF PLASMA AND SERUM CONSTITUENTS

Changes in total contents (Co) of plasma and serum constituents were calculated:

a)

$$\% \Delta Co = - \frac{Cnpost\ [Hbpre\ (100 - Hctpost)]}{Cnpre\ [Hbpost\ (100 - Hctpre)]/100}$$

(van Beaumont et al 1981)

where Cnpre is the mean of the 3 pre-race blood concentration values and Cnpost indicates the post-race concentration values.

b) For the study on the runners who collapsed with hyponatraemia (Chapter 8) percent changes in serum total protein and albumin content for both the hyponatraemic and normonatraemic runners were calculated as follows:

$$C_{N2} = C_{NE} = \frac{Hct_2(100-Hct_1)}{Hct_1(100-Hct_2)} \times C_{N1}$$

and, therefore:

$$\% \Delta C_N = \frac{C_{NM} - C_{NE}}{C_{NE}} \times 100\%$$

(van Beaumont et al 1973)

where C_{NE} is the expected and C_{NM} the measured concentration

2.4.5. CREATININE CLEARANCE

Creatinine clearance was calculated using the conventional formula (White et al 1976) with the clearance during the race calculated from the mean plasma creatinine concentration during this period. The clearances for the subsequent days were calculated in a similar manner.

2.4.6. UREA AND CREATININE PRODUCTION

The 24 hourly rates of urea and creatinine production were calculated by summing the 24 hour urinary excretion rates for these substances with the additional amounts retained in the body during the same period on the assumption that the volumes of the urea and creatinine spaces are 60% of the body weight on that day (Peters and Van Slyke 1946).

2.5. **STATISTICAL ANALYSIS**

Statistical analysis were performed by two-way analysis of variance (ANOVA). Significance was determined at the 0.05 level. In Chapter 8, where a comparison was made between hyponatraemic and normonatraemic runners, statistical analysis was performed using the Student's T-test for paired data, and using Analysis of Variance with post-hoc Dunnett test for unpaired data. Significance was again determined at the 0.05 level.

CHAPTER III

THE IMMEDIATE AND DELAYED EFFECTS OF MARATHON RUNNING ON RENAL FUNCTION

3.1. INTRODUCTION

In order to understand the pathological renal response to prolonged exercise it is necessary first to understand the normal physiological response to marathon running.

However it is clear that the renal response to marathon running, particularly in the recovery phase, has not been clearly defined. In part this is because most studies have not been continued into the post-race days when changes in renal function are still occurring. It is also at that time that subjects are often first admitted to hospital with acute renal failure (Dancaster et al 1969). In addition, twenty-four hour urine collections are likely to give a better indication of trends in renal function than do single samples; the latter has been the more common procedure for studying renal function in previous studies (Boileau et al 1980; Dancaster and Whereat 1971; Siegel et al 1979). Throughout this study we have collected all the urine passed during each study period.

Many of the parameters discussed in this chapter have been studied previously after marathon running, but the information reported is often incomplete. For example, glomerular filtration rate has been measured after marathon running but only 6 hours later when the subjects were rehydrated (Neviackas and Bauer 1981) or only 2-3 weeks later (Dancaster and Whereat 1971). Urine output is considered to decrease but no comparison with pre-race values has been reported (Dancaster and Whereat 1971). It is uncertain whether the decrease in renal concentrating ability recorded after ski-racing (Castenfors et al 1967; Refsum and Stromme 1977) also occurs after marathon running. While a decrease in urine sodium excretion has been recorded, this has often been reported as altered urine sodium/potassium ratios (Dickson et al 1982). Increases in urine potassium excretion have been reported with mild hypokalaemia and fatigue (Viru and Korge 1971). Whether this is a universal finding is uncertain. Finally, blood urea nitrogen concentration is used to assess renal damage but has been shown to increase in marathon running due to increased urea production (Decombaz et al 1979) and may not, therefore, indicate renal damage. The duration of this effect is, however, not known.

To answer these and other questions, the renal function of runners who took part in 5 races was studied:- the 1982, 42.2 km Kellerprinz Marathon, the 1983 and 1986, 56 km Two

Oceans Marathons, the 1984, 90 km Comrades Marathon and the 1983, 201 mile 24-hour Relay Race. In order to study the time course of changes, renal function was studied for at least 8 consecutive days in most of these studies.

3.2. METHODS AND MATERIALS

3.2.1. SUBJECTS

The personal details, training distances and racing times of the 17 athletes who took part in these studies are given in Tables 3.1.-3.5. Five of these athletes participated in more than one of the study races, and all except one were experienced runners. The one exception (KC), who took part in the 1982 42.2 km marathon (Table 3.1.) had previously run no more than 10km in training. However his results did not differ materially from the other athletes and he was included in this study.

All were healthy individuals with no history of renal disease or unusual diets. None of them took any medication during the races. The 2 runners who took part in the 1983 24 hours 201 mile Relay Race (Table 3.5.) were each given one litre of intravenous normal (0.9%) saline after 18 hrs and 20 hrs respectively.

The two subjects who participated in the 1983 24-hours, 201 mile Relay Race (Table 3.5.) were the most experienced athletes; each had run more than 50 42.2 km marathons and they had the two fastest personal best marathon times (2 hrs 22 mins and 2 hrs 26 mins respectively).

3.2.2. STUDY PROTOCOLS

3.2.2.1. The 1982 42 km Kellerprinz Marathon

Daily blood samples and 24 hour urine collections were taken for two days before and for five days after the 1982 Kellerprinz 42 km Marathon, run over a hilly course in cool and rainy conditions - mean dry bulb temperature = 13,8°C; Range over the race period = 13,4°C-14,8°C, with mean humidity of 82% (range 77-90%). Diet and fluid intake were not controlled during the study but, except for extra carbohydrate consumed before the race, it seemed that no major dietary changes occurred for the duration of the study. During the race the subjects maintained an adequate fluid intake by drinking according to their individual preferences.

The runners were weighed on a Seca electronic scale (Vogel and Halke, Hamburg, West Germany) and blood samples were drawn by venepuncture with minimal stasis and in a sitting position which was maintained for 5 minutes (Eisenberg 1963) each day at 10h00 hours. On the race day, however, these procedures were repeated at 05h30 hours and again immediately after each runner had completed the marathon which began at 06h00.

All unclotted (plasma) samples were placed immediately on ice whereas samples for serum analysis were first allowed to clot before also being placed on ice. Samples were centrifuged at 2000 rpm for 10 minutes and the serum or plasma stored frozen until analysis. The blood was analyzed for urea, creatinine, sodium, potassium and C-reactive protein concentrations, osmolality and creatine kinase activity.

All urine passed each day, with the exception of the race day, was collected and analyzed as a single 24 hour collection. On the race day, the runners passed their last urine immediately before starting the race, and then collected any urine passed during or immediately after the race into a separate container; the remainder of the day's urine collection was collected into a third container. Urine collections were made into one litre plastic bottles, protected from light by silver foil and stored in the refrigerator. After the urine volumes had been measured each day, 2 x 80 ml aliquots were retained and stored frozen, without the addition of any preservative medium, and protected from light by silver foil. The urine was later analyzed for urea, creatinine, sodium, potassium concentrations and for osmolality.

3.2.2.2. The 1983 and 1986 56 km Two Oceans Marathon and 1984 90 km Comrades Marathon

All these races took place over hilly demanding courses with environmental conditions as follows:

(i) The 1983 56 km Two Oceans Marathon: The mean dry bulb temperature was 21.9°C (Range 17.3-24.8°C). Mean humidity was 64% (Range 47-85%).

(ii) The 1984 90 km Comrades Marathon: The mean dry bulb temperature was 17.9°C (Range 10.5-21.5°C). Mean humidity was 60% (Range 41-92%).

(iii) The 1986 56 km Two Oceans Marathon: The mean dry bulb temperature was 17.0°C (Range 16.1-17.9 °C). Mean humidity was 78% (Range 53-91%).

The protocol for each of these studies was similar to that described in the previous section for the Kellerprinz Marathon. Only in the 1986 Two Oceans was the diet partially controlled as the subjects ate a low collagen diet for 5 days before and 3 days after the race.

For both Two Oceans Marathon studies, blood samples were drawn by venepuncture with minimal stasis in a consistent posture on 3 occasions during the week preceding the race, immediately on completion of the race and then daily for 6 days thereafter. A similar protocol was followed before the 1984 90 km Comrades Marathon but that study was continued

daily for 8 days and then, on alternate days, for a further 6 days. Blood samples were analyzed for the same substances as in the previous study, with the exception of the 1986, 56 km Two Oceans Marathon, in which serum AST and LDH activities and uric acid concentrations were also measured.

Urine samples were collected as follows: daily 24 hour urine collections were made for 6 days prior to the 1983 and 1986 Two Oceans Marathon and for 5 days prior to the 1984 Comrades Marathon. Urine collections on the race days were as described for the 1982 Kellerprinz marathon. Thereafter daily 24-hour collections were made for 5 and 6 days after the 1986 and 1983 Two Oceans marathons, respectively. For the 1984 Comrades Marathon, these samples were initially collected daily for 8 days and then on alternate days for a further 6 days. Urine was analyzed for the same substances as in the 1982 Kellerprinz Marathon.

3.2.2.3. Twenty-four hour relay record attempt

A successful world record attempt was made in 1983 by 2 athletes who ran one mile at a time sequentially for a 24-hour period. Daily blood and 24 hour urine collections were made for 2 days before and for 2 days after the 24 hours of the race. The race was run on a tartan track under mild environmental conditions (range of Wet Bulb Globe Temperature Index = 9.7 - 16.3^{o}C). During the race, the

athletes were weighed every hour on an electronic scale (Vogel and Halke, Hamburg, West Germany) and their rectal temperatures were measured. Blood samples were drawn by venepuncture every 3 hours and all urine passed was collected, the volumes were measured and aliquots were stored frozen for subsequent analysis. Blood samples were centrifuged and plasma stored frozen for subsequent analysis as in the previous studies. All food and drink consumed during the 24 hours was also recorded. Urine was analyzed as in the 1982 Kellerprinz Marathon.

The maximum rates of oxygen consumption (VO_2 max), maximum heart rates, peak treadmill running velocities, the race pace as a percentage of VO_2 max, the oxygen cost at race pace and the estimated kilojoules expended over the race were measured for each runner as well as changes in free fatty acid and insulin concentrations (Table 3.6.)

3.3. **RESULTS**

3.3.1. CREATININE AND OSMOLAL CLEARANCE, URINE FLOW RATE AND URINE OSMOLALITY

Creatinine and osmolal clearance, urine flow rate and urine osmolality before, during and after the 5 races are shown in Figures 3.1-3.5.

Creatinine clearance was maintained in the 1982 42.2 km Kellerprinz Marathon (Mean temperature 13.8^{o}C (Figure 3.1.)) and the 1986 56 km Two Oceans Marathon (Mean temperature 17^{o}C (Figure 3.3.)). Although creatinine clearance decreased by 36% during the 1984 90 km Comrades (mean temperature 17.9^{o}C (Figure 3.4.)), this fall was not significant.

During the 1983 56 km Two Oceans Marathon (Mean temperature 21.9^{o}C (Figure 3.2.)) there was, however, a significant decrease in creatinine clearance. Similarly, during the 1983 201 mile Relay Race (temperature range over 24 hrs, 9.7-16.3^{o}C), the creatinine clearance of each runner decreased by 46% (from the pre-race value of 77.7 $\pm$ 10.1 to 41.7 ml/min) and 44% (from the pre-race value of 113.3 $\pm$ 7 to 63.7 ml/min), respectively, (Figure 3.5.).

However, during the post-race days creatinine clearance was usually elevated, frequently significantly so (Figures 3.1., 3.3. and 3.4.).

Urine output was well maintained during all the races (Figures 3.1.-3.5.). Although urine output tended to increase during the post-race recovery period (Figures 3.1.-3.4.), only after the 1982 42 km marathon was this increase significant (Figure 3.1.).

Osmolal clearance was decreased during the longest races, the 1984 90 km Marathon (Figure 3.4.) and the 1983 201 mile relay race (Figure 3.5.) and also immediately after the 1982 42.2 km Marathon (Figure 3.1.). However osmolal clearance increased during the post-race days (Figures 3.1. and 3.2.).

Urine osmolality decreased significantly during the 1986 56 km Marathon (Figure 3.3.) and the 1983 201 mile relay (Figure 3.5.).

3.3.2. FREE WATER CLEARANCE

Free water clearance is shown in Figure 3.6. This was increased (less negative) during the 1986 56 km Two Oceans Marathon and the 1984 90 km Comrades marathon and the 1983 201 mile Relay Race. However free water clearance was negative during the recovery period after all the races.

3.3.3. PLASMA OSMOLALITY

Changes in plasma osmolality are shown in Figure 3.7. Plasma osmolality was elevated on Day 1 after the 1983 201 mile Relay but was significantly decreased during the post-race days in two of the shorter races.

3.3.4. URINE SODIUM AND POTASSIUM EXCRETION

Twenty-four hour urine sodium and potassium excretions are given in Figure 3.8. and 3.9. A decrease in urine sodium excretion occurred in all races except the 24 hour race. Sodium excretion was decreased for at least 24 hours after all races. During the post-race days, there was a tendency for urine sodium excretion to increase but only on Day 2 after the 1983 56 km Marathon was this increase significant (Figure 3.8.).

Urine potassium excretion tended to increase during the race day and to decrease during the post-race days (Figure 3.9.), but these changes were not always significant.

Urine sodium and potassium concentrations are recorded in Tables 3.7. and 3.8. The urine sodium concentrations were decreased below pre-race values over the race and remainder of the race day in all the races. This decrease extended to

Day 1 after the 1984 90 km Comrades marathon (Table 3.7.). Urine potassium concentration was increased significantly only during the 1982 42 km Kellerprinz and 1984 90 km Comrades marathons as well as during the race day after the 1983 56 km Two Oceans marathon (Table 3.8.).

Plasma potassium concentrations before, during and after 5 marathons are shown in Table 3.9. The only significant changes are shown on Days 3 and 4 after the 1986 56km Two Oceans Marathon when there was an increase in the plasma potassium concentrations.

Urine sodium/potassium ratios were decreased during all the races and immediate post-race period and were significantly increased during the days after the two 56 km Two Oceans marathons (Figure 3.10.)

3.3.5. PLASMA RENIN ACTIVITY

Plasma renin activity was measured immediately after the 3 races, on Day 1, and again on Day 6 after the races (Figure 3.11.). There were significant increases over resting values at the end of the 1983 56 km Two Oceans and the 1984 90 km Comrades marathons.

3.3.6. PLASMA ENZYME ACTIVITIES, C-REACTIVE PROTEIN CONCENTRATIONS AND SERUM URIC ACID CONTENT

Plasma CK activity and C-reactive protein concentrations are shown in Figures 3.12. and 3.13. These were often elevated during the race but always peaked on Day 1. Serum AST and LDH activities also peaked on the same day after the 1986 56 km Two Oceans Marathon and remained elevated for at least 5 days (Figure 3.14.). Serum uric acid concentration after the 1986 Two Oceans marathon remained unchanged, but when this was adjusted for the change in plasma volume, the total plasma content was increased on Day 1 (Figure 3.14.)

3.3.7. UREA AND CREATININE PRODUCTION AND EXCRETION

Changes in plasma urea and creatinine concentrations, measured urine creatinine and urea excretion rates as well as calculated creatinine and urea production rates are given in Figures 3.15.-3.19. Plasma creatinine concentration was generally elevated during each race (Figures 3.15.-3.17., 3.19.), usually in association with increased rates of creatinine production (Figures 3.15.-3.17.). Only during the 1983 201 mile 24-hours relay did the urine creatinine excretion decrease (Figure 3.19.). A second increase in production and excretion can be seen on Day 3 after the 1982 42.2 km marathon (Figure 3.15.).

The plasma urea concentration was usually elevated at the end of each race (Figures 3.15., 3.17., 3.19.) and remained elevated on Day 1 after the 1986 56 km marathon (Figure 3.17.). Urea production was sometimes increased (Figures 3.17., 3.19.) whereas urine urea excretion remained constant (Figures 3.15.-3.18.).

During the post-race days, urine urea excretion was often increased (Figures 3.15.,3.16.,3.18.) whereas on days 3-5 after the 1982 42.2 km Kellerprinz marathon, the rates of both urea production and excretion were significantly decreased (Figure 3.15.).

Urine urea and creatinine concentrations over the 5 race periods are shown in Tables 3.10. and 3.11. Urine urea concentrations increased after 3 of the marathons but were decreased below pre-race values, on days 3-5, only after the 1983 42 km Kellerprinz marathon (Table 3.10.). No significant changes were found in urine creatinine concentrations (Table 3.11.)

Table 3.1. SUBJECT DETAILS: THE 1982 42.2 KM KELLERPRINZ MARATHON

Subject	Age (yrs)	Height (cm)	Pre-race Weight (kg)	Distance Run per Week (km)	Personal Marathon Record (hrs:min)	Time Recorded (hrs:min)
GI	33	177	74.0	50	2:47	2:55
TN	33	185	83.2	80	2:50	3:05
PB	32	160	63.6	70	3:10	3:25
AI	38	176	71.5	30	3:24	3:27
KC	25	170	60.0	30	-	4:18
RR	28	178	80.3	80	3:09	3:47
MEAN	32	174	72.1	57	3:04	3:31
SEM	±1.7	±3.5	±3.7	±9.5	±6.9	±12.3

Table 3.2. SUBJECT DETAILS: THE 1983 56 KM TWO OCEANS MARATHON

Subject	Age (yrs)	Height (cm)	Pre-race Weight (kg)	Distance Run per Week (km)	Personal Marathon Record (hrs:min)	Time Recorded (hrs:min)
GI	34	177	75.4	50	2:47	3:59
DL	22	173	74.4	100	3:03	4:07
TN	34	185	83.0	80	2:50	4:17
RZ	38	180	79.7	50	3:05	4:55
AI	39	176	73.0	20	3:24	4:59
RR	29	178	78.9	80	3:09	5:07
MEAN	33.0	178	77.4	63	3:03	4:34
SEM	±2.6	±1.6	±1.5	±12	±0.05	±0.12

Table 3.3. · SUBJECT DETAILS: THE 1986 56 KM TWO OCEANS MARATHON

Subject	Age (yrs)	Height (cm)	Pre-race Weight (kg)	Distance Run per Week (km)	Personal Marathon Record (hrs:min)	Time Recorded (hrs:min)
ML	30	175	72.1	110	2:33	3:37
JK	26	164	60.3	70	2:59	4:19
GI	37	177	73.5	60	2:47	4:24
GG	23	190	75.0	70	2:48	4:41
DT	30	185	80.2	85	3:08	4:46
RR	32	178	80.3	60	2:59	4:52
JH-Z	43	186	73.3	85	3:10	4:53
TN	37	185	81.7	120	2:50	5:24
MEAN	32	180	74.6	82	2:54	4:37
SEM	±2.3	±3.0	±2.4	±8.0	±0.0	±0.1

Table 3.4. SUBJECT DETAILS: THE 1984 90 KM COMRADES MARATHON

Subject	Age (yrs)	Height (cm)	Pre-race Weight (kg)	Distance Run per Week (km)	Personal Marathon Record (hrs:min)
RR	30	178	78.9	80	3:09
GG	21	190	75.5	120	2:57
EP	22	179	78.0	60	3:31
HS	23	185	80.0	60	3:34
MEAN	24	183	78.1	80	3:18
SEM	±2	±3	±1	±14	±0.09

Table 3.5. SUBJECT DETAILS: THE 1983 201 MILE TWENTY-FOUR HOURS RELAY RACE

Subject	Age (yrs)	Height (cm)	Pre-race Weight (kg)	Distance Run per Week (km)	Personal Marathon Record (hrs:min)
BM	37	175	70.3	160	2:22
GD	28	179	70.9	160	2:26
MEAN	32.5	177	70.6	160	2:24
SEM	±4.5	±2	±0.3	±0.0	±0.02

Table 3.6. PHYSIOLOGICAL AND PERFORMANCE PROFILE OF THE TWO SUBJECTS WHO TOOK PART IN THE 1983 201 MILE TWENTY FOUR HOURS RELAY RACE

Athlete	BM	GD
Age (yr)	37	28
Height (cm)	175	179
Weight (kg)	70.3	70.9
VO_2 max (mL O_2/kg/min)	66.8	68.9
Maximum heart rate (beats/min)	185	187
Peak treadmill velocity (km/hr)	23	23
O_2 cost at race pace (13.48 km/hr) (ml O_2 kg/min)	6.3	42.0
Race pace as % VO_2 max (%)	54%	61%
Estimated kJ expended	36 747	42 880
Number of years running	18	11
Best marathon time (hr:min:sec)	2:22:51	2:26:20
Pre-race plasma free fatty acid concentrations (μmol/mL)	311.2	312.3
Post-race plasma free fatty acid concentrations (μmol/mL)	2108.1	1875
Pre-race plasma insulin concentration (μU/mL)	42.9	22.7
Post-race plasma insulin concentration (μU/mL)	10.1	11.5

Table 3.7. MEAN URINE SODIUM CONCENTRATION (MMOL/L) BEFORE DURING AND AFTER 5 MARATHONS

	1982 42 KM KELLERPRINZ MARATHON	1983 56 KM TWO OCEANS MARATHON	1986 56 KM TWO OCEANS MARATHON	1984 90KM COMRADES MARATHON	1983 201 MILE RELAY RACE
Pre-race	117 ±13.4	127 ±8.5	122 ±9.0	142 ±13.4	118.5 ±12.5
Race	79 ±22.5	34** ±9.0	40** ±11.9	49** ±10.9	53 ±8.0
Remainder Race Day	56** ±14.8	65** ±9.3	70.5** ±11.9	36** ±11.5	- -
+1	97 ±15	90 ±18.4	112 ±14	52** ±27.7	29 ±1.0
+2	88 ±11.2	131 ±31	135 ±13.9	117 ±30.4	24.5 ±1.5
+3	92 ±7.3	128 ±12.0	115.5 ±18	141 ±30.3	- -
+4	91 ±11.5	135 ±17.4	115 ±15	151 ±25.6	-
+5	91 ±8.9	126 ±18.2	107 ±7.6	129.5 ±29.4	
+6	- -	107 ±13.3	- -	124 ±29.3	
+7	- -	- -	- -	116.5 ±35.1	
+8	- -	- -	- -	127 ±33.6	
+10	- -	- -	- -	118 ±14.5	
+12	- -	- -	- -	128 ±27.9	
+14	- -	- -	- -	71.5* ±12.1	

Data expressed as means ± standard error of the mean

* $p = < 0.05$ compared with pre-race values

* * $p = < 0.01$ compared with pre-race values

Table 3.8. MEAN URINE POTASSIUM CONCENTRATIONS (MMOL/L) BEFORE, DURING AND AFTER 5 MARATHONS

	1982 42 KM KELLERPRINZ MARATHON	1983 56 KM TWO OCEANS MARATHON	1986 56 KM TWO OCEANS MARATHON	1984 90 KM COMRADES MARATHON	1983 201 MILE RELAY 1RACE
Pre-race	57.5 ±6.7	80 ±7.0	72 ±5.4	43 ±4.9	50 ±11.1
Race	88* ±17.4	98 ±13.7	92.5 ±21.2	76* ±27.9	23.5 ±0.5
Remainder Race Day	51 ±9.6	112* ±17.4	87 ±14.7	46 ±13.0	- -
+1	65 ±11.1	56 ±6.3	60.5 ±8.9	32 ±10.9	50.0 ±13.0
+2	50 ±10.9	59 ±13.2	59 ±6.5	55 ±13.7	60.5 ±5.5
+3	48 ±5.9	56 ±6.3	55 ±9.1	52.5 ±14.8	- -
+4	42 ±6.8	52 ±9.4	49 ±7.7	45 ±10.8	- -
+5	44 ±7.8	65 ±11.1	62 ±8.5	34 ±5.8	- -
+6	- -	64 ±9.7	- -	31 ±7.6	- -
+7	- -	- -	- -	30 4.6	- -
+8	- -	- -	- -	45 ±11.5	- -
+10	- -	- -	- -	50 ±10.9	- -
+12	- -	- -	- -	58 ±14.5	- -
+14	- -	- -	- -	32 ±4.0	- -

Data expressed as means ± standard error of the mean

* $p = < 0.05$ compared with pre-race values

Table 3.9. · MEAN PLASMA POTASSIUM CONCENTRATION (MMOL/L) BEFORE, IMMEDIATELY AFTER AND DURING THE POST-RACE DAYS OF 5 MARATHONS

	1982 42 KM KELLERPRINZ MARATHON	1983 56 KM TWO OCEANS MARATHON	1986 56 KM TWO OCEANS MARATHON	1983 201 MILE RELAY RACE	1984 90KM COMRADES MARATHON
Pre-race	4.5 ±0.1	4.6 ±0.2	4.2 ±0.1	4.4 ±0.2	3.7 ±0.8
Race Day	4.75 ±0.3	4.3 ±0.3	4.0 ±0.1	4.25 ±0.3	4.25 ±0.3
Day +1	4.1 ±0.1	3.9 ±0.1	3.9 ±0.1	3.95 ±0.5	- -
Day +2	4.3 ±0.15	4.4 ±0.4	4.1 ±0.1	4.2 ±0.3	4.3 ±0.3
Day +3	4.3 ±0.2	4.4 ±0.4	5.0** ±0.2	- -	3.9 ±0.5
Day +4	4.2 ±0.1	4.7 0.5	4.7** ±0.3	- -	3.7 ±0.8
Day +5	4.3 ±0.1	4.7 ±0.6	4.0 ±0.1	- -	3.7 ±0.1
Day +6	- -	4.5 ±0.3	4.0 ±0.1	- -	3.7 ±0.1
Day +7	- -	- -	- -	- -	3.8 ±0.2
Day +8	- -	- -	- -	- -	3.4 ±0.4
Day +10	- -	- -	- -	- -	3.6 ±0.1
Day +12	- -	- -	- -	- -	3.7 ±0.1
Day +14	- -	- -	- -	- -	3.8 ±0.2

Data expressed as means ± standard error of the mean
** $p < 0.01$ compared with pre-race values

Table 3.10. MEAN URINE UREA CONCENTRATIONS (MMOL/L) BEFORE, DURING AND AFTER 5 MARATHONS

	1982 42 KM KELLERPRINZ MARATHON	1983 56 KM TWO OCEANS MARATHON	1986 56 KM TWO OCEANS MARATHON	1983 201 MILE RELAY RACE	1984 90KM COMRADES MARATHON
Pre-race	432 ±178	293 ±17.5	299 ±20	237.5 ±17.9	243 ±24
Race Day	430 ±93	208 ±45	230 ±54	96 ±22	203 ±24
Remainder Race Day	528 ±99	305 ±73	416.5* ±69	- -	469** ±94
+1	563 ±77	436* ±62	411* ±45	511.5 ±54.5	461* ±126
+2	366 ±66	308 ±62	293 ±26.5	673 ±11	451* ±100
+3	212.5* ±42.5	309 ±36	251 ±41	- -	396 ±138
+4	208.5** ±46	304 ±92	257 ±42	- -	311 ±76
+5	232* ±35	275 ±51	289 ±48	- -	205 ±33
+6	- -	299 ±34	- -	- -	227.5 ±37
+7	- -	- -	- -	- -	199.5 ±31
+8	- -	- -	- -	- -	216.5 ±45
+10	- -	- -	- -	- -	284.5 ±58
+12	- -	- -	- -	- -	233 ±58
+14	- -	- -	- -	- -	180 ±43

Data expressed as means ± standard error of the mean

* $p = < 0.05$ compared with pre-race values

** $p = < 0.01$ compared with pre-race values

Table 3.11: MEAN URINE CREATININE CONCENTRATIONS (MMOL/L) BEFORE, DURING AND AFTER 5 MARATHONS

	1982 42 KM KELLERPRINZ MARATHON	1983 56 KM TWO OCEANS MARATHON	1986 56 KM TWO OCEANS MARATHON	1983 201 MILE RELAY RACE	1984 90KM COMRADES MARATHON
Pre-race	11.7 ±1.6	12.5 ±10.7	10.6 ±0.8	6.9 ±1.1	8.6 ±0.8
Race	14.5 ±3.5	15.9 ±5.9	13.6 ±3.6	2.45 ±0.4	10.0 ±4.3
Remainder Race day	12.6 ±2.3	16.5 ±2.4	14.2 ±2.7	- -	13.4 ±2.3
+1	14.9 ±2.2	16.6 ±2.3	12.5 ±1.6	11.25 ±0.1	11.65 ±3.0
+2	9.5 ±1.8	11.4 ±2.3	10.35 ±1.0	13.6 ±2.9	12.6 ±2.4
+3	9.9 ±1.2	12.4 ±1.6	9.4 ±1.5	- -	11.55 ±3.0
+4	9.0 ±1.8	10.0 ±2.0	9.5 ±1.6	- -	9.3 ±1.9
+5	8.85 ±1.9	11.2 ±2.3	10.8 ±2.1	- -	7.9 ±1.6
+6	- -	11.8 ±1.6	- -	- -	8.5 ±1.4
+7	- -	- -	- -	- -	7.2 ±1.0
+8	- -	- -	- -	- -	9.6 ±1.6
+10	- -	- -	- -	- -	12.4 ±2.4
+12	- -	- -	- -	- -	9.6 ±1.5
+14	- -	- -	- -	- -	8.4 ±2.3

Data expressed as means ± standard error of the mean

* $p = < 0.05$ compared with pre-race values

* * $p = < 0.01$ compared with pre-race values

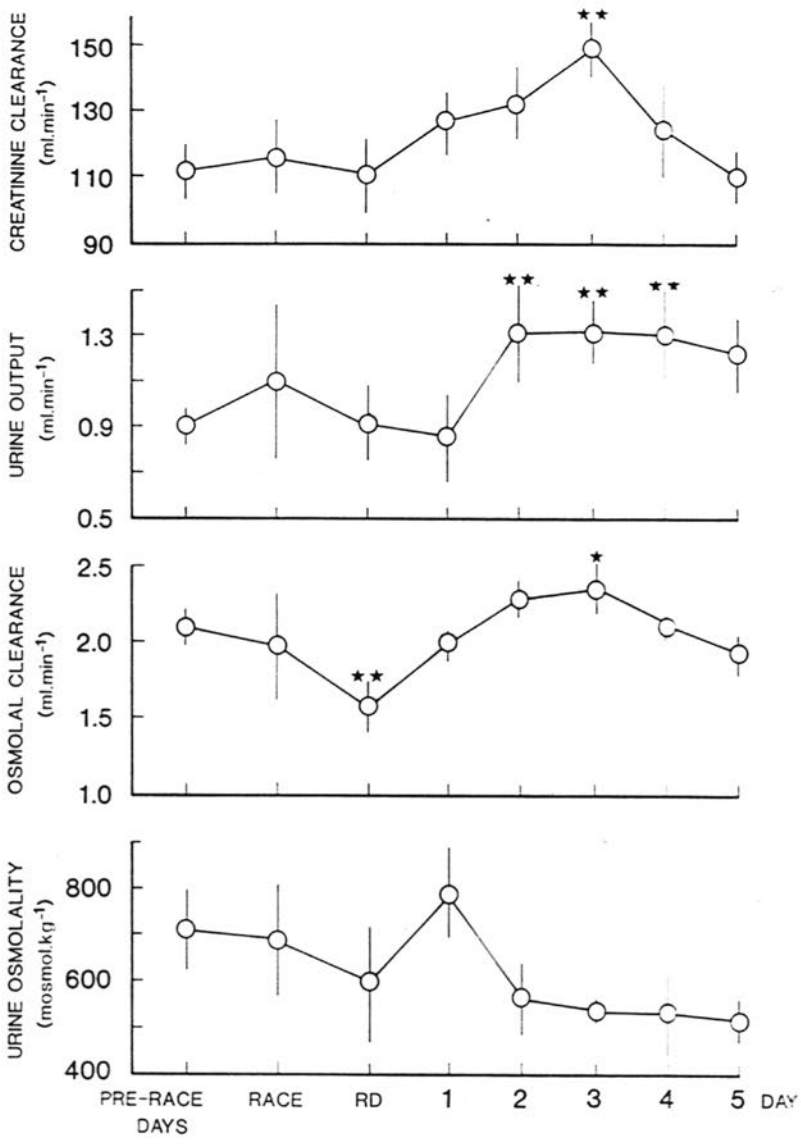

Figure 3.1. Mean (± SEM) changes in creatinine and osmolal clearance, urine output and urine osmolality before, during and after the 1982 42.2 km Kellerprinz Marathon. Race indicates the period of the race while RD indicates the remainder of the day

* p = < 0.05 compared with mean pre-race values

* * p = < 0.01 compared with mean pre-race values

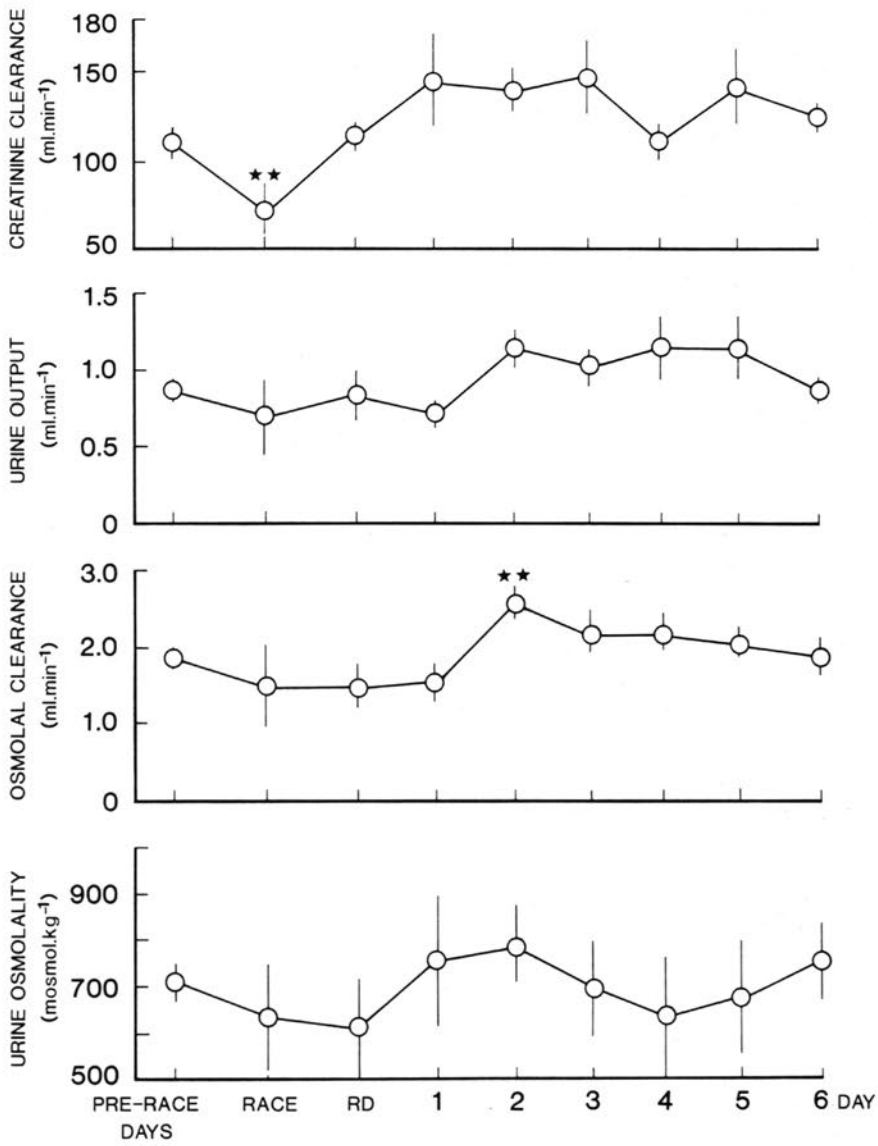

Figure 3.2. Mean (± SEM) changes in creatinine and osmolal clearance, urine output and urine osmolality before, during and after the 1983 56 km Two Oceans Marathon.

* $p = < 0.05$ compared with mean pre-race values

* * $p = < 0.01$ compared with mean pre-race values

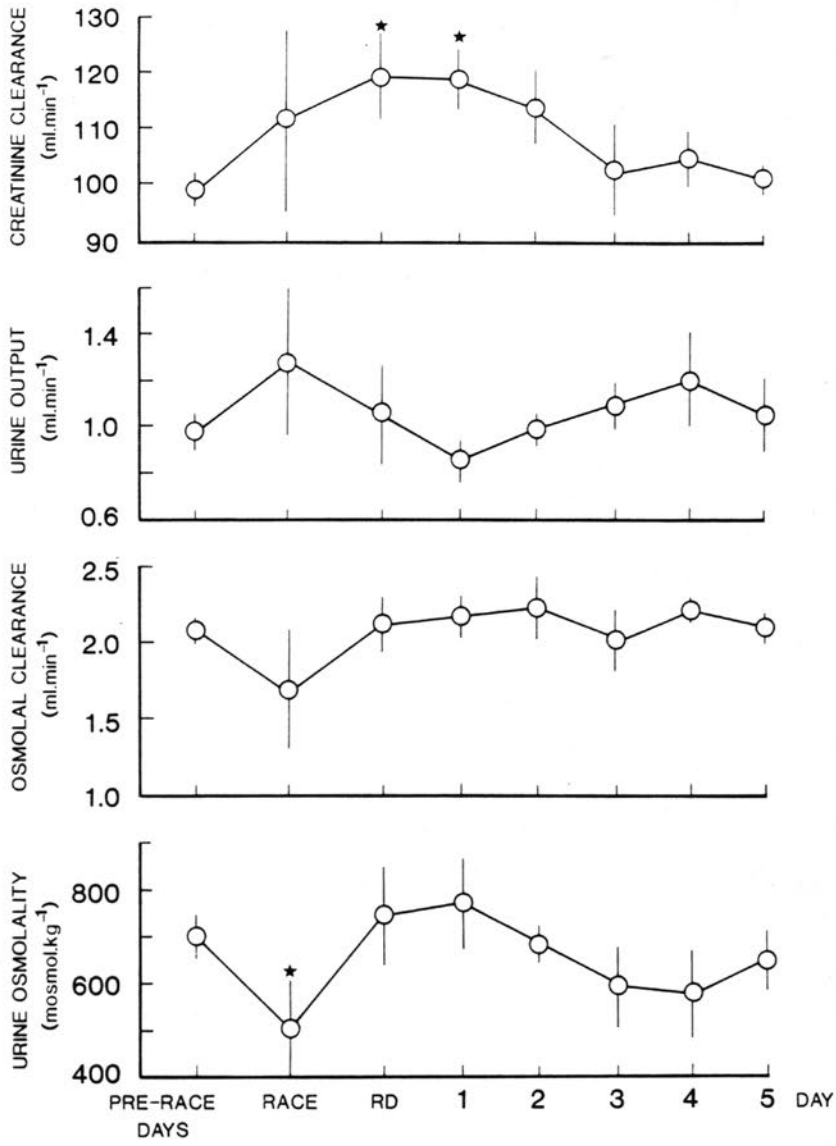

Figure 3.3. Mean (± SEM) changes in creatinine and osmolal clearance, urine output and urine osmolality before, during and after the 1986 56 km Two Oceans Marathon.

* $p = < 0.05$ compared with mean pre-race values

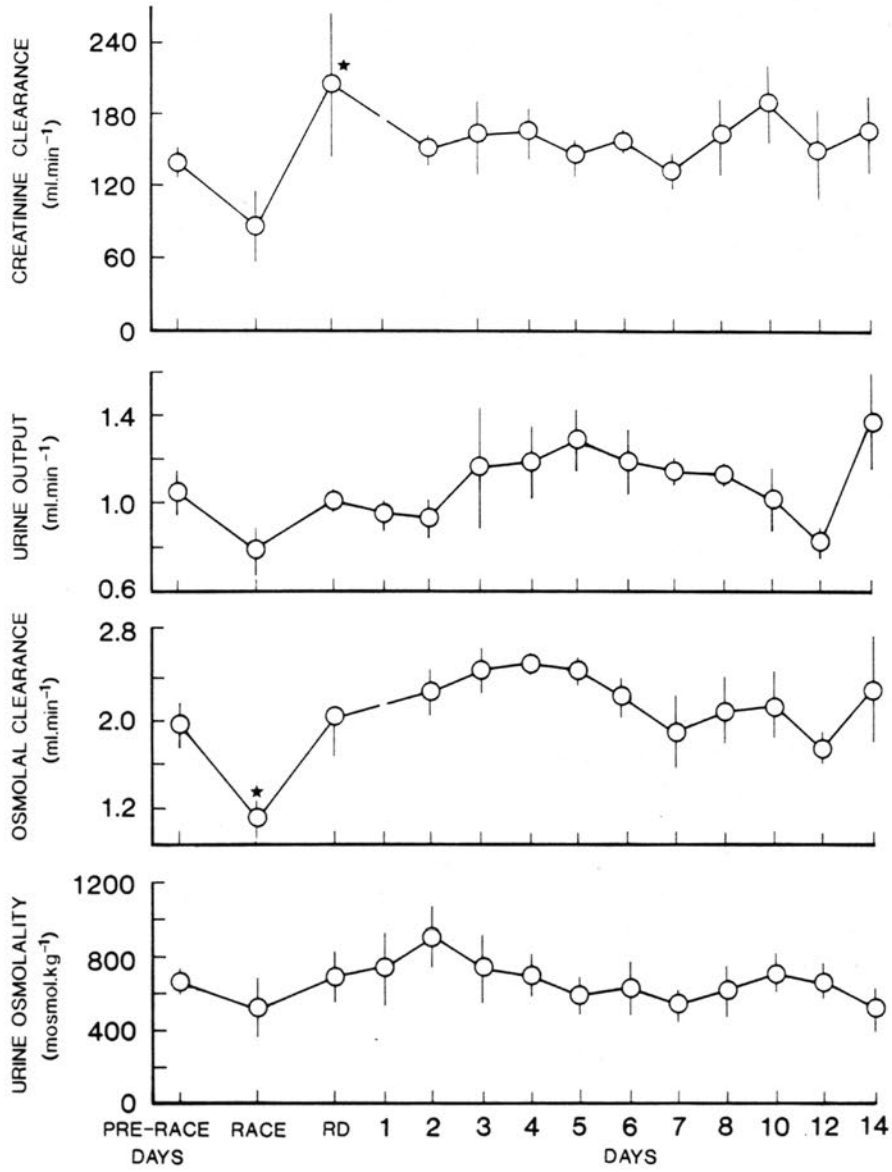

Figure 3.4. Mean (± SEM) changes in creatinine and osmolal clearance, urine output and urine osmolality before, during and after the 1984 90 km Comrades Marathon.

* $p = < 0.05$ compared with mean pre-race values

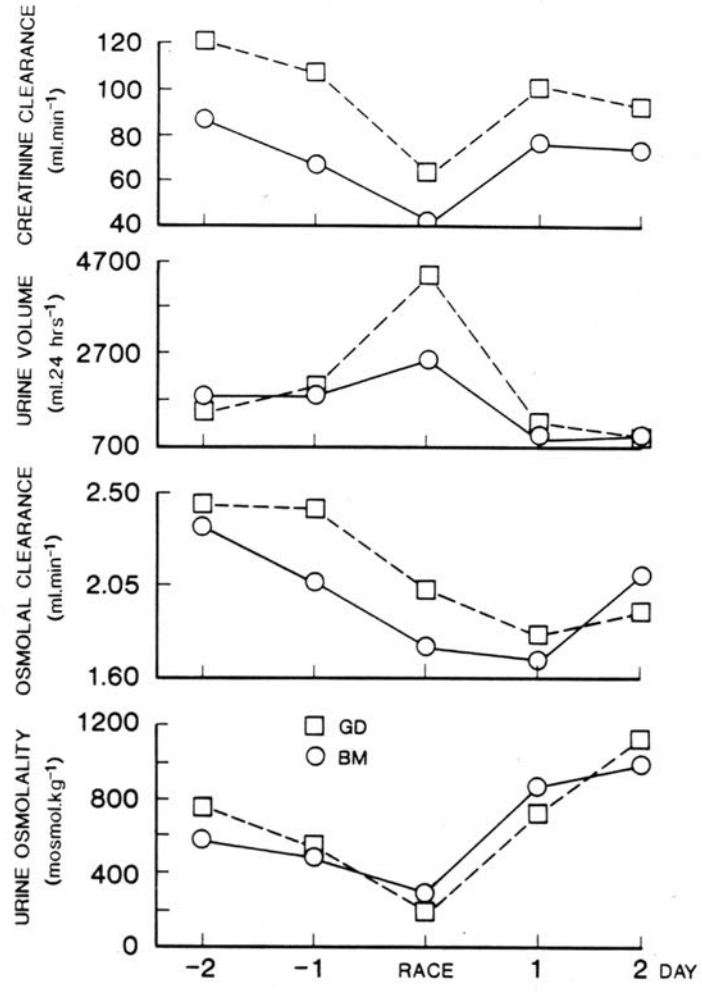

Figure 3.5. Changes in creatinine and osmolal clearance, urine volume and urine osmolality in the two runners who took part in the 1983 210 mile 24 Hours Relay Race.

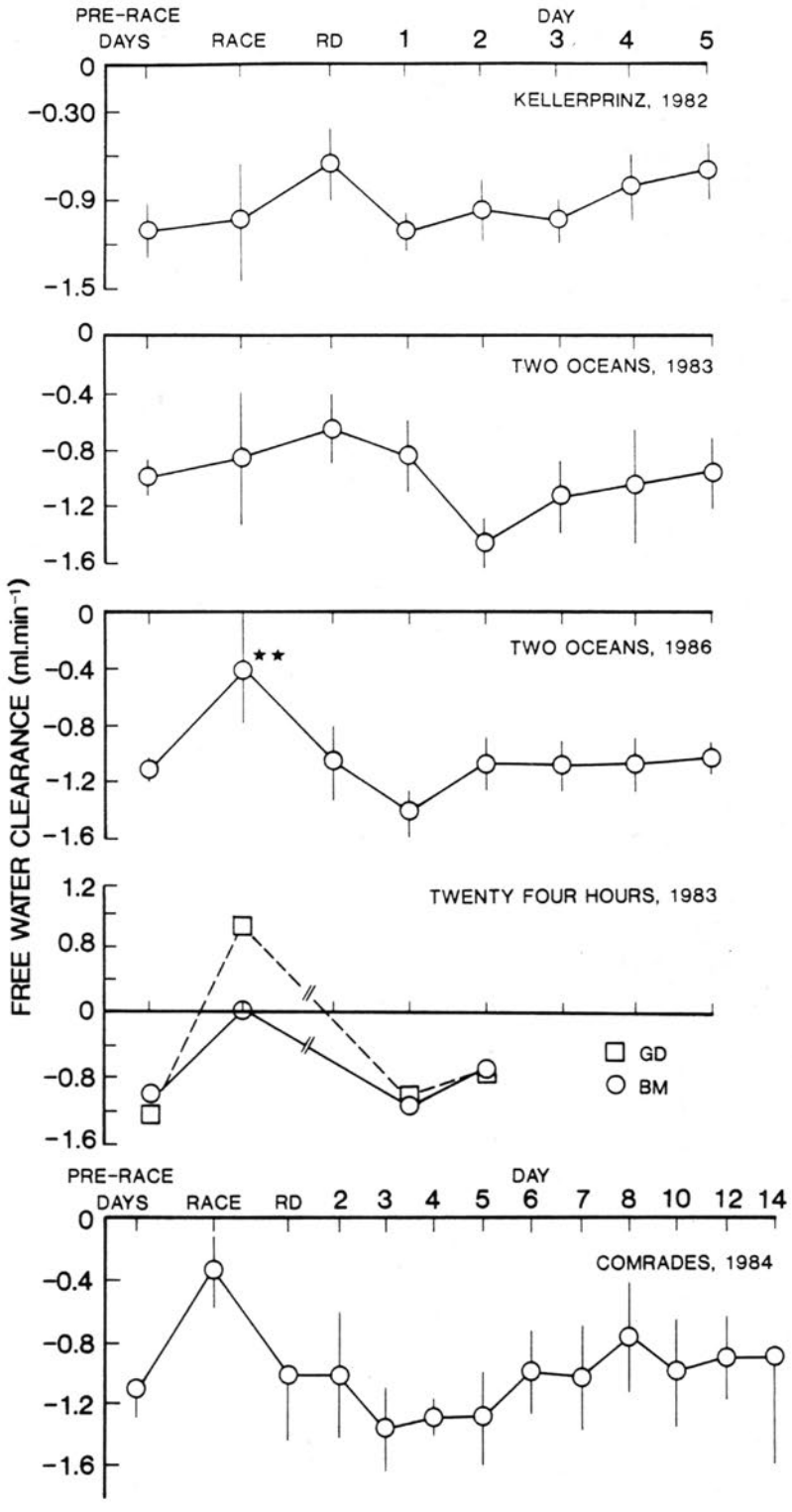

Figure 3.6. Mean (± SEM) negative free water clearance before, during and after the 1982 42.2 km Kellerprinz Marathon, the 1983 and 1986 56 km Two Oceans Marathons and the 1983 201 mile 24 Hours Relay Race and the 1984 90 km Comrades Marathon.

* * p = < 0.01 compared with mean pre-race values

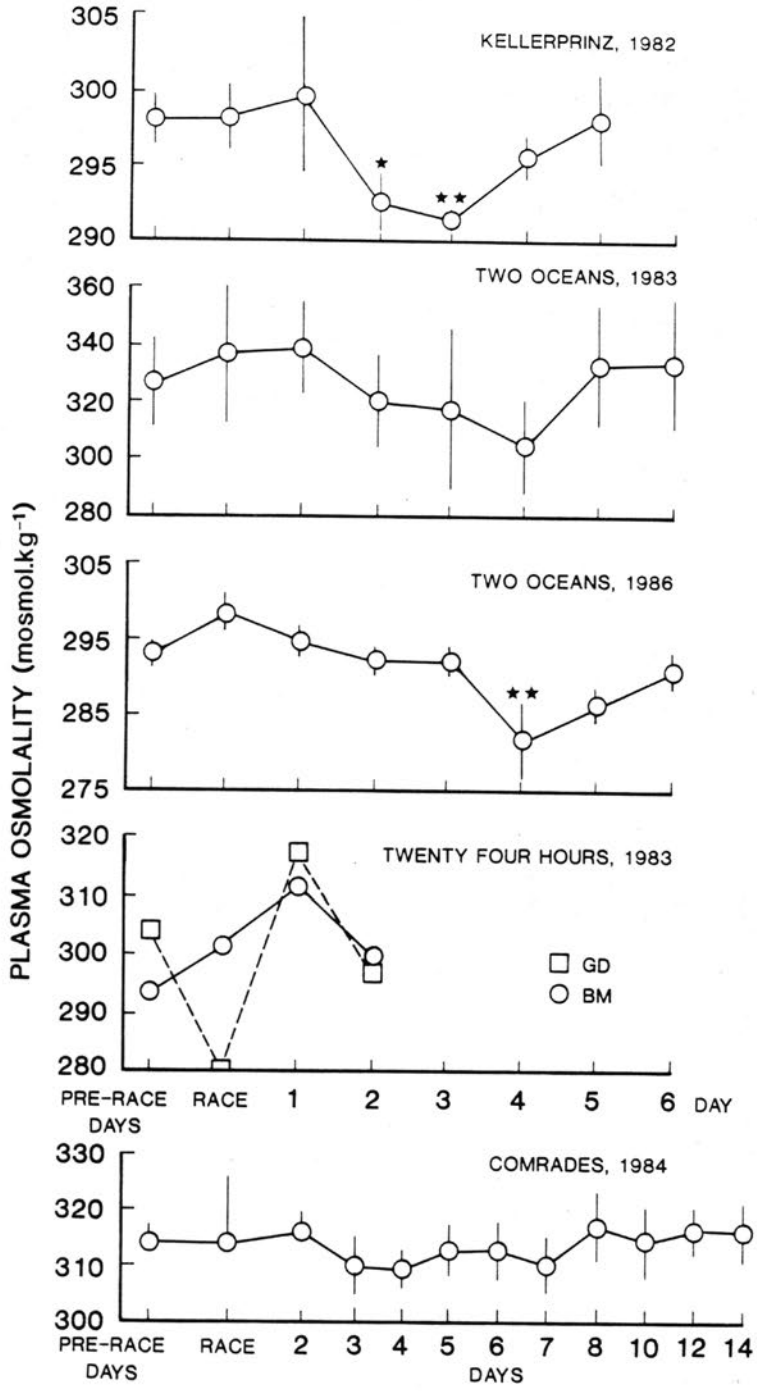

Figure 3.7. Mean (± SEM) plasma osmolality before and after the 1982 42.2 km Kellerprinz Marathon, the 1983 and 1986 56 km Two Oceans Marathons, the 1983 201 mile 24 Hours Relay Race and the 1984 90 km Comrades marathon.

* p = < 0.05 compared with mean pre-race values

* * p = < 0.01 compared with mean pre-race values

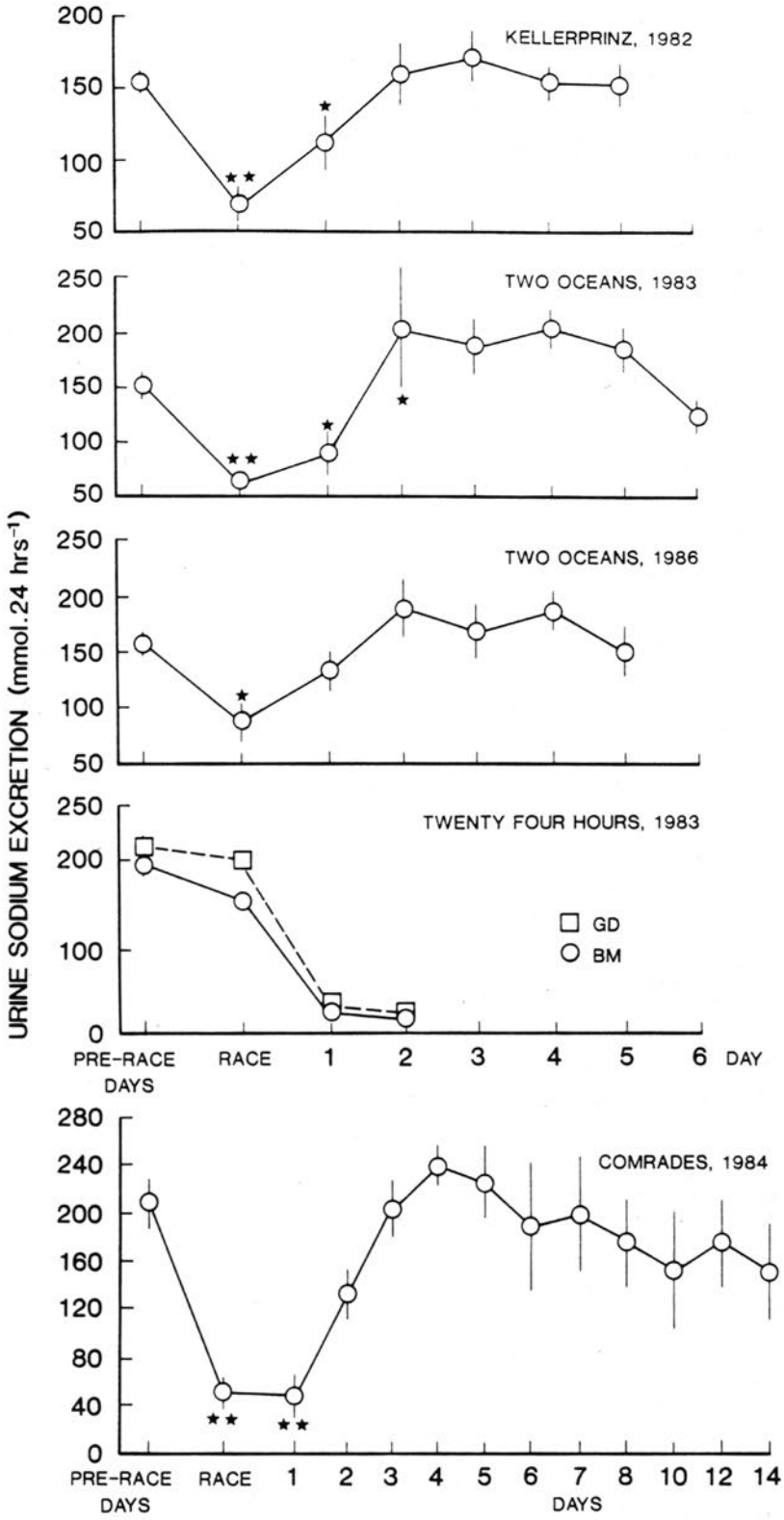

Figure 3.8. Mean (± SEM) twenty-four hours urine sodium excretion before, during and after the 1982 42.2 km Kellerprinz Marathon, the 1983 and 1986 56km Two Oceans Marathons, the 1983 201 mile Relay Race and the 1984 90km Comrades Marathon.

* $p = < 0.05$ compared with mean pre-race values

* * $p = < 0.01$ compared with mean pre-race values

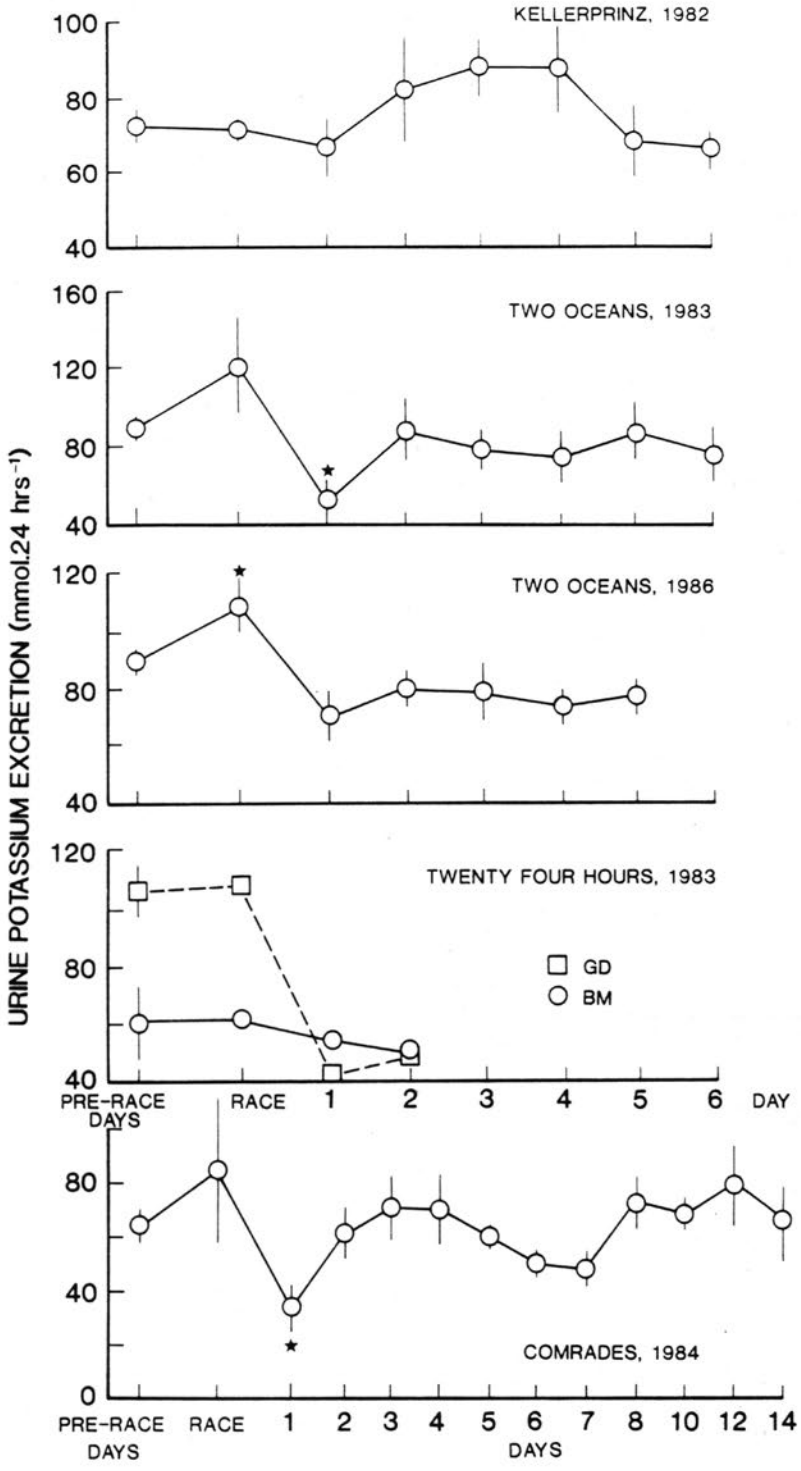

Figure 3.9. Mean (± SEM) 24-hour urine potassium excretion before, during and after the 1982 42.2 km Kellerprinz, the 1983 and 1986 56 km Two Oceans Marathons, the 1983 201 mile 24hrs Relay Race and the 1984 90 km Comrades Marathon.
* $p = < 0.05$ compared with mean pre-race values

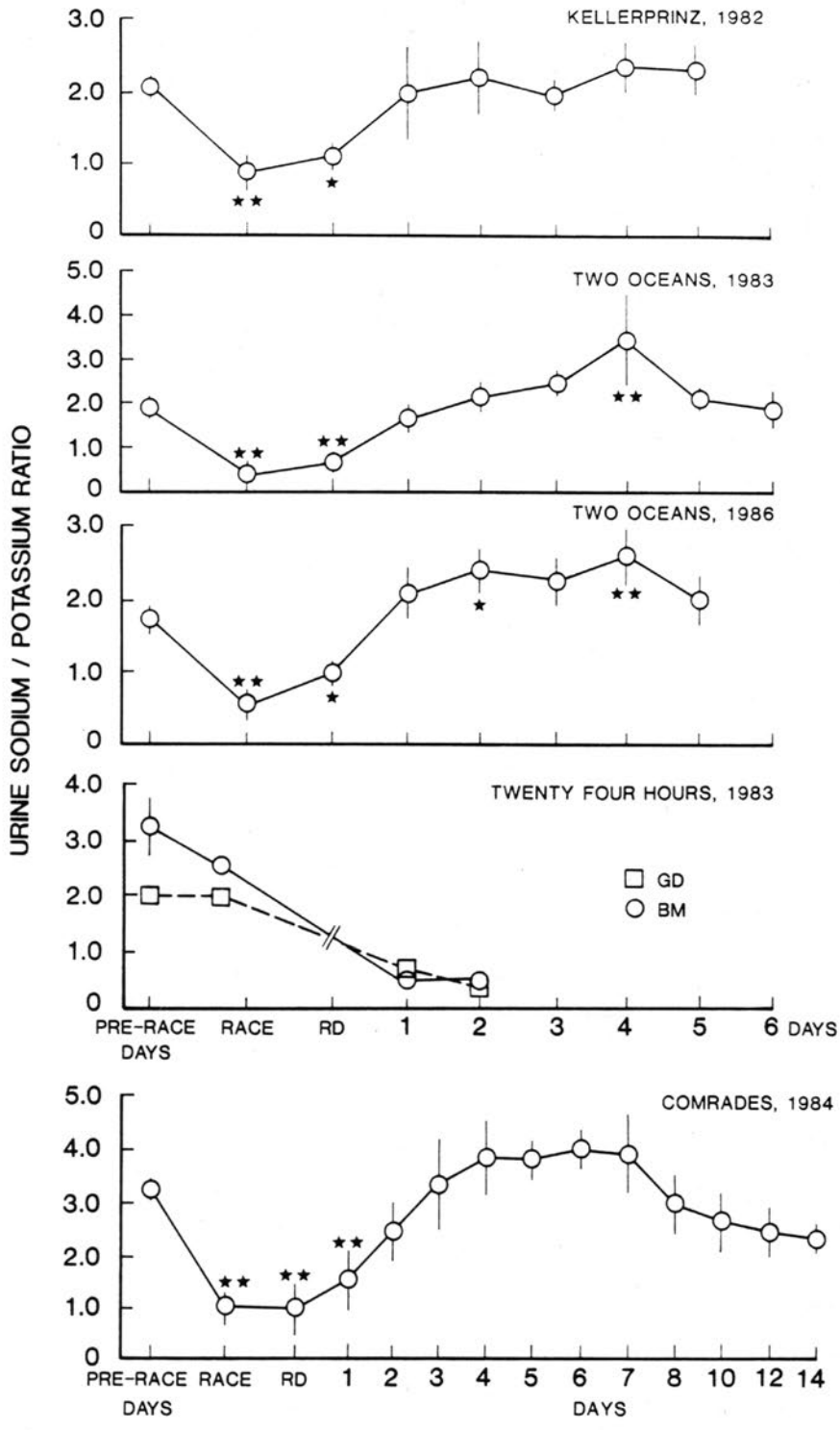

Figure 3.10. Mean (± SEM) urine sodium/potassium ratios after the 1982 42 km Kellerprinz marathon, the 1983 and 1986 56 km Two Oceans marathons, the 1983 24 hrs Relay Race 201 mile relay race and the 1984 90 km Comrades marathon.

* $p = < 0.05$ compared with mean pre-race values

* * $p = < 0.01$ compared with mean pre-race values

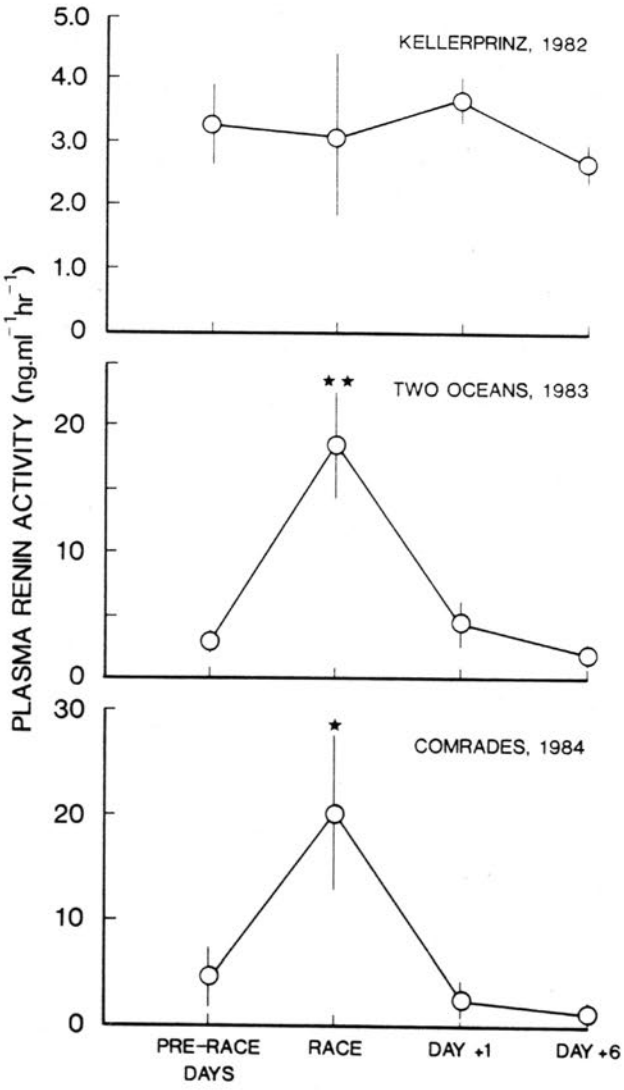

Figure 3.11. Mean (± SEM) plasma renin activity after the 1982 42 km Kellerprinz, the 1983 56 km Two Oceans and the 1984 90 km Comrades marathon races.

* p = < 0.05 compared with mean pre-race values

* * p = < 0.01 compared with mean pre-race values

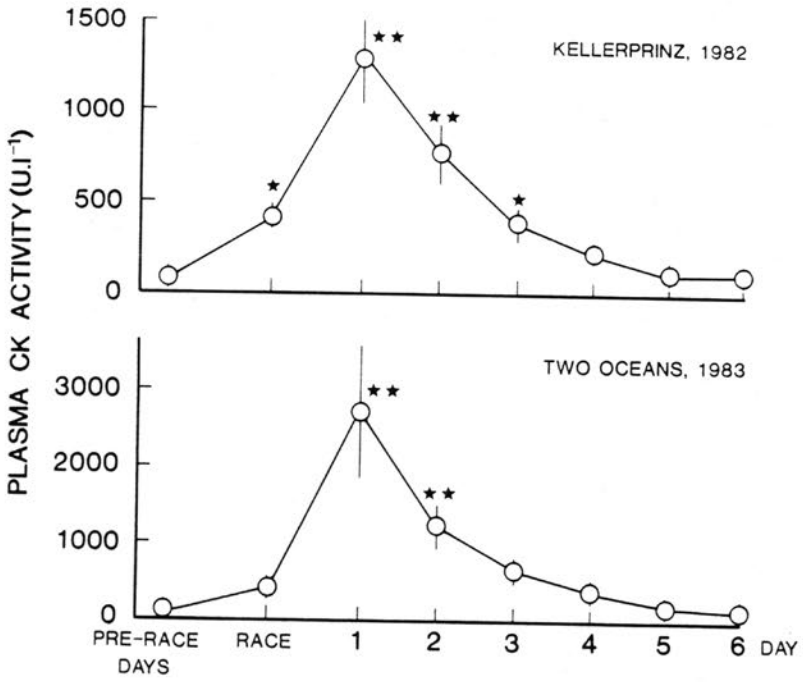

Figure 3.12. Mean (± SEM) daily plasma creatine kinase activity before and after the 1982 42.2 km Kellerprinz and the 1983 56 km Two Oceans Marathons.

* p = < 0.05 compared with mean pre-race values

* * p = < 0.01 compared with mean pre-race values

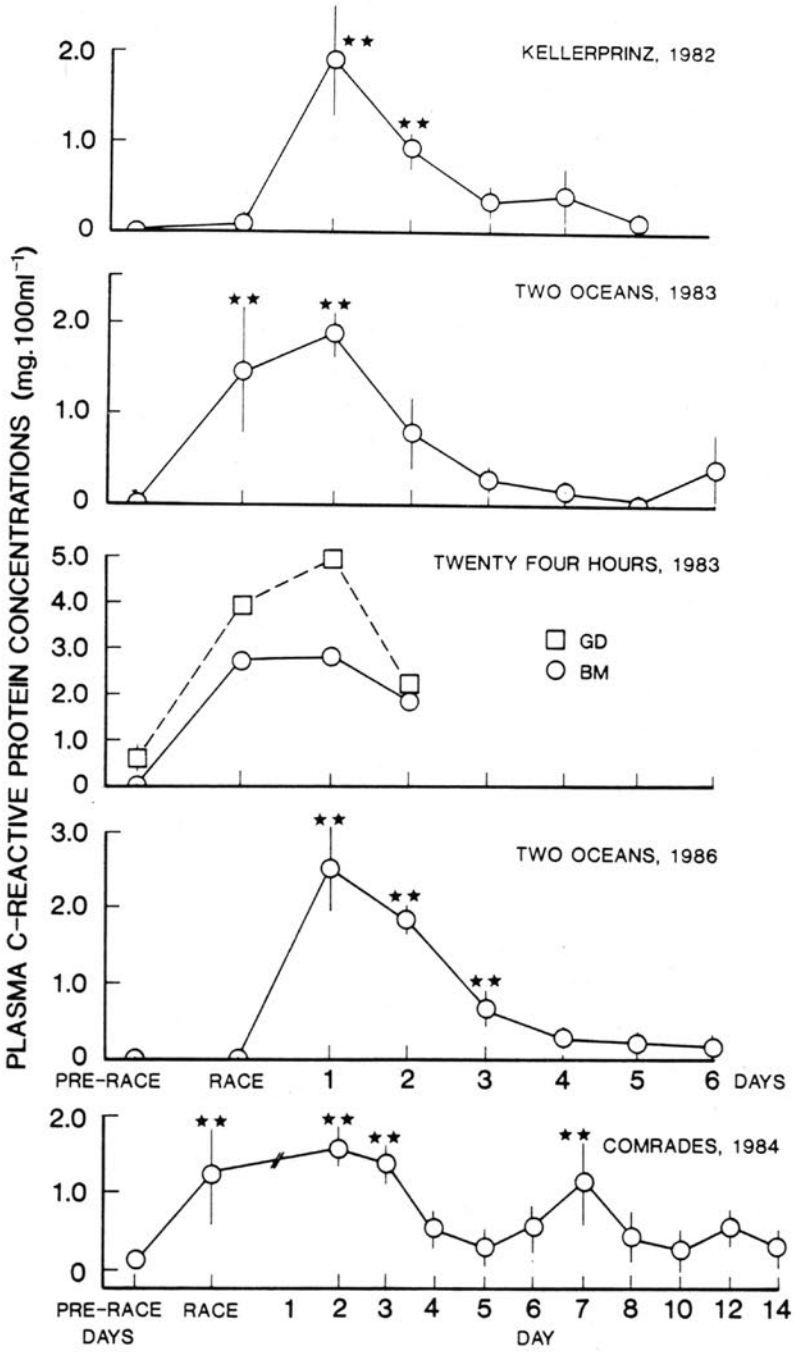

Figure 3.13. Mean (± SEM) daily plasma C-reactive protein concentrations before and after the 1982 42.2 km Kellerprinz, the 1983 and 1986 56 km Two Oceans Marathons, the 1983 201 mile 24 hrs Relay Race and the 1984 90 km Comrades Marathon.

* * p = < 0.01 compared with mean pre-race values

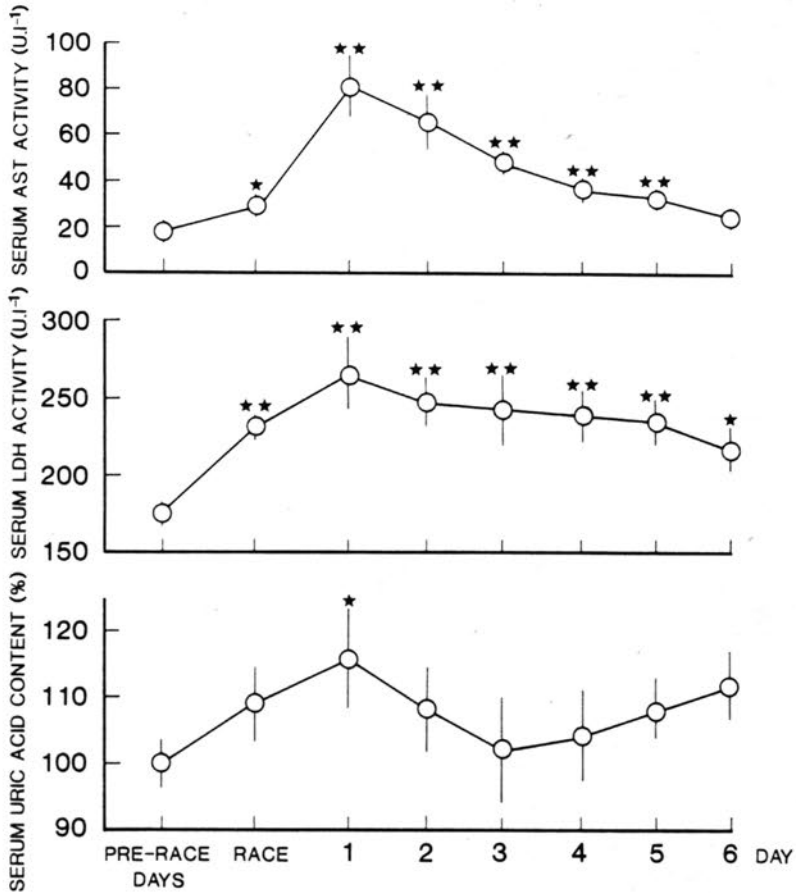

Figure 3.14. Mean (± SEM) daily serum AST and LDH activities and the % changes in the serum uric acid content before and after the 1986 56 km Two Oceans Marathon.

* p = < 0.05 compared with mean pre-race values

* * p = < 0.01 compared with mean pre-race values

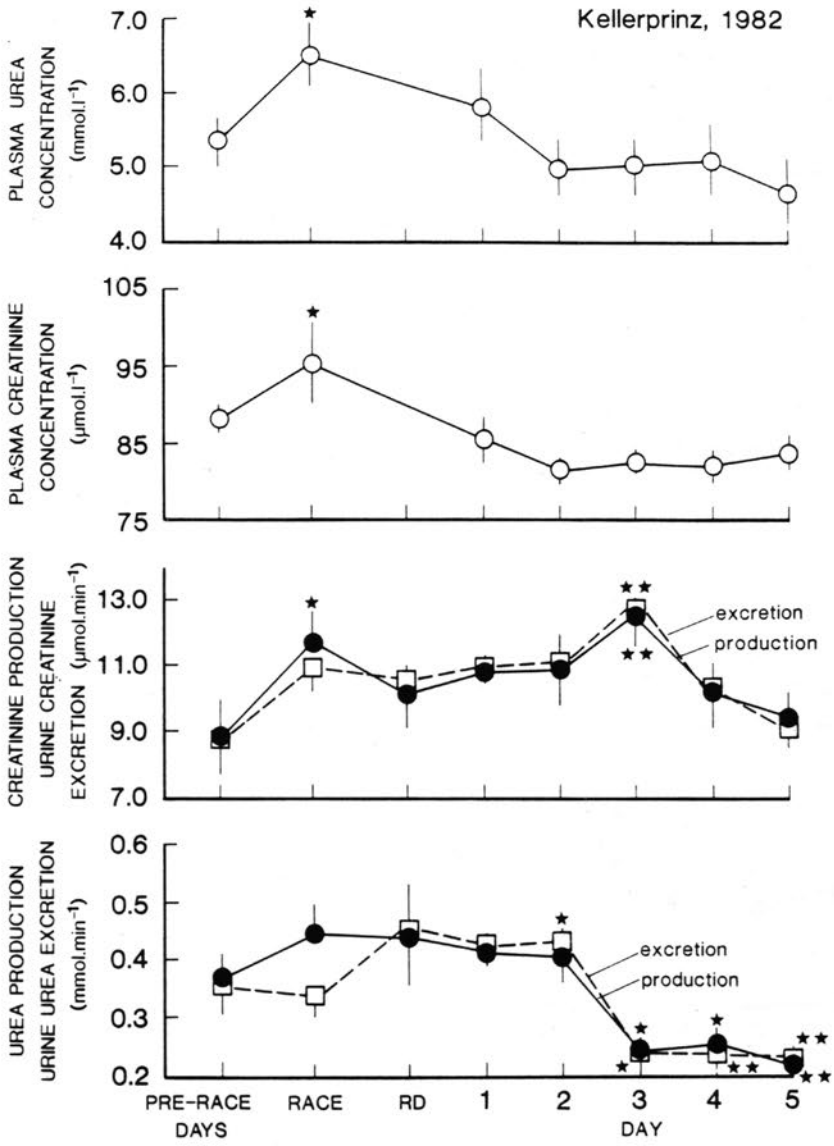

Figure 3.15. Mean (± SEM) daily plasma urea and creatinine concentrations, the urine urea and creatinine excretion rates and the calculated urea and creatinine production rates before and after the 1982 42.2 km Kellerprinz Marathon.

* p = < 0.05 compared with mean pre-race values

* * p = < 0.01 compared with mean pre-race values

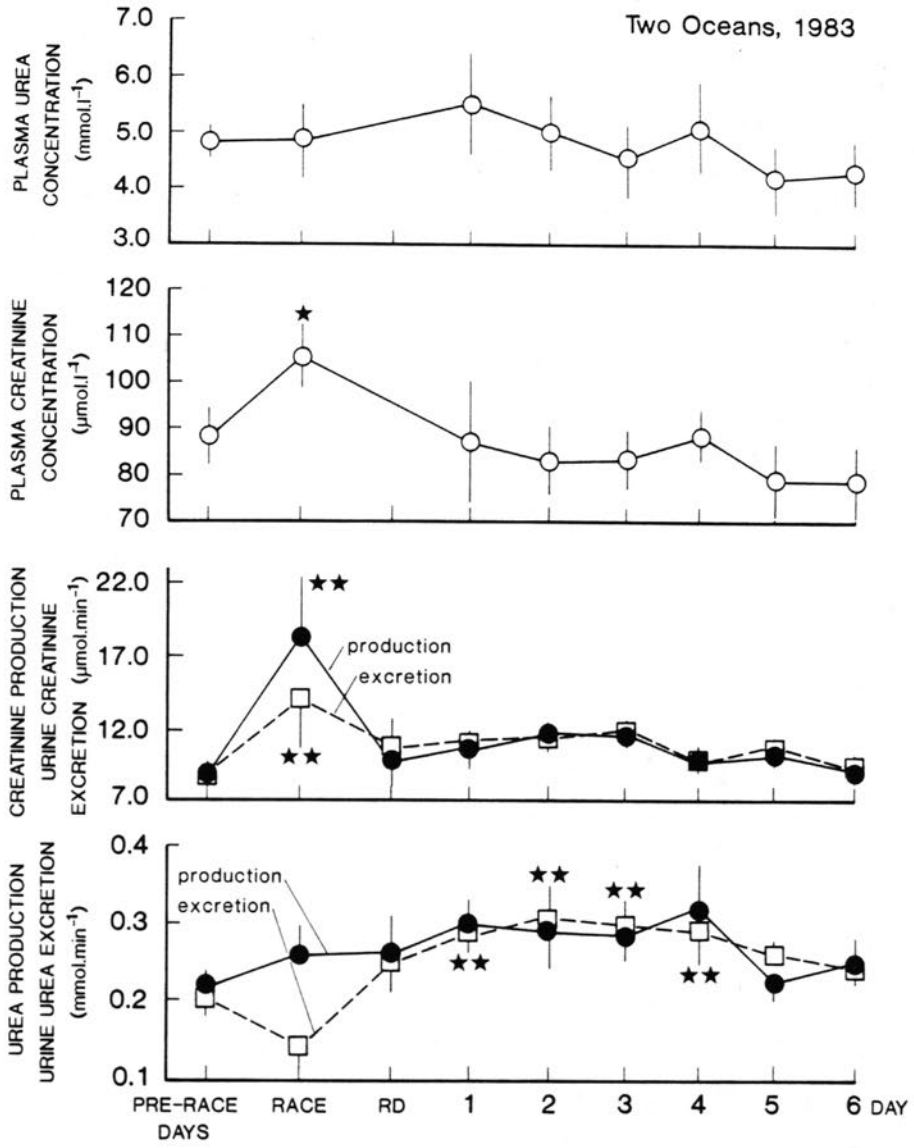

Figure 3.16. Mean (± SEM) daily plasma urea and creatinine concentrations, the urine urea and creatinine excretion rates and the calculated urea and creatinine production rates before and after the 1983 56 km Two Oceans Marathon.

* p = < 0.05 compared with mean pre-race values

* * p = < 0.01 compared with mean pre-race values

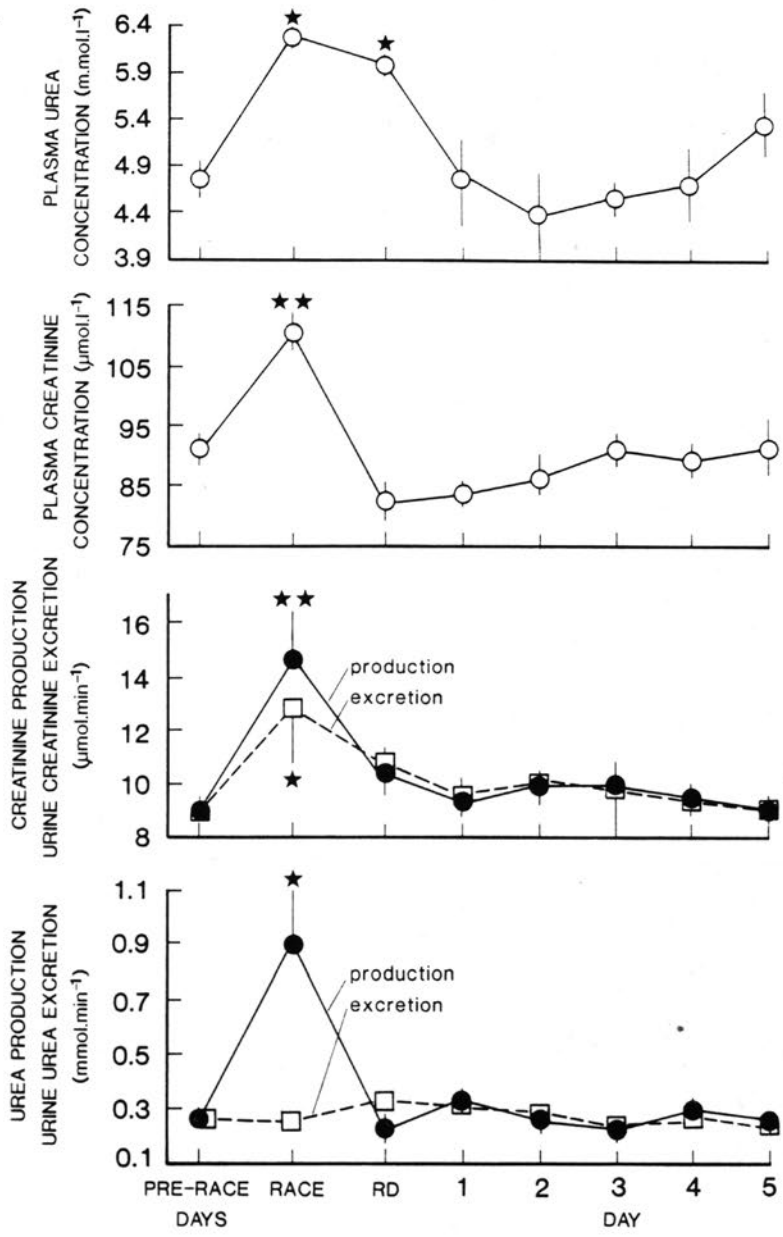

Figure 3.17. Mean (± SEM) daily plasma urea and creatinine concentrations, the urine urea and creatinine excretion rates and the calculated urea and creatinine production rates before and after the 1986 56 km Two Oceans Marathon.

* p = < 0.05 compared with mean pre-race values

* * p = < 0.01 compared with mean pre-race values

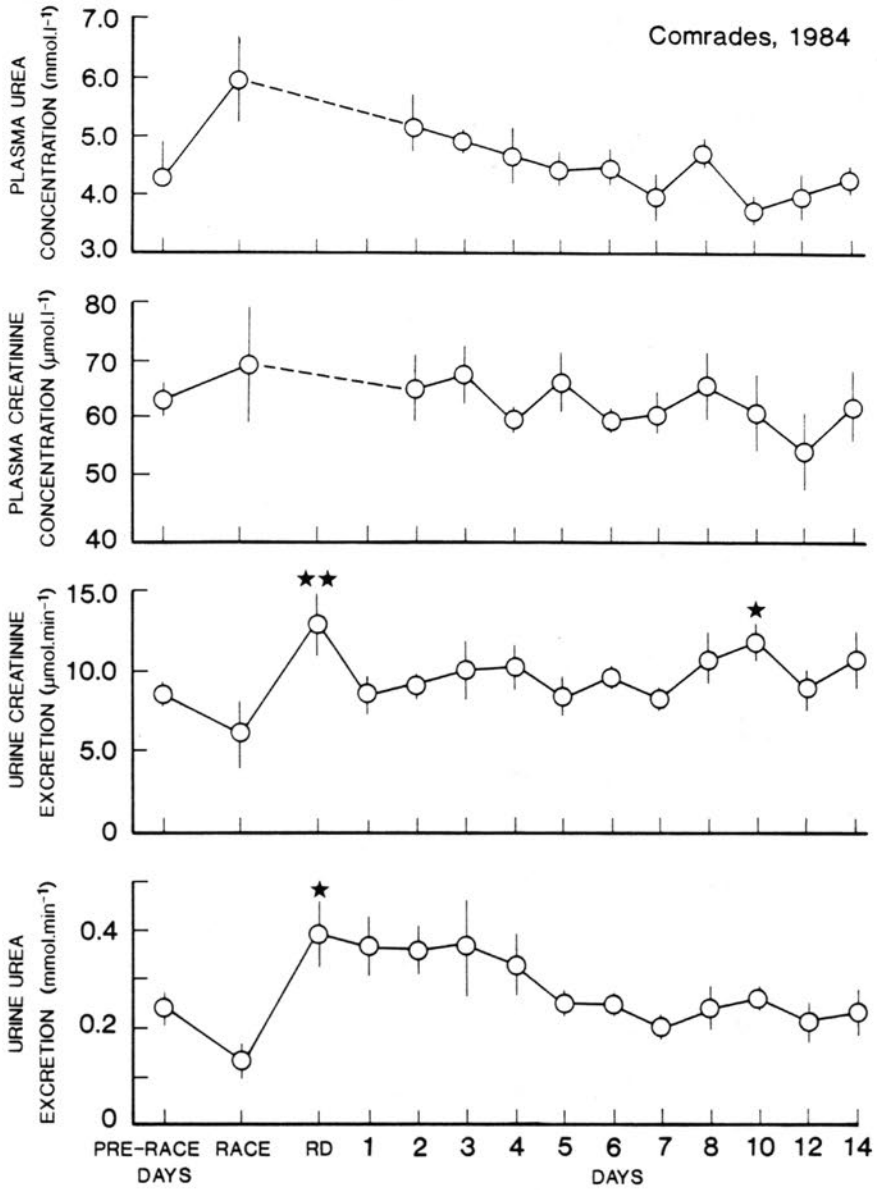

Figure 3.18. Mean (± SEM) daily plasma urea and creatinine concentrations, the urine urea and creatinine excretion rates before and after the 1984 90 km Comrades Marathon.

* p = < 0.05 compared with mean pre-race values

* * p = < 0.01 compared with mean pre-race values

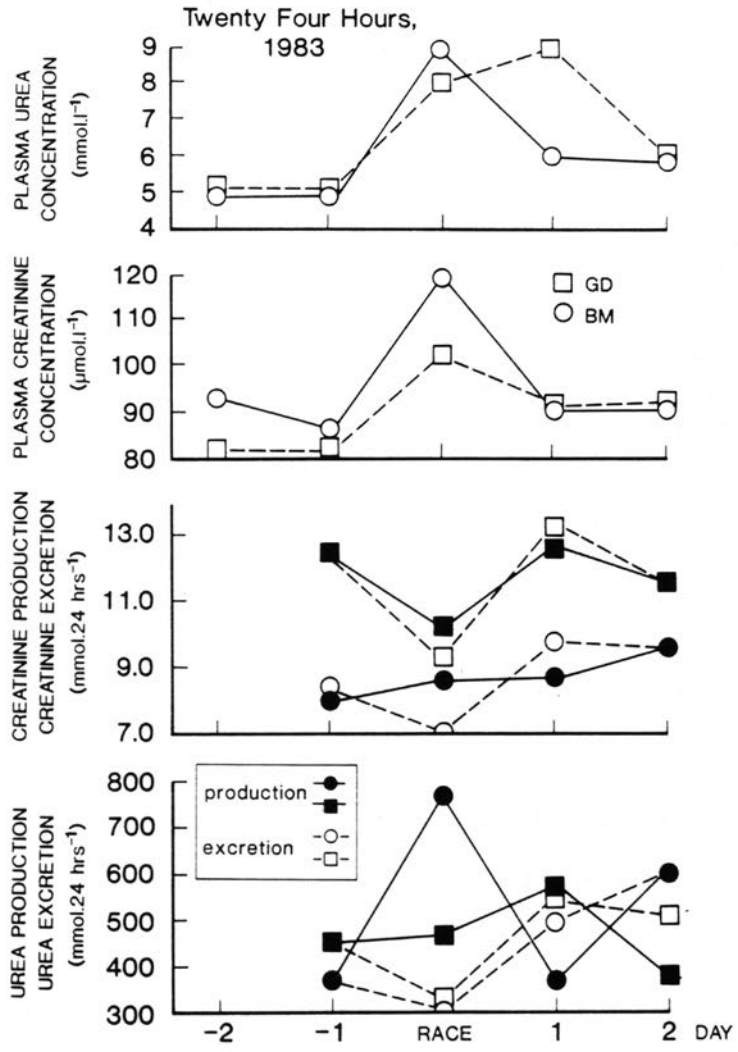

Figure 3.19. Daily plasma urea and creatinine concentrations, 24 hour urine creatinine and urea excretion rates and the 24 hour creatinine and urea production rates for the 2 runners who took part in the 1983 201 mile 24 hrs Relay Race.

3.4. DISCUSSION

3.4.1. RENAL FUNCTION DURING A MARATHON

During most forms of exercise, creatinine and osmolal clearance as well as urine output decrease (Castenfors 1967; Grimby 1965; Kachadorian and Johnson 1970; Poortmans 1984; Refsum and Stromme 1975, 1977). It is generally believed, with incomplete evidence, that marathon running exerts the same effect and that the acute renal failure that is found in marathon runners is due to a reduced renal blood flow, associated with dehydration, heat stroke, rhabdomyolysis and myoglobinuria (Bar-Sela et al 1979; Dancaster et al 1969; Stewart and Posen 1980; Vertel and Knochel 1967).

However these studies show that during marathon races, creatinine and osmolal clearance and urine osmolality are generally well maintained (Figures 3.1.-3.5.). Only during the 1983 56km Two Oceans Marathon (Figure 3.2.) did the creatinine clearance decrease significantly. This was run under warmer conditions than the other marathons (mean temperature 21.9^{o}C. Range during the race 17.3-24.8^{o}C). Neviackas and Bauer (1981) have shown that the creatinine clearance of 3 marathon runners decreased after warm weather marathons (Temperatures 10^{o}C and 27.8^{o}C), but not after one run in cold weather (Temperature -12.2^{o}C). They suggested

that environmental temperature may influence renal function during marathon running.

We also found that creatinine clearance was reduced during the 1983 201 mile Relay which was run under moderate environmental conditions. Possibly the much greater running distance caused the fall in creatinine clearance in that race (Figure 3.5.).

With adequate water intake, urine output in particular remains high (Figure 3.1.-3.5.) and can even increase compared to pre-race levels (as in the 1983 201 mile Relay (Figure 3.5.)). The intravenous infusions given to these 2 runners during the latter part of the race must, however, have influenced this result. However it is of interest to note that even a 100% increase in 24 hour urine output in that race was insufficient to prevent a decrease in creatinine clearance (Figure 3.5.).

Similarly, the transient impairment of the renal concentrating capacity which has been described after long-distance ski-racing (Castenfors et al 1967; Refsum and Stromme 1977) is not a feature of marathon running, at least at distances up to 56 km. Only during the longer races - the 1984 90 km Comrades Marathon and the 1983 201 mile Relay - did the osmolal clearance decrease (Figure 3.4., 3.5.). Only in the 1986 56 km Marathon was urine osmolality and

negative free-water clearance reduced (Figure 3.3., 3.6.). The latter still, however, remained negative (Figure 3.6.)

In spite of a usually maintained urine osmolality, urine sodium excretion was always decreased for at least 24 hours (Figure 3.8.), and sometimes for up to 48 hours after exercise (Figure 3.8.) after exercise. The maintained sodium excretion during the 24 hours of the 1983 201 mile Relay would have been due to the intravenous sodium chloride received by these runners during the race (Selkurt 1976). Although dietary sodium intake was not controlled during any of these studies, it seems unlikely that a reduced sodium intake could explain these findings since none of the subjects knowingly altered their normal dietary patterns during any of these studies. In addition, this finding has been reported previously after other types of exercise (Castenfors et al 1967; Refsum and Stomme 1975). Significant increases in PRA were measured after 2 marathons (Figure 3.11.) which confirms the findings of Nelson et al (1989) and Newmark et al (1976).

Viru and Korge (1971) showed an increase in urine potassium excretion immediately after a standard marathon with no increase found in 2 exhausted runners. In our studies we showed a maintained urine potassium excretion (Figures 3.9.), except in the 1986 56 km Marathon (Figure 3.9.), in which urine potassium excretion increased. There was no

hypokalaemia recorded and none of the runners collapsed or was excessively fatigued at the end of their races. We, therefore, could not confirm the hypothesis of Viru and Korge (1971) which linked a maintained urine potassium excretion and fatigue.

Plasma creatinine concentration increased in all the races as a result of increased rates of production (Figures 3.15.-3.18.). Only during the 1983 201 mile Relay was the increase in plasma creatinine concentration caused by a decrease in urine creatinine excretion (Figure 3.19.).

Plasma urea concentration, which can be an indication of renal function, increased in almost all the races (Figures 3.15., 3.17., 3.19.), in spite of sweat urea losses. Although the latter were not measured, losses through this route can be considerable (Haralambie and Berg 1976; Lemon and Mullin 1980), but were clearly insufficient to prevent the increases in plasma urea concentration. Urine urea excretion did not decrease (Figure 3.15.-3.19.) and the increase in plasma urea concentrations must have been due to increased production. This increased production was, however, only calculated after one race (Figure 3.17.). An increased urea production results from an increased rate of amino acid catabolism (Haralambie and Berg 1976) which does not necessarily involve muscle protein catabolism (Decombaz et al 1979).

3.4.2. RENAL FUNCTION DURING THE POST-RACE PERIOD

Creatinine clearance increased in the post-race recovery period in almost all the races in which observations were continued for several days (Figures 3.1.-3.4.). This cannot be explained by either increased plasma creatinine levels (Figures 3.15.-3.18.) or by increased rates of creatinine production (Figures 3.16.-3.17.) as these did not increase on the same day as the increase in creatinine clearance.

The only exception was after the 1982 42 km Kellerprinz marathon (Figure 3.15.) where there was an increased creatinine production on the same day that an increase in creatinine clearance occurred. As inulin clearance, which is regarded as a good measure of glomerular filtration rate (GFR) (Ganong 1977), and creatinine clearance are comparable after marathon running (Neviackas and Bauer 1981), this finding indicates that there is a consistent increase in GFR during the recovery period after marathon running.

Increased creatinine clearance has been recorded in military trainees exercising in a hot climate (Knochel et al 1974), and it was suggested that this might be due to an adaptive mechanism providing increased resistance to exercise-induced renal damage. The findings from these studies suggest that

this increase in more likely a component of the recovery response after severe exercise.

It has been shown that dietary protein loading (Bosch et al 1983; Brenner et al 1982; Pullman et al 1954; White and Rolfe 1948), amino-acid infusions (Graf et al 1983) and burn damage (Loirat et al 1978) can elicit an acute increase in GFR as measured by increases in both creatinine and inulin clearances. The physiological mechanism for this is unclear (Bosch et al 1983). The dietary protein intake of our runners was neither measured nor controlled in most of the races. However, the self-report of the runners indicated that the dietary intake of protein did not increase greatly during the recovery period. Furthermore it seems unlikely that all the runners after all the races would simultaneously increase their protein intakes sufficiently to produce this uniform effect. In addition for 8 days of the 1986 56 km Two Oceans study the runners were on a low collagen diet and their response was not different. It therefore seems unlikely that an increased dietary protein intake can explain these findings.

Skeletal muscle injury has been recorded after marathon running. This damage has been identified by muscle biopsies (Hikida et al 1983; Warhol et al 1985) and is associated with increases in serum enzyme activities (Kielblock et al 1979; Noakes and Carter 1976, 1982; Siegel et al 1981, 1983)

and increased serum CRP concentrations; the latter have been correlated with increases in plasma CK activity (Strachan et al 1984).

Plasma CK activity was increased (Figure 3.12.) indicating increased membrane permeability. Increases in CRP concentrations (Figure 3.13.), in serum AST and LDH activities (Figure 3.14.) and in the serum uric acid content (Figure 3.14.) are also likely indicators of muscle damage. All these parameters peaked on post-race Day 1. Further indicators of muscle damage were the increase in plasma creatinine concentrations (Figures 3.15.-3.17.), which were caused by increased rates of production (Figures 3.15.-3.17.).

It seems likely that the consistent increase in GFR during the recovery phase after marathon running may be due to protein by-products of skeletal muscle damage. However, as in the case of amino-acid infusions (Graf et al 1983) and dietary protein loading (Bosch et al 1983), the physiologic mechanism for this response is unclear.

During the post-race days there was a tendency for increases in urine output and in osmolal clearance (Figures 3.1.-3.2., 3.4.) as well as in urine sodium excretion (Figures 3.8.). This may result from sodium and water retention as has been shown after several days of hill-walking (Williams et al

1979). The major control for water excretion is ADH, the secretion of which is regulated primarily by changes in plasma osmolality, however small. Goldberg (1981) has shown that a greater than 3% decrease in plasma osmolality can cause a sharp rise in urine flow. After both the 1982 42.2km Kellerprinz Marathon and 1986 56 km Two Oceans Marathon plasma osmolality decreased more than this amount (Figure 3.7.).

The decreases in plasma osmolality (Figure 3.7.) as well as the increases in urine output and osmolal clearance (Figures 3.1., 3.2., 3.4.) and urine sodium excretion (Figure 3.8.) during the post-race days may be indications of body fluid shifts during the recovery period. Plasma volume changes during and after the 1986 56 km Two Oceans Marathon are reported in Chapter 5 while the abnormal body fluid response of athletes who developed the hyponatraemia of exercise is discussed in Chapter 8.

Finally during the recovery period after one race, the 1982 42.2 km Kellerprinz Marathon, there was a sharp decrease in the 24-hour rates of urine urea excretion and calculated rates of urea production (Figure 3.15.) leading to maintained plasma urea concentrations (Figure 3.15.) in spite of the increased creatinine clearance (Figure 3.1.). None of the runners was a vegetarian and none willfully altered their protein intake after the race.

It is possible that the reduction in urea excretion indicated anabolic processes in skeletal muscle with reduced protein de-amination to repair the muscle damage shown by the elevated serum creatine kinase activity (Figure 3.12.) and C-reactive protein concentrations (Figure 3.13.). However this was not a consistent finding and was noted only after this specific race.

CHAPTER IV

THE INFLUENCE OF LONG-DISTANCE RUNNING ON URINARY PROTEIN EXCRETION

4.1. INTRODUCTION

The presence of protein in the urine can indicate renal disease (Peterson et al 1969) which depending on the molecular weight of the proteins present in urine, can be differentiated into a glomerular or tubular type (Butler and Flynn 1958; Creeth et al 1963; Flynn and Platt 1960; Peterson et al 1969).

It has long been recognized that exercise can also induce proteinuria (Collier 1907). This proteinuria was originally though to be caused by physical trauma (Amelar and Solomon 1954). The finding that proteinuria can also occur in non-traumatic sports, however, disproved this hypothesis (Alyea et al 1958). Furthermore, runners were shown to excrete more protein than cyclists, swimmers and rowers (Poortmans et al 1982). Plasma proteins were shown to comprise 57% of the urine proteins, but this percentage increased to 82% after a standard marathon (Poortmans and Jeanloz 1968). The major fraction of this increase comprises albumin (Nedbal and Seligar 1958; Poortmans and von Kerchove 1962).

None of these changes are of a pathological nature and the term "athletic pseudonephritis" has been coined to indicate that this is believed to be a benign, transient and reversible condition (Gardener 1956).

Unfortunately the renal changes associated with marathon running are not always benign and the increased proteinuria can be associated with acute renal failure (Dancaster et al 1969; MacSearraigh et al 1979; Stewart and Posen 1980). It is, therefore, important that more is known of the usual changes in the proteinuria induced by marathon running.

A glomerular proteinuria with no evidence of changes in renal tubular function has previously been shown after marathon running (Poortmans and Haralambie 1979; Poortmans and Jeanloz 1968). Although Poortmans and Haralambie (1979) studied urine samples from the marathon runners in the post-race day, sequential studies during the prolonged recovery phase after marathon running have, to our knowledge, not yet been reported. In addition, short-term exercise has been shown to cause transient impairment of both tubular and glomerular function (Poortmans and Vancalk 1978; Poortmans et al 1988). As renal biopsies from runners with acute renal failure have shown tubular necrosis (MacSearraigh et al 1979), it is important to establish whether reversible impairment of tubular function can also be caused by marathon running.

It was therefore decided to study changes in plasma and urine $beta_2$-microglobulin, and urine total protein concentrations in runners during and for several days after the 5 different marathon footraces described in the previous chapter. $Beta_2$-microglobulin is a low molecular weight protein (molecular weight 11 800) which is excreted in increased amounts in cases of tubular proteinuria (Peterson et al 1969; Poortmans and Vancalk 1978). The 5 races studied were the 1982 42.2 km Kellerprinz marathon, the 1983 and 1986 56 km Two Oceans marathons, the 1984 90km Comrades Marathon and the 1983 201 mile relay race.

4.2. METHODS AND MATERIALS

4.2.1. SUBJECTS

The subjects were the same athletes who took part in the studies described in Chapter 3. The details are recorded in Tables 3.1.-3.5. The protocols for the 5 races are described in Chapter 3 while the methods for determination of plasma and urine $beta_2$-microglobulin concentrations and urine total protein concentrations are described in Chapter 2. Renal $beta_2$-microglobulin clearance was calculated as in Chapter 2.

$Beta_2$-microglobulin is denatured by a pH below 7.0. No preservative medium was added to the urine prior to storage by freezing and the pH was not measured. It is, therefore, possible that the determination of urine $beta_2$-microglobulin concentration may have been underestimated in some of these urine samples.

4.3. **RESULTS**

4.3.1. PLASMA BETA$_2$-MICROGLOBULIN CONCENTRATION

During only one race, the 1983 201 mile 24 hour Relay Race, did plasma beta-microglobulin concentrations increase (Figure 4.4.). However, beta$_2$-microglobulin concentrations increased on the third day of recovery after both the 1982 42.2 km marathon (Figure 4.1.) and the 1983 56 km marathon (Figure 4.2.). There was no change from pre-race values after the 1984 90 km marathon (Figure 4.5.). Plasma beta$_2$-microglobulin concentrations were not measured after the 1986 56 km marathon.

4.3.2. URINE BETA$_2$-MICROGLOBULIN EXCRETION

There were increases in the urine beta$_2$-microglobulin excretion rates during the 1983 and 1986 56 km marathons (Figure 4.2. and 4.3.) as well as during the 1983 201 mile Relay Race (Figure 4.4.). The excretion rate also increased on Day 1 after the 1983 56 km marathon (Figure 4.2.) and on Day 7 after the 1984 90 km marathon (Figure 4.5.). The increase in urine beta$_2$-microglobulin excretion rate during the 1982 42.2 km marathon (Figure 4.1.) was not significant.

Urine $beta_2$-microglobulin concentrations are given in Tables 4.1.-4.5. They were increased over pre-race values only on Day 1 after the 1983 56 km Two Oceans Marathon (Table 4.2.) and during the 1986 56km Two Oceans Marathon (Table 4.3.).

4.3.3. RENAL $BETA_2$-MICROGLOBULIN CLEARANCE

Only during the race, and on Day 1 only after the 1983 56 km marathon did the renal $beta_2$-microglobulin clearance rate increase significantly (Figure 4.2.). The increases during the 42.2 km marathon (Figure 4.1.) and on Day 7 after the 1984 90 km marathon (Figure 4.5.) were not significant although in the latter case, the increase was 1.8 fold over pre-race values.

4.3.4. URINE TOTAL PROTEIN EXCRETION

Although the urine total protein excretion rate did not increase during either the 1982 42.2 km marathon (Figure 4.1.), the 1983 56 km marathon (Figure 4.2.), or the 1984 90 km marathon (Figure 4.5.), protein excretion rates did increase during the 1986 56 km marathon (Figure 4.3.) and the 1983 201 mile Relay Race (Figure 4.4.). Protein excretion rates were also increased on Day 1 after the 1982 42.2 km marathon (Figure 4.1.) and on Day 4 after the 1984 90 km marathon (Figure 4.5.).

There was a decrease in the urine protein excretion rates of both runners on Days 1 and 2 after the 1983 201 mile Relay Race (Figure 4.4.) as well as a significant decrease on days 4 and 5 after the 1982 42.2 km marathon (Figure 4.1.).

Urine total protein concentrations are given on Tables 4.1.-4.5. There was an increase over pre-race values only on Day 1 after two races, the 1982 42.2 km Kellerprinz and the 1983 56 km Two Oceans Marathons.

Table 4.1. URINE TOTAL PROTEIN AND BETA$_2$-MICROGLOBULIN CONCENTRATIONS BEFORE, DURING AND AFTER THE 1982 42.2KM KELLERPRINZ MARATHON

	Urine Total Protein Concentration (g/L)	Urine beta$_2$-microglobulin Concentration (μg/L)
Pre-race	0.12 ±0.02	708.7 ±169.8
During Race	0.13 ±0.03	996 ±307
Remainder Race Day	0.13 ±0.03	648 ±200
Day +1	0.27* ±0.11	461 ±210
Day +2	0.08 ±0.02	588 ±203
Day +3	0.07 ±0.02	408 ±119
Day +4	0.03 ±0.01	462 ±109
Day +5	0.03 ±0.01	837 ±194

Data expressed as means ± standard error of the mean

* $p = < 0.05$ compared with pre-race values

Table 4.2. URINE TOTAL PROTEIN AND BETA$_2$-MICROGLOBULIN CONCENTRATIONS BEFORE, DURING AND AFTER THE 1983 56KM TWO OCEANS MARATHON

	Urine Total Protein Concentration (g/L)	Urine beta$_2$-microglobulin Concentration (μg/L)
Pre-race	0.16 ±0.03	523 ±86.4
During Race	0.19 ±0.07	3687 ±1424
Remainder Race Day	0.35 ±0.2	4087 ±2992
Day +1	0.52* ±0.31	6657** ±6269
Day +2	0.15 ±0.24	1755 ±991
Day +3	0.14 ±0.05	1089 ±857
Day +4	0.14 ±0.06	450 ±139
Day +5	0.11 ±0.04	533 ±177
Day +6	0.17 ±0.03	1550 ±776

Data expressed as means ± standard error of the mean

* $p = < 0.05$ compared with pre-race values

** $p = < 0.01$ compared with pre-race values

Table 4.3. URINE TOTAL PROTEIN AND BETA$_2$-MICROGLOBULIN CONCENTRATIONS BEFORE, DURING AND AFTER THE 1986 56KM TWO OCEANS MARATHON

	Urine Total Protein Concentration (g/L)	Urine beta$_2$-microglobulin Concentration (mg/L)
Pre-race	0.19 ±0.02	< 0.1 -
During Race	0.19 ±0.03	0.44* ±0.3
Remainder Race Day	0.16 ±0.03	0.11 ±0.01
Day +1	0.22 ±0.07	0.1 ±0.001
Day +2	0.21 ±0.04	< 0.1 -
Day +3	0.19 ±0.04	< 0.1 -
Day +4	0.16 ±0.03	< 0.1 -
Day +5	0.15 ±0.02	< 0.1 -
Day +6	- -	< 0.1 -

Data expressed as means ± standard error of the mean

* p = < 0.05 compared with pre-race values

Table 4.4. URINE TOTAL PROTEIN AND BETA$_2$-MICROGLOBULIN CONCENTRATIONS BEFORE, DURING AND AFTER THE 1983 201 MILE RELAY RACE

	Urine Total Protein Concentration (g/L)		Urine beta$_2$-microglobulin Concentration (μg/L)	
	Runner BM	Runner GD	Runner BM	Runner GD
Day -2	0.10	0.08	1775	976
Day -1	0.06	0.10	946	2013
Race	0.10	0.06	2934	1714
Day +1	0.08	0.08	1403	580
Day +2	0.06	0.10	854	921

Table 4.5. URINE TOTAL PROTEIN AND BETA$_2$-MICROGLOBULIN CONCENTRATIONS BEFORE, DURING AND AFTER THE 1984 90 KM COMRADES MARATHON

	Urine Total Protein Concentration (g/L)	Urine beta$_2$-microglobulin Concentration (μg/L)
Pre-race	0.17 ±0.06	450 ±60
During Race	0.61 ±0.33	485 ±80
Remainder Race Day	0.17 ±0.05	725 ±260
Day +1	0.14 ±0.05	530 ±80
Day +2	0.23 ±0.1	720 ±110
Day +3	0.17 ±0.08	605 ±150
Day +4	0.43 ±0.23	440 ±80
Day +5	0.24 ±0.11	370 ±90
Day +6	0.19 ±0.14	510 ±150
Day +7	0.17 ±0.14	775 ±270
Day +8	0.26 ±0.14	745 ±270
Day +10	0.18 ±0.07	460 ±50
Day +12	0.09 ±0.07	730 ±410
Day +14	0.13 ±0.09	335 ±70

Data expressed as means ± standard error of the mean

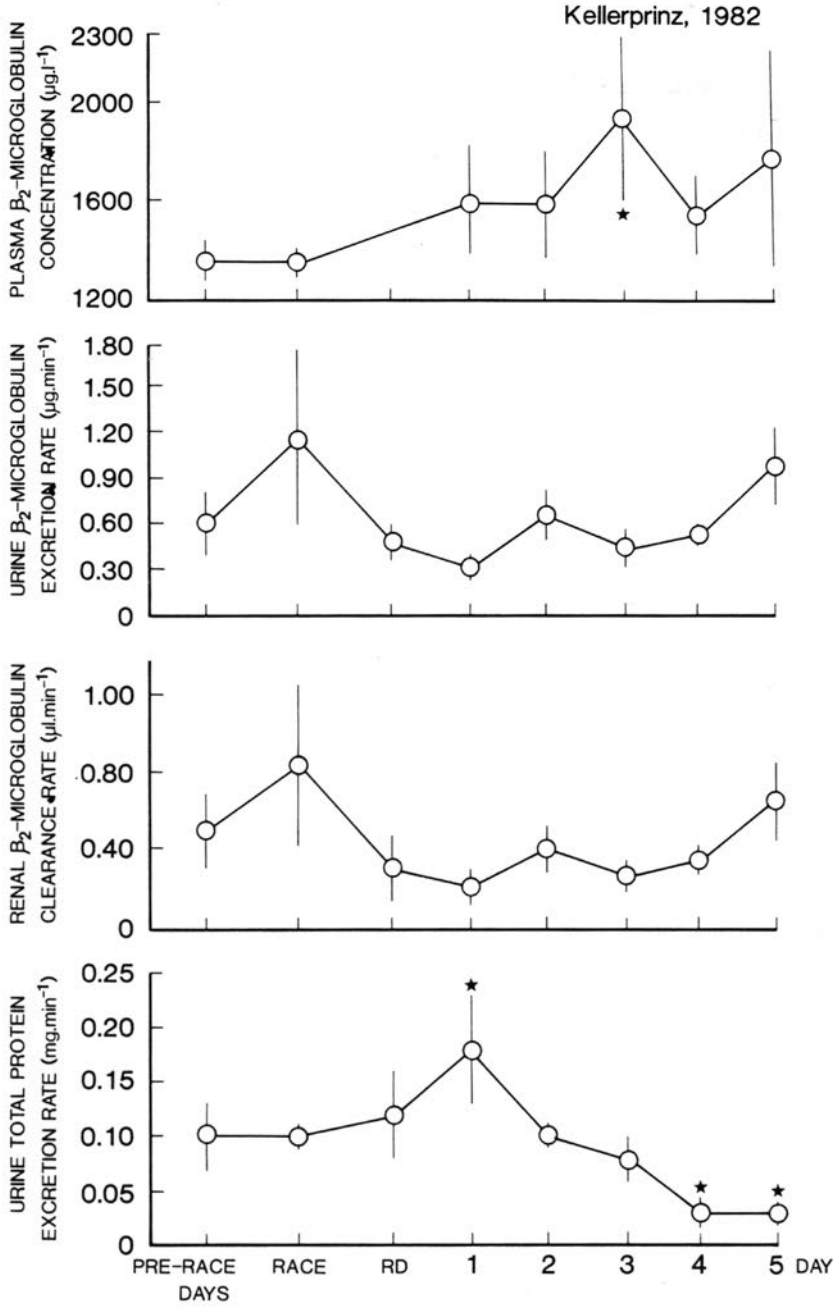

Figure 4.1. Mean (± SEM) plasma beta$_2$-microglobulin concentration, urine beta$_2$-microglobulin and total protein excretion rates and the renal beta$_2$-microglobulin clearance rates for 6 runners before, during and after the Kellerprinz 1982 42 km marathon. Race is the race period and RD is the remainder of the day.

* $p = < 0.05$ compared with the pre-race mean

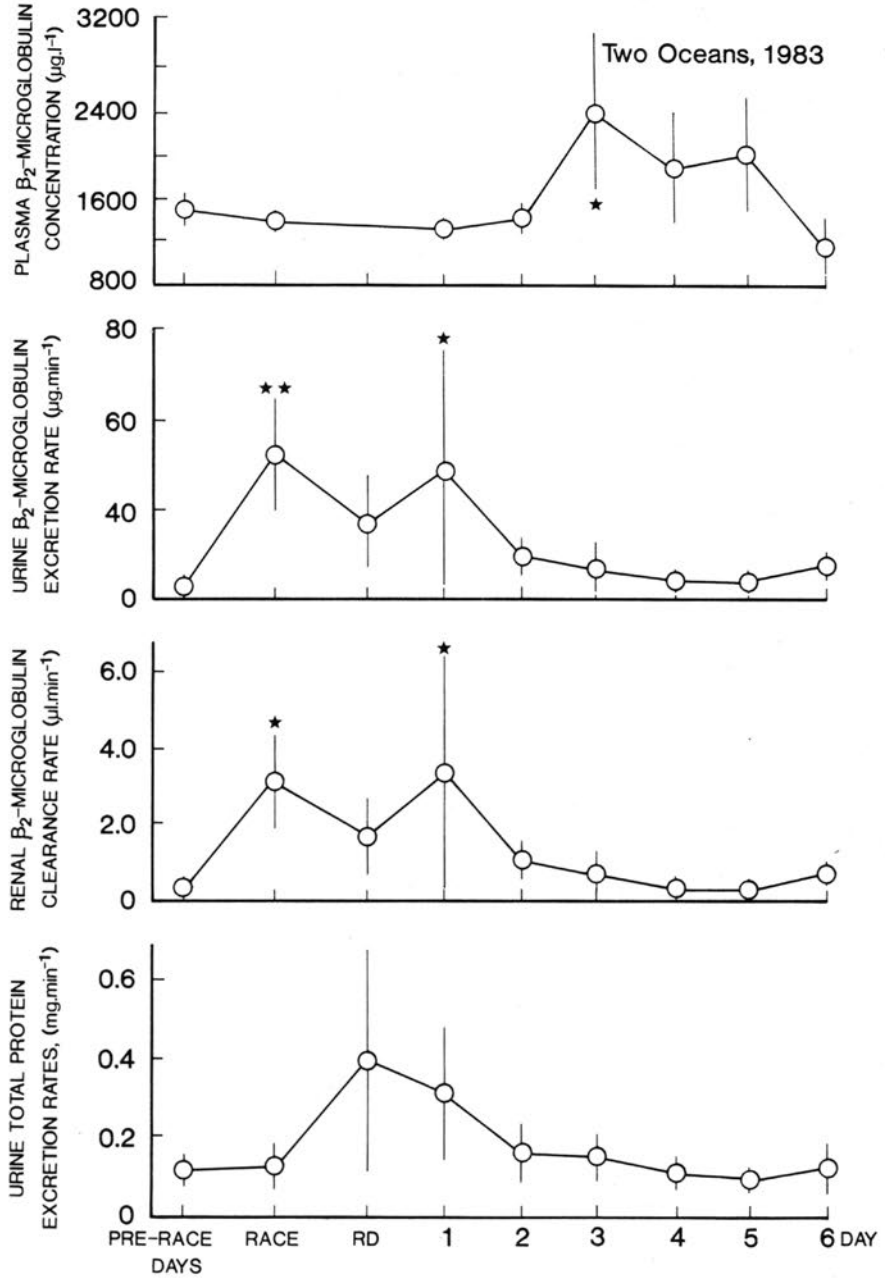

Figure 4.2. Mean (± SEM) plasma beta$_2$-microglobulin concentration, urine beta$_2$-microglobulin and total protein excretion rates and the renal beta$_2$-microglobulin clearance rates for 6 runners before, during and after the 1983 Two Oceans 56 km ultramarathon. Key as in Figure 1.

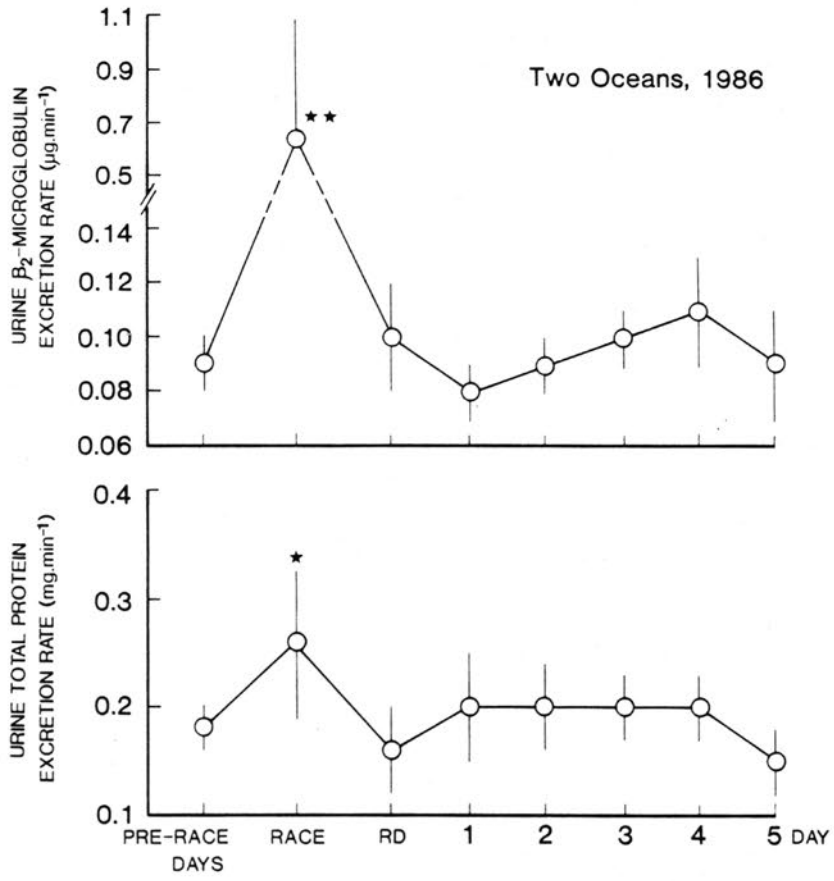

Figure 4.3. Mean (± SEM) urine beta$_2$-microglobulin and total protein excretion rates for 7 runners before, during and after the 1986 Two Oceans 56 km ultramarathon. Key as in Figure 1.

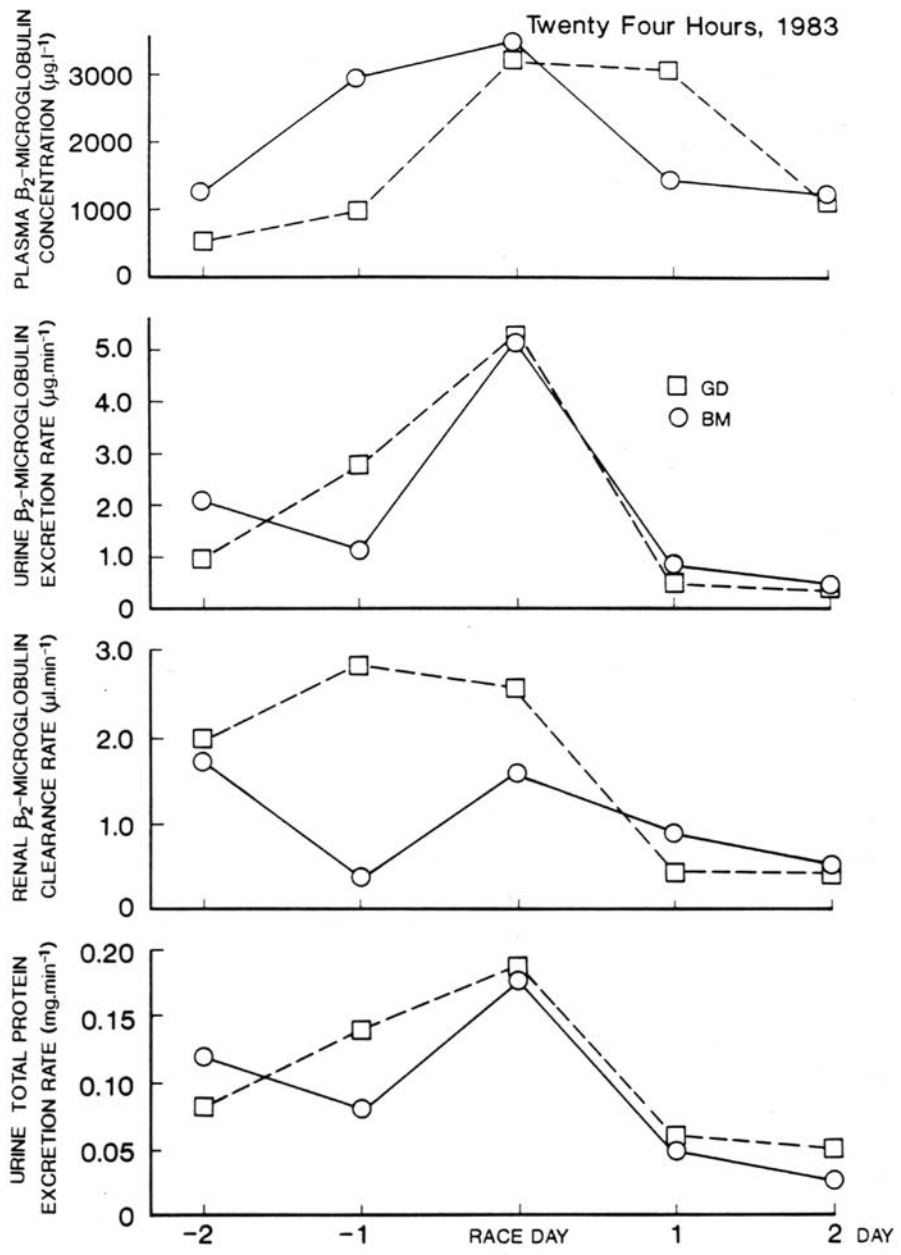

Figure 4.4. Mean (± SEM) plasma beta$_2$-microglobulin concentration, urine beta$_2$-microglobulin and total protein excretion rates and the renal beta$_2$-microglobulin clearance rates for 2 runners for 2 days prior to, during and after the 201 mile 24-hour relay record attempt.

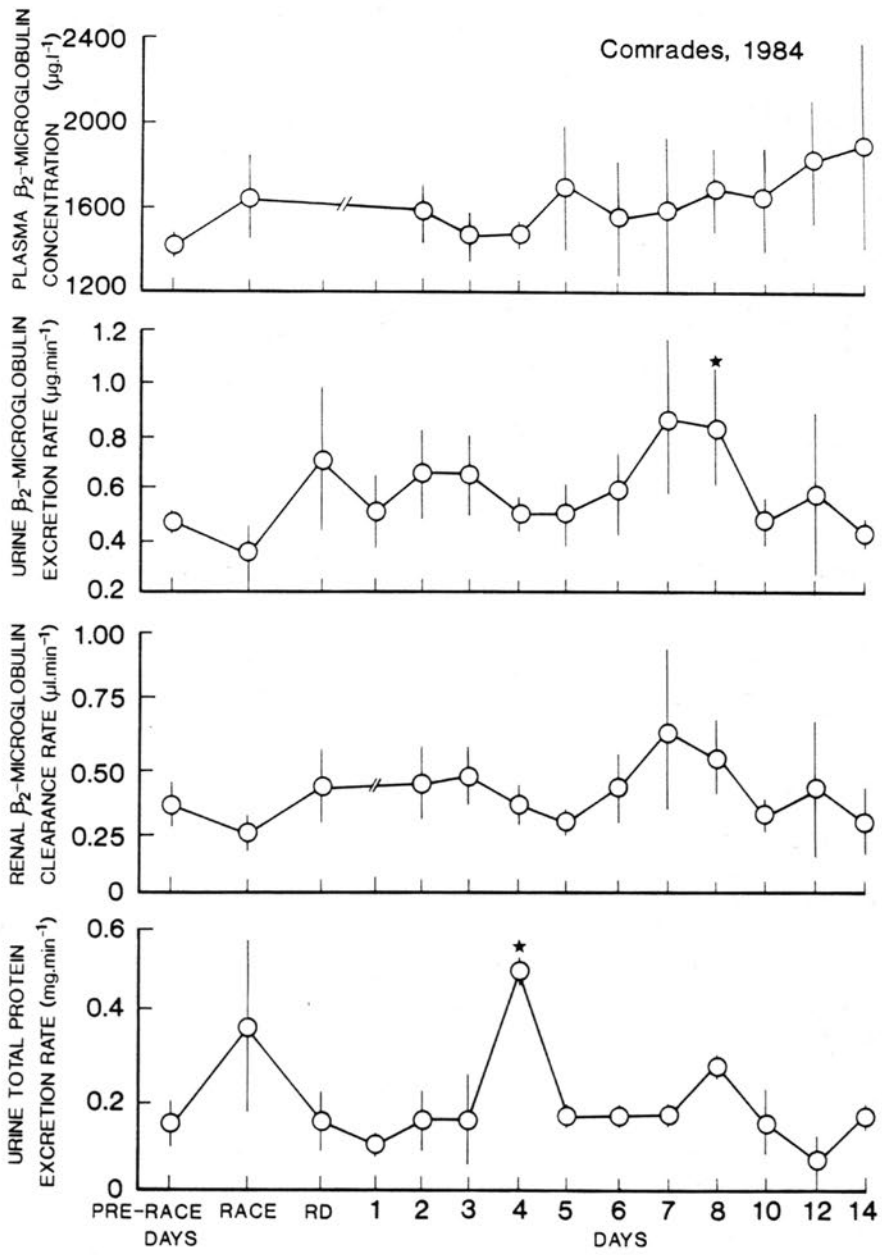

Figure 4.5. Mean (± SEM) plasma beta$_2$-microglobulin concentration, urine beta$_2$-microglobulin and total protein excretion rates, and the renal beta$_2$-microglobulin clearance rate for 4 runners prior to, during and after the 1984 90km Comrades Marathon. Race is the race period and RD is the remainder of the day.

* $p = < 0.05$ compared to pre-race values

4.4. DISCUSSION

4.4.1. THE TYPE OF PROTEINURIA INDUCED BY MARATHON RUNNING

It has been suggested that the proteinuria that develops during and after long-distance running is associated with an increased glomerular permeability without any significant change in the proximal tubular reabsorption processes (Poortmans and Haralambie 1979; Poortmans and Jeanloz 1968). Impairment of tubular reabsorption has been recorded only after exhaustive exercise of short duration (Poortmans 1972; Poortmans and Vancalk 1978; Poortmans et al 1988).

Our studies generally agree with these findings as increases in urine $beta_2$-microglobulin excretion rates (Figure 4.4. and 4.5.) were associated with increased plasma $beta_2$-microglobulin concentrations. Consequently changes in renal $beta_2$-microglobulin clearance rates were not significant and renal tubular dysfunction was not found. There was a however a 100% increase in urine $beta_2$-microglobulin excretion rates during the 1986 56 km marathon (Figure 4.2.), but unfortunately plasma $beta_2$-microglobulin concentrations were not measured in that study.

Assuming that the filtered urinary proteins measured in this study were mainly albumin (Poortmans 1984; Poortmans and Haralambie 1979), and that $beta_2$-microglobulin is reasonably

representative of low molecular weight proteins (Poortmans and Vancalk 1978), our results would indicate that there was an increase only in glomerular permeability after most marathons, and that the proteinuria that develops after long-distance running is generally of the glomerular type. Furthermore, owing to the increased rate of $beta_2$-microglobulin excretion after marathon running, it is vital that the renal clearance of $beta_2$-microglobulin be measured if renal tubular function is to be studied. A diagnosis of renal tubular impairment can therefore not be made on the basis of urine $beta_2$-microglobulin excretion rates alone.

Temporary renal tubular impairment can, however, occur during marathon races, as after short-term exhaustive exercise (Poortmans and Vancalk 1978; Poortmans et al 1988). To our knowledge this has not previously been reported and is shown by the increase in both the urine $beta_2$-microglobulin excretion rate and the renal $beta_2$-microglobulin clearance rate (Figure 4.2.) both during the 1983 56km Two Oceans marathon, and on Day 1 after that race. During the immediate post-race period the total protein excretion was also increased 5 fold (Figure 4.2.). However, owing to the large individual variations the increase was not significant. One runner (AI) who showed the largest increase in $beta_2$-microglobulin clearance rate is discussed in Chapter 6. However, even excluding AI's results, the

changes shown by the remaining runners are significant compared with pre-race measurements (Figure 6.7.).

These renal tubular changes were transient and protein excretion during the post-race days 2-6 was all within the pre-race range. The reason for the increase in $beta_2$-microglobulin clearance are unclear. With the exception of AI, the runners were all experienced marathon runners who were well trained (Table 3.2.). However, the Two Oceans Marathon is run over a hilly demanding course and the ambient temperature at 21.9^{o}C (Range 17.3-24.8^{o}C) was warmer than the other marathons. These may have been contributing factors. It was also the only race where creatinine clearance decreased during the event (Figure 3.2.).

It should be noted that during these studies of the physiological response to marathon running, 2 out of the 27 runners developed renal tubular dysfunction (see Chapter 6). Neither case would normally have been reported. Whether this is an unusually high percentage and its consequent clinical relevance requires investigation.

4.4.2. THE ONSET OF INCREASED GLOMERULAR PERMEABILITY

After exhaustive short-term exercise, increased rates of urinary total protein and albumin excretion had returned to resting values after approximately 4 hours (Poortmans et al

1989). After marathon running increases in urinary total protein excretion can be recorded during the post-race days (Figure 4.1. and 4.5.). The reason for the delay in the onset of increased glomerular permeability is presently unclear. Further work is required, in particular, to determine whether the increase in urinary total protein excretion on Day 4 after the 90 km Comrades Marathon is indeed related to the ultramarathon race, and not to other factors.

4.4.3. GLOMERULAR AND TUBULAR CHANGES OCCURRING ON DIFFERENT DAYS

The mechanisms involved in post-exercise proteinuria are, as yet, not fully understood (Poortmans 1984). It is, therefore of interest to note that the urine $beta_2$-microglobulin excretion and urine total protein excretion do not always increase on the same day (Figure 4.5.). This possibly indicates that different mechanisms are involved in the increase in glomerular permeability and the impairment of proximal tubular function. Unfortunately plasma and urine albumin concentrations which would have given a more definite indication of changes in glomerular permeability were not measured and further work is required to confirm the possibility. In addition, although the increase in urine $beta_2$-microglobulin excretion was significant, when changes in plasma $beta_2$-microglobulin were accounted for,

the increase in renal $beta_2$-microglobulin clearance was not significant (Figure 4.5.)

4.4.4. A POSSIBLE POST-RACE DECREASE IN GLOMERULAR PERMEABILITY

During Days 4 and 5 after the 1982 Kellerprinz Marathon there was a reduction in urine total protein excretion. This may indicate a change in glomerular permeability. However this finding was only noted after one marathon and unfortunately was not confirmed by measurements of plasma and urine albumin concentrations.

4.4.5. PLASMA $BETA_2$-MICROGLOBULIN CONCENTRATION AS A MEASURE OF GLOMERULAR FILTRATION RATE

Changes in serum $beta_2$-microglobulin concentrations have been suggested as an indirect measure of glomerular filtration rate (GFR) (Wibell 1973). From our studies it is clear that large changes in plasma $beta_2$-microglobulin concentrations occur which are unrelated to changes in creatinine clearance. Thus appropriate caution should be applied if plasma $beta_2$-microglobulin concentration is used as a measure of GFR after long distance running.

CHAPTER V

PLASMA VOLUME DURING AND AFTER MARATHON RUNNING

5.1. INTRODUCTION

It was shown in Chapter 3 that urine sodium excretion falls both during and after marathon running, but can increase during the post-race days. During this period there can also be an increase in urine output and osmolal clearance (Figures 3.1. and 3.2.) and a decrease in plasma osmolality (Figure 3.7.). It is probable that fluid shifts, occurring not only during the race, but also during the recovery phase could explain these findings.

Indeed the terms "overshoot rehydration" or "dilutional anaemia" have been used to describe this phenomenon (Dickson et al 1982) and an expanded plasma volume has been described after marathon running (Kolka et al 1978; Maron et al 1977). The principle factor initiating this plasma volume expansion is considered to be an increase in plasma sodium content (Maron et al 1977). Whether there is an increase in total whole body sodium content and whether there are associated changes in plasma protein content is unclear.

A number of studies have shown that plasma volume usually falls during marathon running (Costill 1977; Costill and Fink 1974; Maughan et al 1985; Myhre et al 1982, 1985; Wells et al 1982). It is not established whether these changes in plasma volume result from solute shifts or whether the plasma volume decrease is merely a result of increased hydrostatic pressures (Myhre et al 1985). Furthermore other studies have found that plasma volume is maintained during marathon running (Costill 1972; Poortmans and Haralambie 1979) and may even increase during other types of prolonged weight-bearing exercise (Pugh 1969 a,b). The reasons for these variations are unclear.

To investigate further these changes and, in particular, to determine the effects that changes in plasma volume and plasma solutes have on renal function, we studied plasma volume changes not only during a marathon race but also during the subsequent recovery days.

5.2. METHODS AND MATERIALS

The subjects were the 8 runners who took part in the 1986 56 km Two Oceans Marathon (Table 3.3.). The race protocol has already been described in Chapter 3.

Pre-race plasma volumes were measured one week, and again 2 days prior to the race, using the Evans Blue method (Gregerson 1944) while subsequent changes were calculated from measurements of haematocrit and haemoglobin (Strauss et al 1951). Serum water was also measured from blood samples drawn daily. To measure changes in mean cell volume (MCV), mean cell haemoglobin concentrations were measured (Costill and Fink 1974). Changes in body weight, plasma sodium concentration and plasma osmolality were also measured as were changes in serum total protein, albumin and chloride concentrations. Red and white cell and platelet counts were also made.

Changes in total contents of plasma or serum were calculated according to the formula given by Van Beaumont et al (1981). The calculations for this and for percentage changes in plasma volume and mean cell volume are given in Chapter 2.

5.3. **RESULTS**

5.3.1. BODY WEIGHT, PLASMA VOLUME AND PLASMA OSMOLALITY CHANGES DURING AND AFTER THE 1986 56 KM TWO OCEANS MARATHON

Mean body weight decreased, during the race, by 2.0 ± 0.4 kg (2.6 ± 0.5%) compared with the pre-race day (Figure 5.1.). By Day 3 mean body weight had increased 1.0 kg compared to Day -3 (prior to 'carbohydrate-loading'). However due to individual variation (range -1.0 to 2.3 kg), this change was not significant.

Plasma volume did not change significantly during the race from the pre-race values of 3 838 ± 191 mL. Thereafter plasma volume increased from Days 1-4 with a peak 12.5% increase (equivalent to 479 mL) on day +2 (Figure 5.1.). After declining on day +5, plasma volume rose again on Day +6.

Plasma osmolality increased from the mean pre-race concentration of 293 ± 1.5 mosmol/kg to 298.4 ± 2.6 mosmol/kg during the race, but fell to 282 ± 4.9 mosmol/kg on Day +4 (Figure 5.1.).

5.3.2. CHANGES IN SERUM ALBUMIN, TOTAL PROTEIN, SODIUM AND CHLORIDE CONTENT DURING AND AFTER THE RACE

Serum total protein content increased by 8.3 ± 3.8% on Day +1 and was increased again on Day +6. Serum albumin content was also increased on those days but, in addition, increased during the race (Figure 5.2.). This increase was 9.3 ± 3.7% over the pre-race level on Day +1 equivalent to an influx of 17.1 g of albumin into the intravascular space.

Plasma sodium content was significantly higher than the pre-race levels on Days +1 to +6 with a maximum increase of 12.8 ± 3.1% on Day 3 (Figure 5.2.). Serum chloride content, however, only increased significantly on Day +1 (Figure 5.2.).

5.3.3. CHANGES IN SERUM WATER CONTENT DURING AND AFTER THE RACE

In contrast to the changes in plasma volume (Figure 5.1.), serum water content decreased during the race (Figure 5.3.) but was also increased on Day +2.

5.3.4. THE RED AND WHITE CELL AND PLATELET COUNTS BEFORE, DURING AND AFTER THE RACE

There was a significant decrease in the red cell count on Day +1 and +2 (Figure 5.4.), whereas the white cell count increased during the race (from 5.1 $\pm$ 0.2 to 14.0 $\pm$ 1.3 x 10^6/L). However, when the red cell count was adjusted for plasma volume changes, post-race changes in the former were no longer significant. There was no correlation between the race-induced leukocyte increase, training distance or time recorded.

5.3.5. SERUM TOTAL PROTEIN, ALBUMIN AND CHLORIDE CONCENTRATIONS, PLASMA SODIUM AND POTASSIUM CONCENTRATIONS AND PERCENT CHANGE IN MEAN CELL VOLUME BEFORE, DURING AND AFTER THE RACE

Serum total protein and albumin concentrations were decreased on Days 2 and 3 after the marathon, while plasma potassium concentration was increased on Days 3 and 4. There were no changes in plasma sodium or serum chloride concentrations nor in the mean cell volume (Table 5.1.).

Table 5.1. MEAN SERUM TOTAL PROTEIN, ALBUMIN AND CHLORIDE CONCENTRATIONS, PLASMA SODIUM AND POTASSIUM CONCENTRATIONS AND PERCENT CHANGE IN MEAN CELL VOLUME BEFORE, IMMEDIATELY AFTER AND DURING THE POST-RACE DAYS OF THE 1986 56 KM TWO OCEANS MARATHON

	Serum Total Protein Conc (g/L)	Serum Albumin Conc (g/L)	Plasma Sodium Conc (mmol/L)	Plasma Potassium Conc (mmol/L)	% change Mean Cell Vol (%)	Serum Chloride Conc (mmol/L)
Pre-race	67.5 ±1.0	45.0 ±0.65	136 ±1.1	4.2 ±0.1	100 ±1.95	100.3 ±1.2
Race Day	69.1 ±1.5	46.9 ±1.2	137 ±1.5	4.0 ±0.1	101.5 ±1.7	98 ±2.3
Day +1	65.8 ±1.2	44.4 ±0.7	133 ±1.2	3.9 ±0.1	99.3 ±0.7	101.5 ±1.3
Day +2	63.1* ±1.2	42.0* ±1.0	136 ±1.3	4.1 ±0.1	98.2 ±1.3	98.9 ±1.3
Day +3	63.6* ±2.2	42.0* ±1.4	136 ±0.9	5.0** ±0.2	99.9 ±2.1	97.5 ±2.2
Day +4	65.0 ±2.1	42.9 ±1.2	133 ±3.0	4.7** ±0.3	97.6 ±1.7	98.2 ±1.5
Day +5	67.6 ±1.7	44.5 ±1.2	138 ±0.6	4.0 ±0.1	98.5 ±2.1	100.5 ±1.1
Day +6	68.9 ±0.9	45.5 ±0.6	136 ±1.4	4.0 ±0.1	100.4 ±1.3	101.4 ±0.8

Data expressed as means ± standard error of the mean

* $p = < 0.05$ compared with pre-race values

** $p = < 0.01$ compared with pre-race values

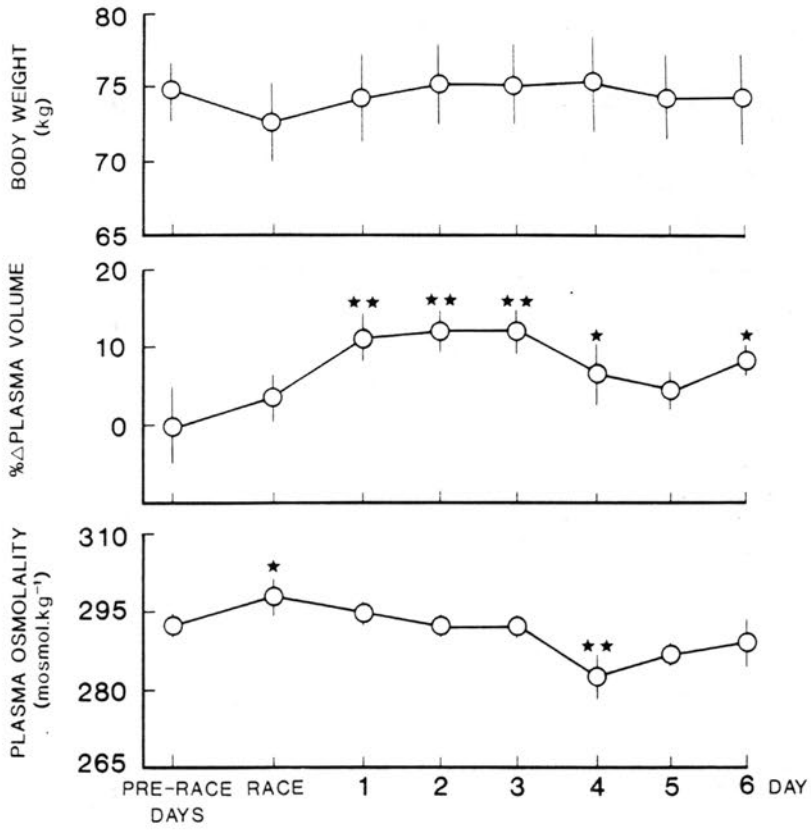

Figure 5.1. Mean (± SEM) daily change in body weight, plasma osmolality and plasma volume

* p = < 0.05 compared with the pre-race values

* * p = < 0.01 compared with the pre-race values

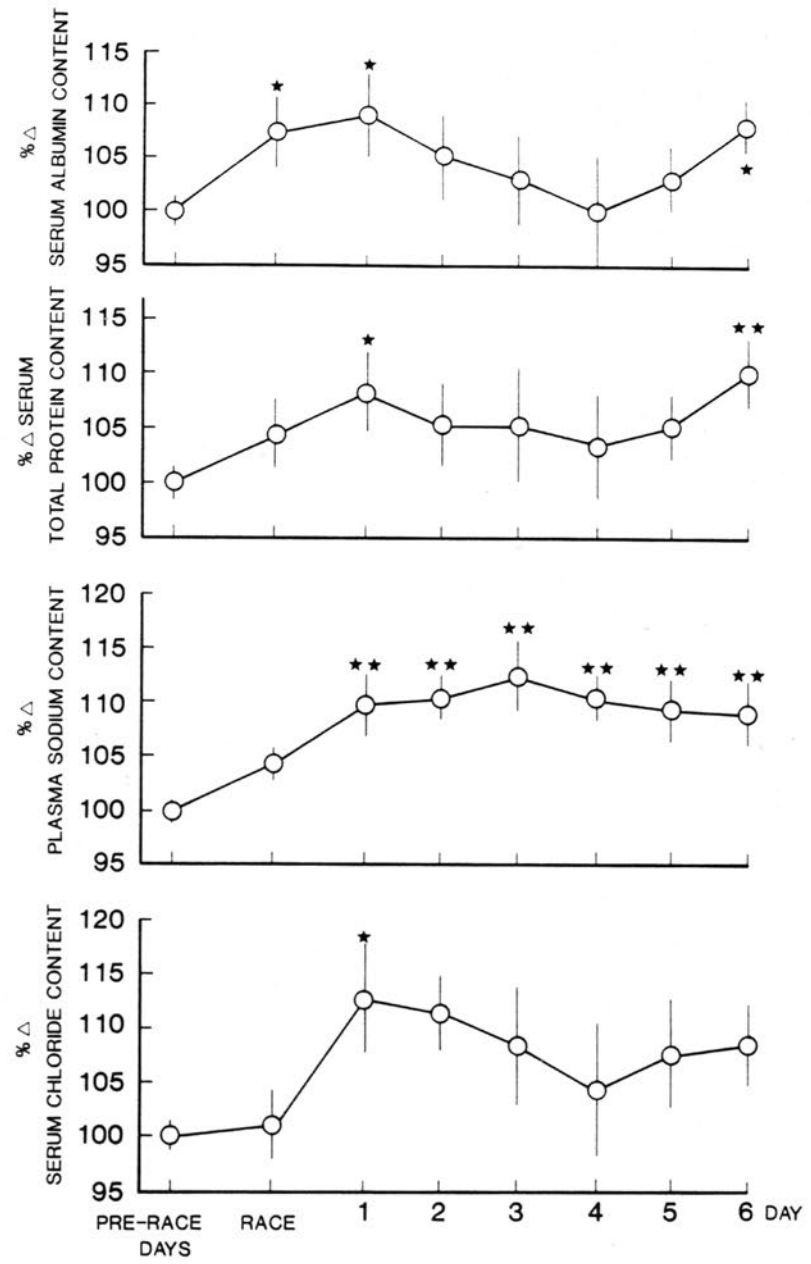

Figure 5.2. Mean (± SEM) daily percent change in serum albumin, total protein and chloride content and the percent change in plasma sodium content.

* p = < 0.05 compared with the pre-race values

* * p = < 0.01 compared with the pre-race values

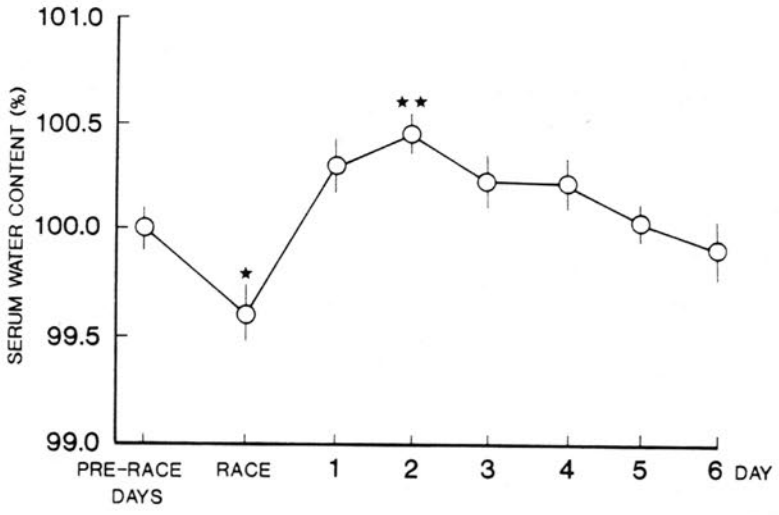

Figure 5.3. Mean (± SEM) daily percent change in serum water content

* p = < 0.05 compared with the pre-race values

* * p = < 0.1 compared with the pre-race values

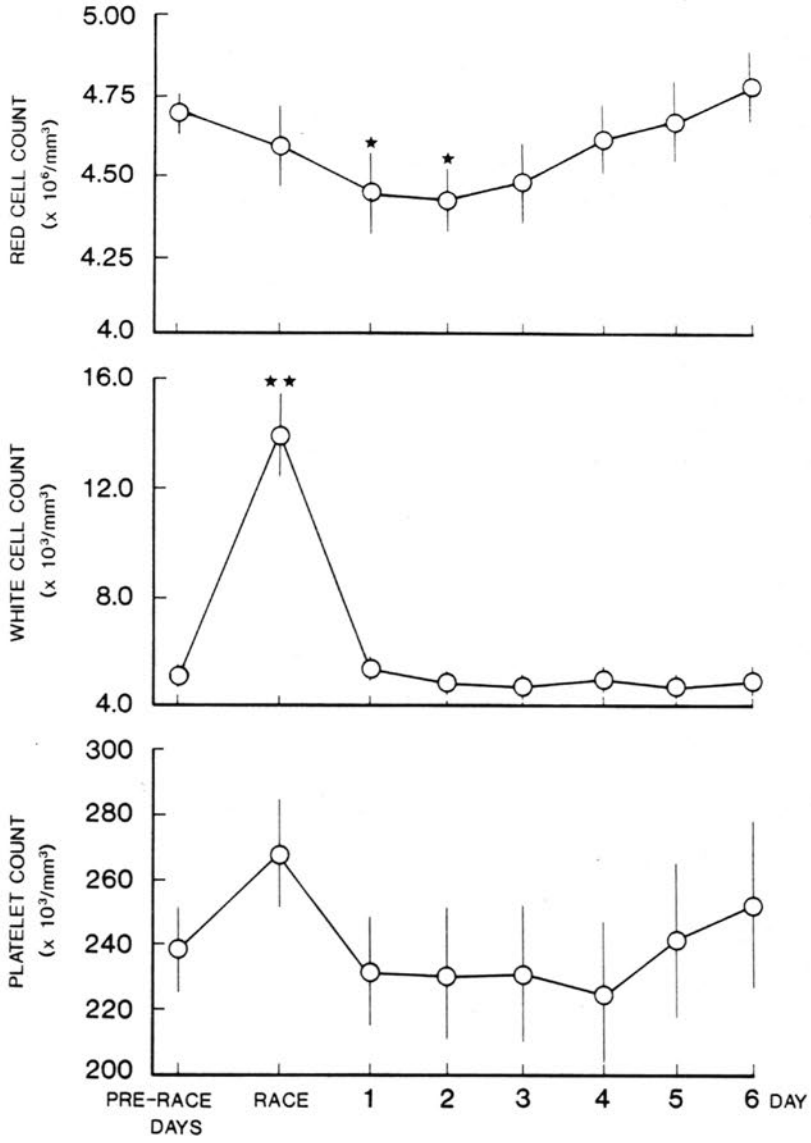

Figure 5.4. Mean (± SEM) red and white cell and platelet counts after the 1986 Two Oceans ultramarathon

* p = < 0.05 compared with the pre-race values

* * p = < 0.01 compared with the pre-race values

5.4. DISCUSSION

5.4.1. MEASUREMENTS OF PLASMA VOLUME CHANGES IN MARATHON RUNNERS

In this study the Evans Blue method (Gregerson 1944) was used to measure pre-race plasma volumes. Post-race changes in plasma volumes were calculated on the basis of measurements of haematocrit and haemoglobin (Strauss et al 1951) with a consistent posture being assumed (Eisenberg 1963; Hagan et al 1978, 1980). Some authors consider this method to be superior to the Evans Blue technique (Senay 1970; Senay and Christensen 1965) owing to the large increase in serum protein content that occurs after exercise (Figure 5.2.).

However for these calculations to be accurate, minimal red cell destruction must have taken place during the exercise and the mean cell volume must not alter (Costill et al 1974). That there is minimal red cell destruction even during very prolonged exercise has been confirmed by several authors (Dickson et al 1982; Poortmans and Haralambie 1979; Steenkamp et al 1986).

To measure MCV, calculations based on MCHC were used as it is believed that the Coulter Counter technique alters this

parameter (Costill and Fink 1974). The MCV was unchanged in this study (Table 5.1.). No correction was made for differences between venous and whole-body haematocrit (Harrison et al 1982). The double precaution of calculating plasma volume changes on the basis of measurements of both haematocrit and haemoglobin concentrations was also taken.

5.4.2. SERUM WATER CONTENT AS A MEASURE OF PLASMA VOLUME

We found serum water content (Figure 5.3.) to be a poor indicator of plasma volume changes during and after marathon running, and therefore do not recommend it as a means of following changes in this variable under these circumstances.

Plasma volume and serum water content did not change in concert as can be seen in Figures 5.1. and 5.3. To determine serum water, solute mass is measured and this alters after long-distance running owing to the intravascular flux of protein and electrolytes (Figure 5.2.).

5.4.3. PLASMA VOLUME CHANGES DURING AND AFTER MARATHON RUNNING

In this study, plasma volume was maintained during the 1986 56 km Two Oceans Marathon. A reduction in plasma volume has

been reported after short-term submaximal exercise (Kilburn 1966; Galbo et al 1975, 1976; Wilkerson et al 1977) and after the first 6 km of a 42 km race (Myhre et al 1985). The same may have occurred during the initial stages of this race. However over the succeeding 3.5-5 hours, fluid shifts are likely to have occurred probably on the basis of influx of albumin and electrolytes into the intravascular fluid compartment causing plasma volume to remain at pre-race levels during the race. Others have concluded, without direct measurement, that plasma volume is relatively unaltered during ultra-marathon running (Poortmans and Haralambie 1979) and standard 42.2 km races (Costill 1972; Maron et al 1975). Still others have calculated that plasma volume is reduced after standard 42 km marathon races (Maughan et al 1985; Myhre et al 1982; Wells et al 1982). Meanwhile, others have found a wide variation in plasma volume changes in the same study (Maughan et al 1989).

From calculations based on the data supplied in those articles, it would seem that this discrepancy might be explained by either a negative (Myhre et al 1985) or minor intravascular protein influx (a 1.2% increase in albumin content (Maughan et al 1985)) or egress (a 3.9% decrease in serum albumin content (Wells et al 1982)). This can be compared to increases in albumin content of 7.8% in our study (Figure 5.2.) and of 8.3 % in the study of Poortmans and Haralambie (1979). Maron et al (1975) did not measure

serum albumin concentrations but the total serum protein content of their runners increased by 9.8% during the marathon. These increases in intravascular protein content would provide the osmotic force necessary to retain water and sodium within the vascular space (Senay 1979), thereby maintaining plasma volume during exercise.

This has previously been shown to be the critical event in the plasma volume expansion associated with heat acclimatization (Senay et al 1976). Possible reasons for the elevated intravascular protein content are an increase in lymph flow (Olszewski et al 1977; Senay 1970, 1979; Wells et al 1982) or a release of protein from damaged tissues (Haralambie 1969).

The maintained plasma sodium content measured during the race (Figure 5.2.) was associated with a reduction in urine sodium excretion which continued during the remainder of the race day (Figure 3.9.) and must have been a factor contributing to the maintenance of plasma volume during the race.

The race was run under moderate environmental conditions (dry bulb temperature range 7.3-18.3^{o}C) and it is possible that under warmer environmental conditions greater sweat sodium losses would have lead to a proportionally greater loss of sodium from the extracellular fluid compartment.

By the post-race day (Day 1), compared with pre-race contents (Figure 5.2.), 17g of albumin as well as 96 mmol of sodium had entered the vascular compartment. Although there was no significant increase in serum albumin content on post-race days 2-5, sodium content remained elevated throughout this period. Whether or not this indicates an increase in total body content of sodium is uncertain but this has been shown after consecutive days of exercise (Williams et al 1979). If total body sodium had indeed increased, there would have been an expansion of the ECF volume and an increase in body weight. There was indeed an increase in body weight (from 74.2+2.8 kg on Day -3 to 75.2+2.8 kg on Day +3) (Figure 5.1.), but owing to individual variation this increase was not significant. Plasma volume expansion peaked on Day 2 (a 12.5% increase) which is comparable with a 9.8% increase on Day 3 after a 21.1km road race (Robertson et al 1988), and a 16.5% increase on Day 2 of a study of a 42.2km marathon (Maron et al 1977). The latter increase was also associated with an elevated serum sodium content. Serum albumin was not measured but calculations from data supplied in that article (Maron et al 1977) show that total protein content increased 7.7% when compared with control values.

The secondary increase in plasma volume on day 6 (Figure 5.1.) was associated with a further increase in serum albumin content (Figure 5.2.) as well as a maintained plasma sodium content (Figure 5.2.). The subjects did not exercise until Day 5 when they began gentle jogging. It is possible that there was ongoing skeletal muscle damage (Warhol et al 1985), as shown by the persistence of elevated total serum enzyme activities and increased serum uric acid content (Figure 3.14.). Possibly even this gentle exercise caused a further protein influx into the vascular compartment due to one or both of the aforementioned mechanisms. Repeated long-distance running (Dressendorfer et al 1981) and repeated exercise training (Convertino et al 1980) are known to cause chronically elevated plasma volumes associated with a progressive influx of albumin into the vascular compartment (Convertino et al 1980). Similar mechanisms may have been operative on Day 6 of this study.

5.4.4. TOTAL PLASMA CONTENTS AND PLASMA CONCENTRATIONS

This study shows that there can be large differences between the total contents of plasma or serum solutes and their concentrations.

Serum albumin and total protein concentrations were significantly decreased when measured on Day +2 and +3 (Table 5.1.), whereas the actual contents in the expanded

plasma volume were increased (Figure 5.2.). Similarly, plasma sodium concentrations did not vary from pre-race values throughout the study (Table 5.1.) whereas the total sodium content was increased during the post-race day (Figure 5.2.). This difference was also noted by Maron et al (1977).

It is clear that investigations of plasma constituents after marathon running, whether for medical or research purposes, must take account of the expanded plasma volume.

5.4.5. DILUTIONAL ANAEMIA AFTER MARATHON RUNNING

After the 1986 56 km Two Oceans marathon there was an apparent decrease in the number of circulating red blood cells on days 1 and 2 (Figure 5.4.). However this change ceases to be significant when corrected for PV changes. Although haemolysis of RBC has been reported after exertion (Gilligan and Blumgart 1941; Gilligan et al 1943), and is considered to be due to mechanical trauma in the microcirculation of the feet (Davidson 1969), this is minimized by modern cushioned running shoes (Buckle 1965). Normal RBC survival has been confirmed in recent reports (Steenkamp et al 1986; Poortmans and Haralambie 1979).

This study therefore confirms the phenomenon of dilutional anaemia discussed by Dickson et al (1982).

5.4.6. THE EFFECT OF MARATHON RUNNING ON WHITE CELL AND PLATELET COUNTS

Leukocytosis has been reported after exercise of both short (Bieger et al 1980) and long duration (Dickson et al 1982; Davidson et al 1987; Wells et al 1982; Wilkerson et al 1977). This increase was also apparent in this study (Figure 5.4.). The explanation has been given as a shift from the marginated granulocyte pool to the circulating pool (Athers et al 1961; Bieger et al 1980; Peters et al 1985) although there may be additional factors such as a cortisol-induced release of granulocytes from the bone-marrow (Davidson et al 1987). Exercise-induced leukocytosis has been inversely correlated with prior training (Moorthy and Zimmerman 1978).

The present study, however, show no correlation between the leukocyte increase or the athletes training distance or the time recorded. This lack of correlation was also found by Dickson et al (1982).

CHAPTER VI

THE PATHOLOGICAL RESPONSES OF RENAL FUNCTION TO MARATHON RUNNING

6.1. INTRODUCTION

Acute renal failure may be divided into 2 phases: generation and maintenance (Stein and Sorkin 1976). Generation may be induced by ischaemia resulting from decreased RPF or by nephrotoxic agents. Renal failure may be maintained by one or more of a combination of 4 mechanisms: prolonged ischaemia, altered glomerular permeability, tubular back leak of filtrate or tubular obstruction (Stein and Sorkin 1976).

Nephrotoxic agents which exert a direct toxic action on the renal tubules include myoglobin (Goldberg and Chakrabarti 1966; Koffler et al 1976; Vertel and Knochel 1967), and uric acid (Klineberg et al 1976; Knochel et al 1975; Koffler et al 1976; MacSearraigh et al 1979; Shrier et al 1970). These are released by rhabdomyolysis which is frequently associated with acute renal failure (Bywaters and Beall 1941; Koffler et al 1976).

Muscle damage is a common finding after marathon running as shown by muscle biopsies (Hikada et al 1983; Warhol et al 1985), by detectable levels of myoglobin in serum and urine (Ono 1953; Schiff et al 1978), possibly by increases in serum enzyme activities (Noakes and Carter 1976, 1982, Siegel et al 1981, 1983) and possibly by increases in serum CRP concentrations (Strachan et al 1984).

However, in spite of frequent muscle damage, acute renal failure after marathon running is uncommon. To understand running-induced renal failure, the reason for this must be investigated.

The 90 km Comrades marathon has possibly the highest incidence of acute renal failure in any sporting event in the world (Dancaster et al 1969; MacSearraigh et al 1979). Ten runners developed this condition after the 1986 Comrades Marathon and one runner subsequently died (Myers - personal communication). Accordingly we undertook a study to characterize the normal renal response to this event. In the course of that study one subject who developed temporary tubular dysfunction with oliguria after that race was identified and is described in this chapter. Another runner who developed temporary tubular dysfunction with no oliguria after a 56 km marathon is also described.

6.2. METHODS AND MATERIALS

Subject A, at the time of the 1984 90 km Comrades Marathon was 22 years old. She was 1.70 m in height and weighed 45 kg. During a 2 year running career she had completed 3 marathons and 6 ultramarathons (greater than 42.2 km). Her fastest time for the marathon was 2 hr 50 mins and she was running 180 km per week in training.

The protocol for the 1984 90 km marathon has been previously discussed in Chapter 3. A's results are compared with the group of 4 male runners whose details are recorded in Table 3.4.

Subject AI was 38 years old at the time of the 1983 56 km Two Oceans Marathon. He was 1.76 m in height and weighed 73 kg. In contrast to the above runner he had only completed 2 marathons with a fastest time of 3 hr 24 mins. Prior to that race, AI was training approximately 20 km per week.

The protocol for the 1983 56 km Two Oceans marathon has been described in Chapter 3. AI's results are compared with the 5 other competitors studied in this race whose details are recorded in Table 3.2.

6.3. **RESULTS**

6.3.1. THE INFLUENCE OF A 90 KM MARATHON ON THE RENAL FUNCTION OF RUNNER A

The response of this subject was substantially different from the four other runners who took part in the study. Subject A drank little fluid during the race and lost 11% of body weight (from 45.3 kg to 40 kg). She was anuric when admitted to the medical tent at the end of the race but in response to 2 litres of intravenous fluid produced 1.6 litres of urine during the remainder of the race day (Figure 6.3.).

There was an increase in plasma $beta_2$-microglobulin concentration during the race (from 1.3 $\pm$ 0.03 to 2.4 mg/L) and throughout the study, peaking on Day 6 at 3.2 mg/L (Figure 6.1.). There was also an 84-fold increase in the $beta_2$-microglobulin excretion rate during the race day. This remained elevated above pre-race levels on Day 1, and there was a further small increase on Day 4 (Figure 6.2.). The renal $beta_2$-microglobulin clearance rate showed the same picture with a 50-fold increase after the race (Figure 6.1.). The urine total protein excretion was elevated on Day 5 (Figure 6.2.).

The osmolal clearance also increased immediately after the race, urine osmolality remained low while the creatinine clearance increased towards normal (Figure 6.3.). Plasma urea concentration in Runner A increased from 3.7 $\pm$ 0.3 to 6.0 mmol/L during the race (Figure 6.6.). It should be noted that differences between this runner and the group were present before the race, including a low urine output and increased urine osmolality (Figure 6.3.), suggesting a habitually low fluid intake. The lower urine creatinine excretion (Figure 6.6) was due to the lower body mass and the lower creatinine clearance (Figure 6.3.) was partially due to the gender (Ganong 1977) but also was the result of a predominantly vegetarian diet (Bosch et al 1983).

During the post-race days, osmolal and creatinine clearance remained below pre-race levels throughout the study as did the urine output (Figure 6.3.). These parameters were within the pre-race limits when measured a year later, prior to the next Comrades Marathon. Urine osmolality remained below pre-race values until Day 5. Plasma CRP concentrations were higher than values measured in the comparison group on Days 3-10 but thereafter decreased rapidly (Figure 6.5.).

6.3.2. THE INFLUENCE OF A 56 KM MARATHON ON RUNNER AI

Changes in plasma $beta_2$-microglobulin concentration, urine $beta_2$-microglobulin and total protein excretion and renal $beta_2$-microglobulin clearance of this runner and the five other runners who took part in the 1985 56 km Two Oceans Marathon study are shown in Figure 6.7.

There was no change in AI's plasma $beta_2$-microglobulin concentration whereas the other runners showed a mean increase on Day 3. These runners also showed increases in urine $beta_2$-microglobulin excretion and the renal $beta_2$-microglobulin clearance rate during the race and the remainder of the race day. These measurements were, however, markedly increased in Runner AI during the race and on Day 1 (a 42-fold increase in renal $beta_2$-microglobulin clearance on Day 1 (Figure 6.7.).

Table 6.1. compares creatinine and osmolal clearance, urine output, osmolality, plasma C-reactive protein concentration, and plasma creatine kinase activity of runner AI with the other runners. The urine output of runner AI during the race was higher than with the comparison runners, as was the urine osmolality and osmolal clearance. Runners AI's plasma creatine kinase activity increased 36-fold (from 126 $\pm$ 35 to 4530 iu/L) compared with the groups 20.6-fold increase on

Day 1. The post-race increase also lasted for longer in Runner AI.

Runner AI's peak plasma C-reactive protein concentration on Day 1 was also increased above the mean of the group (2.6 mg%) compared with 1.74 ± 0.21 mg %) and was also elevated for a longer period (Table 6.1.). AI lost 1.4 kg in body weight during the race (a 1.9% decrease), while the other runners lost a mean of 1.2 kg (a 1.6% decrease).

Table 6.1. RENAL FUNCTION IN RUNNER AI; COMPARISON WITH 5 RUNNERS BEFORE, DURING AND AFTER THE 1983 56KM TWO OCEANS MARATHON (The figures in brackets refer to the values measured in Runner AI)

	Creatinine Clearance (mL/min)	Osmolal Clearance (mL/min)	Urine Output (mL/min)	Urine Osmolality (mosmol/kg)	Plasma CRP Conc (mg%)	Plasma CK Activity (iμ/L)
Pre-Race	114.1 ±7.9 (97.0) (±6.8)	1.8 ±0.15 (1.6) (±0.3)	0.9 ±0.1 (0.6) (±0.1)	685 ±78 (828) (±52)	0.1 ±0.1 (0.0)	112.5 ±17 (126) (±36)
During Race	73.4* ±14.2 (86.1)	1.0 ±0.4 (3.7)	0.6* ±0.3 (1.2)	567 ±98 (986)	1.8** ±0.7 (0.0)	444 ±147 (396)
Remainder Race Day	113.9 ±7.5 (95.8)	1.6 ±0.3 (0.6)	0.9 ±0.2 (0.5)	658 ±113 (397)	1.7** ±0.2 (2.6)	- - -
Day +1	146.8 ±32.3 (142.4)	1.5 ±0.3 (1.9)	0.7 ±0.1 (0.6)	694 ±148 (1046)	0.4 ±0.3 (2.4)	2314** ±978 (4530)
Day +2	144.6 ±14.8 (117.3)	2.7 ±0.1 (2.0)	1.2 ±0.1 (0.6)	730 ±83 (1038)	0.2 ±0.2 (0.7)	1110* ±346 (346)
Day +3	155.5* ±23.3 (109.5)	2.1 ±0.3 (2.3)	1.1 ±0.1 (0.8)	664 ±123 (815)	0.0 ±0.0 (0.7)	493 ±171 (1304)
Day +4	118.2 ±5.9 (80.2)	2.1 ±0.3 (2.4)	1.2 ±0.2 (1.1)	652 ±132 (634)	0.0 ±0.0 (0.0)	292 ±109 (734)
Day +5	151.5 ±24.3 (98.0)	2.0 ±0.1 (2.5)	1.0 ±0.5 (1.7)	741 ±110 (429)	0.0 ±0.0 (0.0)	149 ±47 (412)
Day +6	130.6 ±6.0 (97.5)	1.8 ±0.2 (2.2)	0.9 ±0.1 (0.8)	745 ±94 (752)	0.0 ±0.0 (0.0)	122 ±35 (247)

Data expressed as means ± standard error of the mean

* p - < 0.05 compared to pre-race values
* * p = < 0.01 compared to pre-race values

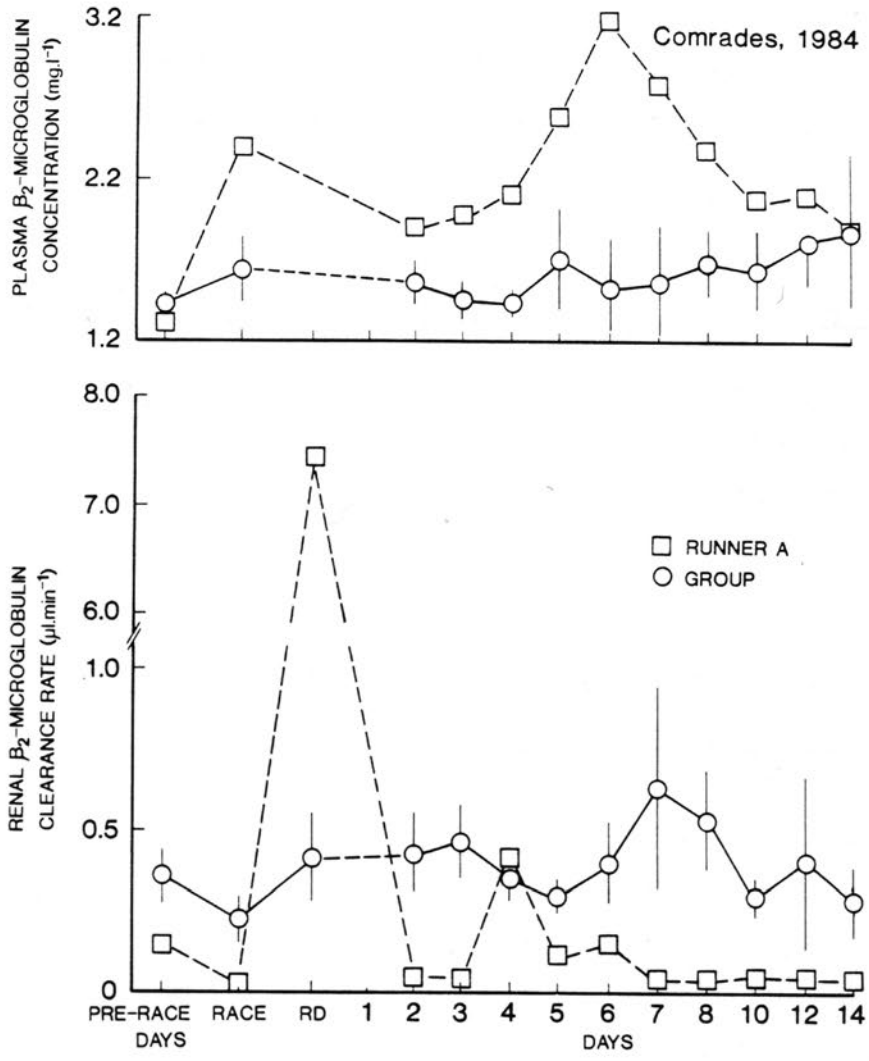

Figure 6.1. Mean (± SEM) plasma beta$_2$-microglobulin concentration and renal beta$_2$-microglobulin clearance rate for 4 runners and runner A prior to, during and after the 1984 90 km Comrades ultramarathon. Race is the race period and RD is the remainder of the race day. Runner A was anuric during and immediately after the race and it was therefore impossible to measure protein excretion during the race.

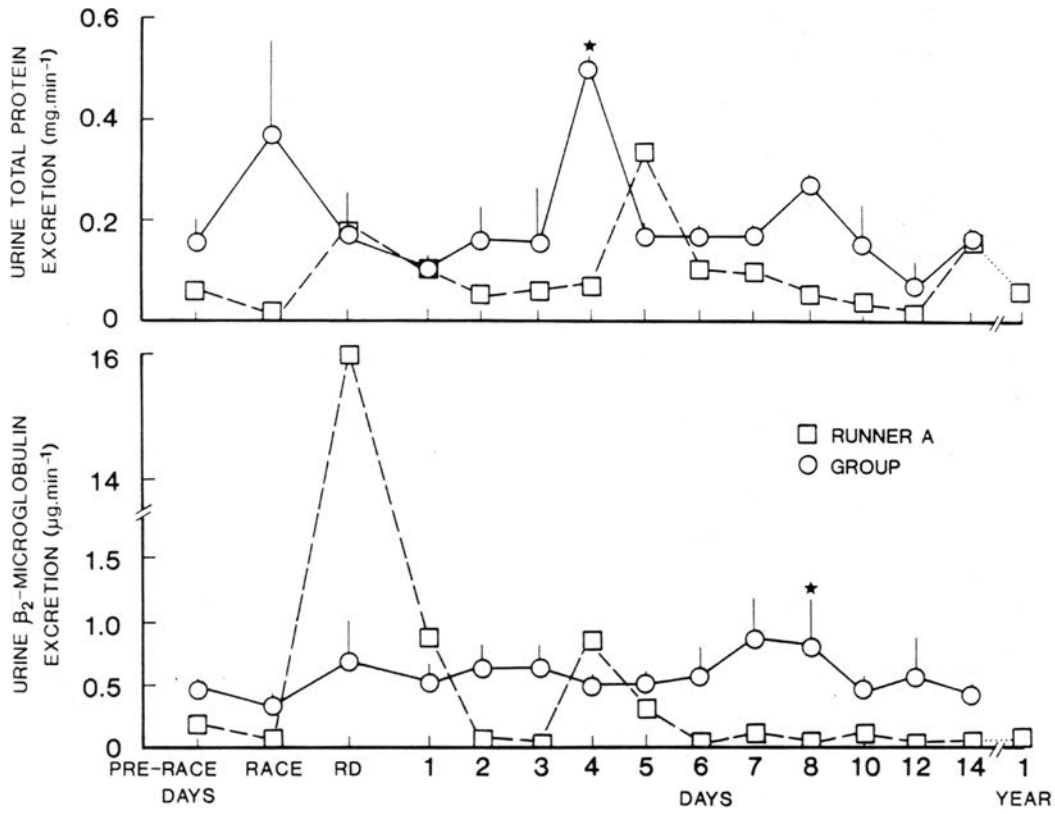

Figure 6.2. Mean (± SEM) urine total protein and B_2 microglobulin daily excretion rates prior to, during and after the 1984 Comrades 90 km ultramarathon. Key as in Figure 6.1.

* p = < 0.05 compared with the pre-race mean.

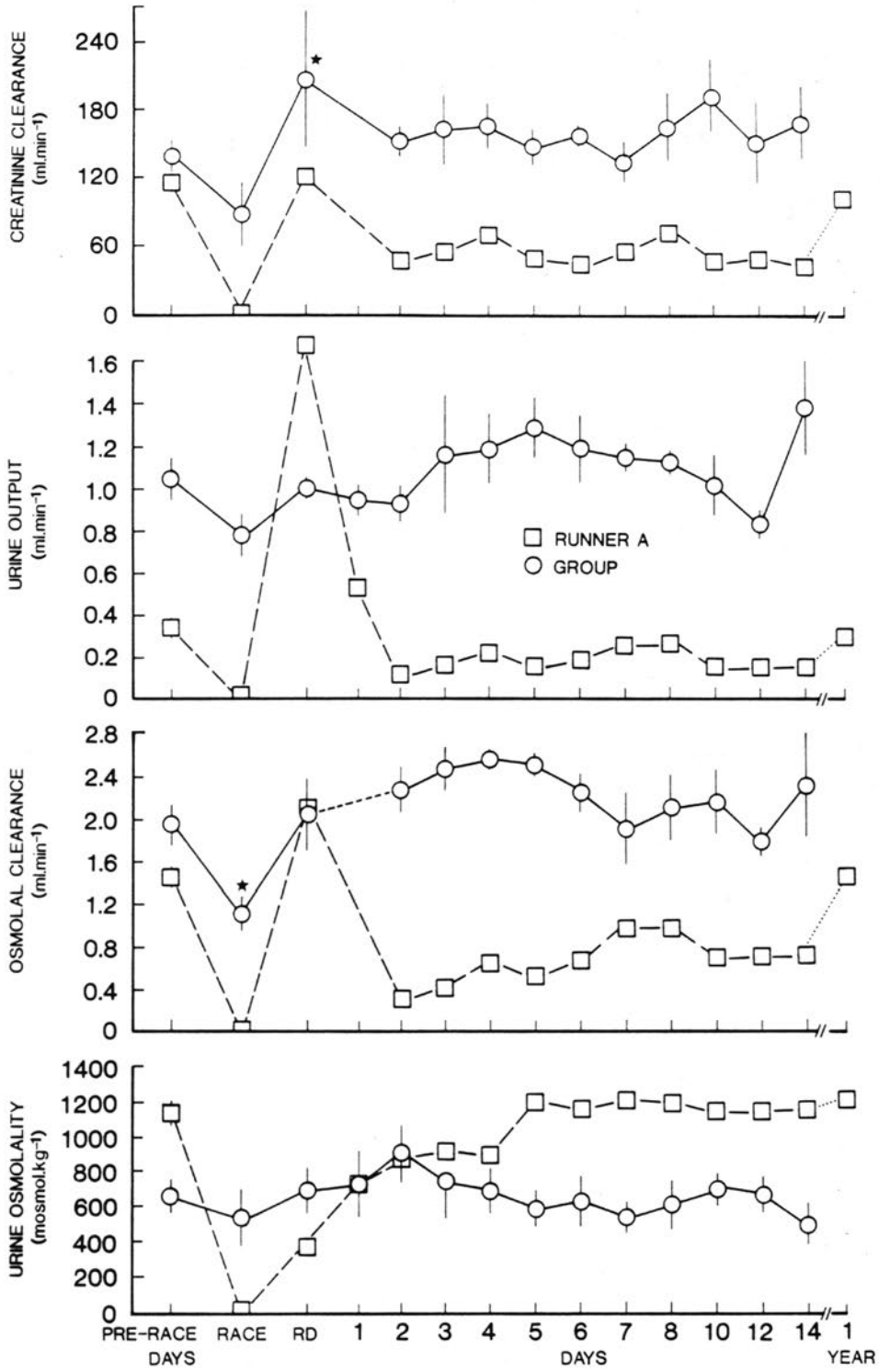

Figure 6.3. Mean (± SEM) changes in creatinine and osmolal clearance, urine output and urine osmolality before, during and after the 1984 90 km Comrades Marathon.

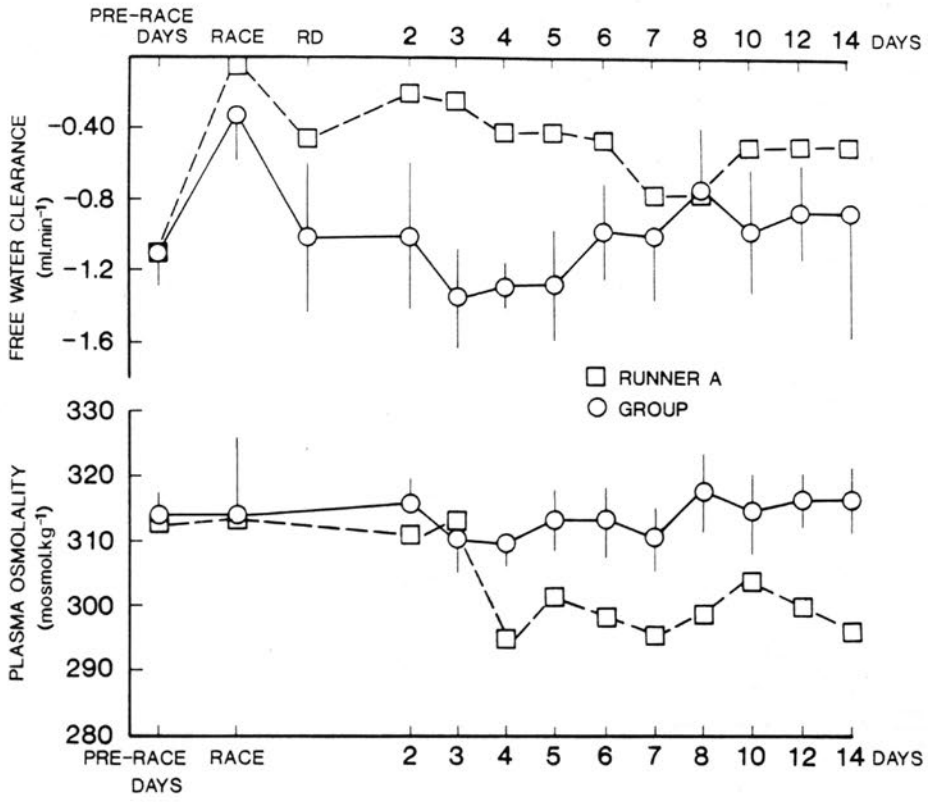

Figure 6.4. Mean (± SEM) changes in plasma osmolality and negative free water clearance before and after the 1984 90 km Comrades Marathon

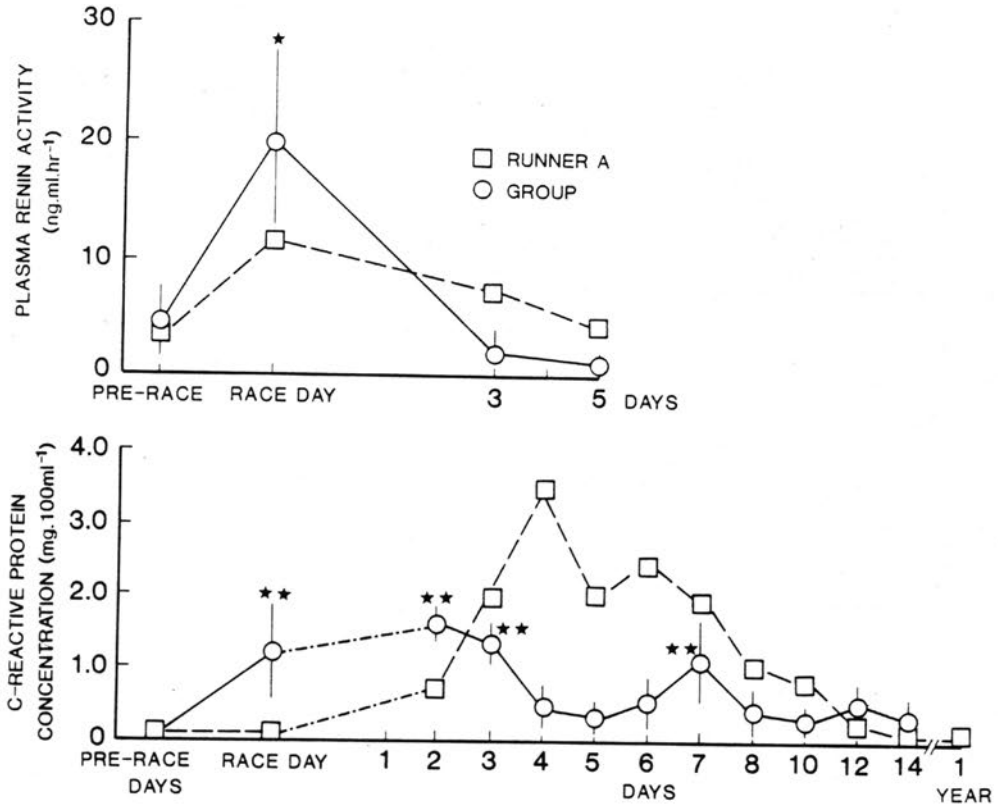

Figure 6.5. Mean (± SEM) daily plasma C-reactive protein concentrations and plasma renin activity before and after the 1984 90km Comrades Marathon.

* p = < 0.05 compared with mean pre-race values

** p = < 0.01 compared with mean pre-race values

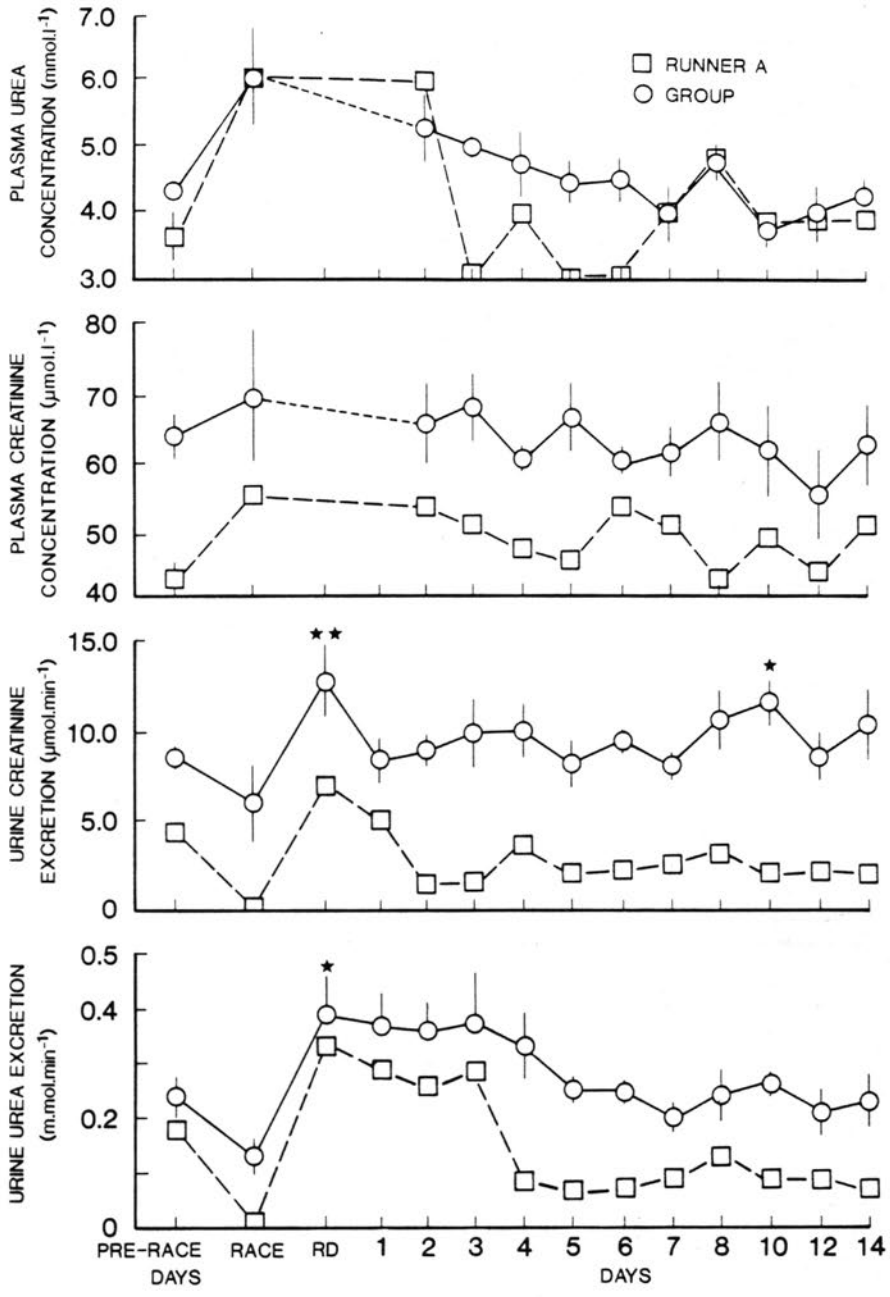

Figure 6.6. Mean (± SEM) plasma urea and creatinine concentrations, the urine urea and creatinine excretion rates before and after the 1984 90 km Comrades Marathon.

* p = < 0.05 compared with mean pre-race values

** p = < 0.01 compared with mean pre-race values

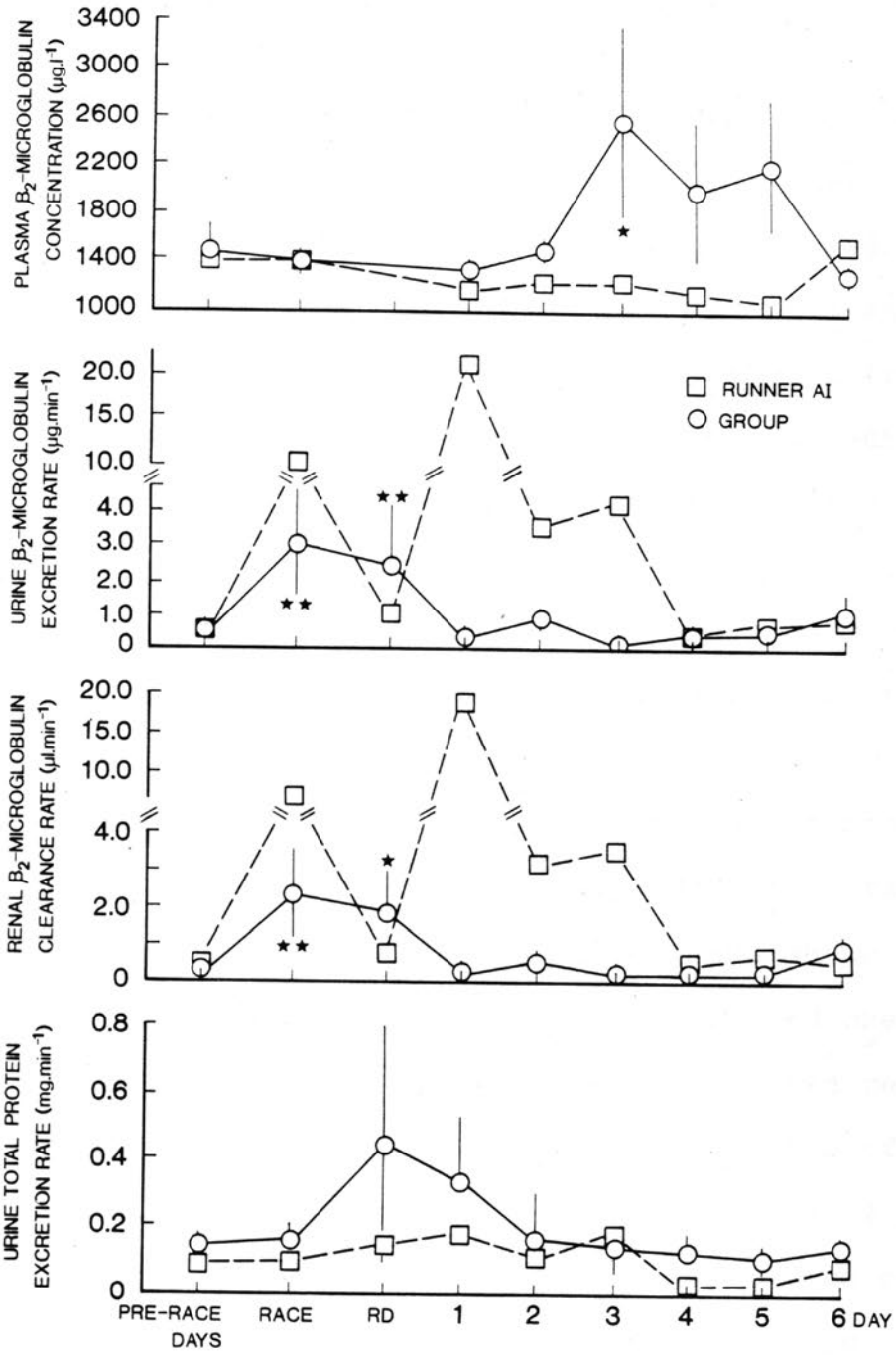

Figure 6.7. Mean (± SEM) plasma β_2-microglobulin concentration, urine beta$_2$-microglobulin and total protein excretion rates and the renal beta$_2$-microglobulin clearance rates for runner AI and 5 other runners before and after the Two Oceans 1983 56 km ultramarathon. Race is the race period and RD is the remainder of the race day.

* p = < 0.05 compared with the pre-race mean.

** p = < 0.01 compared with mean pre-race values

6.4. DISCUSSION

The major factors involved in the genesis of acute renal failure after marathon running are believed to be rhabdomyolysis with the release of nephrotoxic agents such as myoglobin and uric acid, and dehydration with associated reduced renal plasma flow. However, in spite of frequent muscle damage (Hikida et al 1983; Warhol et al 1985), the incidence of acute renal failure in marathon runners is low.

Classically it is believed that many runners complete their marathons in a dehydrated condition (Wyndham and Strydom 1969), with a reduced RPF (Neviackas and Bauer 1981). A decreased RPF is certainly a well established factor in the genesis of non-exercise induced acute renal failure (Stein and Sorkin 1976). However, our studies have shown that a maintained urine output (Figures 3.1.-3.5.) and creatinine clearance (Figures 3.1., 3.3., 3.4.) is a common response to marathon running. Similarly, body weight losses of $2.3 \pm 0.4\%$, $2.9 \pm 0.4\%$ and $2.7 \pm 0.5\%$ after the 42.2km Kellerprinz and the 1983 and 1986 56km Two Oceans marathons, respectively, are not large. They are comparable with another study of 7 marathons in which the weight loss range was between 1.6 ± 1.1 and $3.1 \pm 1.9\%$ (Noakes et al 1988). It is therefore likely that RPF is generally well maintained over the duration of a marathon. This might explain why

acute renal failure occurs infrequently in marathon runners even in the presence of acute muscle damage.

Runner A, a well-trained runner of high ability did, however, develop temporary renal tubular dysfunction with oliguria as shown by an 84-fold increase in the urine $beta_2$-microglobulin excretion rate (Figure 6.2.) and a 50-fold increase in the renal $beta_2$-microglobulin clearance rate immediately after the race (Figure 6.1.). The excretion rate was still elevated on Day 1 (Figure 6.2.) and there was a further increase (2.7-fold) in the clearance rate on Day 4 (Figure 6.1.).

Although the tubular dysfunction was of a temporary nature, and plasma urea and creatinine were not unduly elevated (Figure 6.6.), other indicators of renal dysfunction were present. These included (i) oliguria during and immediately after the race which was reversed only after intravenous fluid replacement (Figure 6.3.); (ii) a low (for this runner) urine osmolality for the first 5 days after the race (Figure 6.3.); (iii) the absence of the normal post-race increase in creatinine clearance and urine output (Figure 6.3.); (iv) the persistently decreased creatinine clearance (Figure 6.3.) and (v) the persistence of a low urine output (Figure 6.3.).

It should be noted however that the body weight of this runner did not increase during the post-race period and the runner's protein and fluid intakes were low, which may have contributed to the low creatinine clearance (Bosch et al 1983; Pullman et al 1954) and low urine output. However, creatinine clearance was within the pre-race limits when re-measured a year later prior to the next Comrades Marathon, suggesting that subject A may indeed have experienced a reduced GFR for at least 14 days after the marathon (Figure 6.3.).

Runner A drank very little during the race and showed a body weight loss of 11%, indicating severe dehydration. The dangers of such levels of dehydration are well described (Dancaster et al 1969; MacSearraigh et al 1979) and almost certainly explain the temporary renal dysfunction experienced by this runner. Although the pre-race fluid intake was low, plasma renin activity did not indicate dehydration (Figure 6.5.) and there was no evidence of pre-race renal impairment as shown by plasma creatinine and urea concentrations (Figure 6.6.).

Another obvious contributing factor is the distance and severity of the course itself. In addition, as the 90 km race extends over most of the day, the environmental temperature is also generally higher than during a 42.2 km marathon, which usually ends mid-morning. It has been shown

that dehydration, heat and exercise have an additive effect on decreases in GFR and RPF (Smith et al 1952).
It is unlikely that this runner has an increased susceptibility to exercise-induced acute renal failure. Subsequent to this marathon she has completed 13 standard marathons and 10 ultramarathons including 4 further Comrades marathons without adverse effect. She has, however, increased her fluid intake during the races.

A potentially important factor in the genesis of the acute renal failure induced by marathon running is that of anti-inflammatory and analgesic drug use. There is a proven correlation with renal damage (Clive and Stoff 1984) but the incidence of use among runners is unknown. Neither of the two runners, discussed in this chapter took drugs during their races and this was not a factor in these cases.

Runner AI also showed temporary renal tubular impairment after a 56 km marathon as indicated by the 42-fold increase in renal $beta_2$-microglobulin clearance on Day 1 (Figure 6.7.). This impairment was temporary and was the only indication of renal damage. The race and post-race urine outputs were increased over pre-race levels (Table 6.1.); creatinine clearance decreased during the race by 11% which was less than the 36% decrease in the other runners (Table 6.1.). Also AI's body weight decrease was only 1.9% which

can be compared with a 1.6% decrease shown by the other runners.

Possible factors involved in this case were the lack of conditioning prior to the race (the average number of kilometers run per week was only 20km compared with a mean of 72km by the other runners (Range 50-100km). Furthermore, the subject had only been training for a few weeks. His age (38 years) was also greater than most of the other subjects (Mean 31 ± 3 yrs) and renal reserve has been shown to be less in older athletes (Refsum and Stromme 1974). Fluid intake during the race would seem to have been adequate as indicated by the urine output (Table 6.1.). Rhabdomyolysis was, at least in part, a contributing factor as shown by the elevated serum CRP concentrations (Table 6.1.) which remained elevated for longer than in the other runners.

There was also a 36-fold increase in serum CK activity (Table 6.1.). In studies of running events lasting 5-24 hours there is normally a 10-20 fold-increase in serum CK activity (Berg and Haralambie 1978; Kanter et al 1986; Kielblock et al 1979; Noakes and Carter 1976, 1982) which is comparable with the 20.6-fold increase shown by other runners in the 1983 Two Oceans Marathon (Table 6.1.). Untrained runners have been shown to have increased CK activity after exercise which may indicate a greater degree

of muscular damage (Hansen et al 1982; Noakes and Carter 1982).

In conclusion, factors likely to have been involved with the above 2 cases of renal tubular impairment, one mild and the other potentially more serious were: (i) an inadequate fluid intake by subject A during her race; (ii) inadequate preparation by subject AI and (iii) the fact that both runners were participating in ultramarathons run over hilly, undulating courses where the dangers of muscle damage are greater and the average environmental temperature is usually higher than over a standard marathon.

Finally, it should be noted that both these runners were participating in studies of the normal physiological response to marathon running. Without these investigations, and presumably as long as Runner A had been given fluids, neither case would have been reported. Thus a total of 2 out of 27 runners where renal $beta_2$-microglobulin clearance was measured developed temporary renal tubular dysfunction. Whether this is an unusually high percentage and its consequent relevance requires investigation.

CHAPTER VII

CRYSTALLURIA AND URINARY STONE FORMATION IN LONG-DISTANCE RUNNERS

7.1. INTRODUCTION

For many centuries the passage of "gravel in the urine" has been associated with renal stone formation (Robertson et al 1969). Hippocrates himself observed the relationship between the passage of "sand" in the urine and kidney or bladder stones (Butt 1956).

Modern studies have shown that there is a quantitative and qualitative difference in the crystalluria of recurrent idiopathic stone formers and their controls under the same conditions of dietary and fluid intake (Robertson et al 1969; Robertson and Peacock 1972). In particular, it has been found that the crystals secreted by the controls were small (3-4 um in diameter) and belonged to a unimodal distribution. In contrast, those secreted by the stone formers belong to a distribution which contains, in addition to the 3-4 um peak, a second peak of much larger particles (20-40 um in diameter). These particles were identified as calcium oxalate dihydrate (COD) crystals and were often found to occur in aggregates of up to 200 um in diameter (Robertson et al 1969).

A survey of entrants in the 1977 New York City Marathon (Milvy et al 1981) found that the incidence of urinary stone formation in these runners was 4.5 times greater than in the matched, non-running, control population. In an attempt to gain insight into this phenomenon, the nature of the calcium crystalluria found in 2 groups of marathon runners was characterized before and after 2 marathons: the 1984 42.2 km Kellerprinz Marathon and the 1985 90 km Comrades marathon.

Furthermore, to establish the effect of long-term storage of urine on particle volume-size analysis, frozen urine samples from the two runners who took part in the 1983 210 km relay race were examined for particle size and number. In addition, urine samples from controls were analyzed at 27^{o}C, 37^{o}C, 47^{o}C and again after freezing for three weeks.

7.2. METHODS AND MATERIALS

7.2.1. CONTROLS

The controls were 15 randomly chosen healthy male members of staff of the School of Chemical Sciences, University of Cape Town. Subjects were aged between 21 and 54 years.

Nocturnal urine specimens (the first voided urine after waking) were collected from control subjects in pre-heated thermos flasks and were analyzed at 37°C within a few hours of voiding. Analyses were repeated at 27°C and 47°C for samples from three controls so that the effect of temperature on the particle size distribution could be examined. To establish the effect of long-term storage, the urine from the 3 controls was refrigerated at -10°C for approximately three weeks after which the analyses were repeated. In these cases, the frozen samples were slowly brought up to temperature and were allowed to equilibrate at 37°C for several hours before particle size counting was commenced.

7.2.2. THE 1984 42.2 KM KELLERPRINZ MARATHON

7.2.2.1. Subjects

The subjects were 7 athletes aged between 22 and 40 years (Table 7.1.), who had previously completed at least 3 marathons. None had a history of urinary stone disease, unusual diet or excess Vitamin C intake.

7.2.2.2. Testing protocol

Nocturnal urine samples from the marathon runners were obtained 2 days before the marathon and immediately on completion of the course. Post-race samples were collected on days 1, 3, 5 and 10 following the marathon. In all cases the urine was collected in pre-heated thermos flasks and subjected to particle counting at 37^{o}C within 3 hours of voiding.

The following analyses were performed on the urine samples, and are described in Chapter 2.

(i) Urine particle number and size distribution were measured using a Model TA II Coulter Counter with Population Accessory unit.

(ii) Urine samples from Day +10 after the 1984 42.2 km Kellerprinz marathon were subjected to selective complexation with EDTA to determine the calcium crystals present (Robertson 1969).

(iii) Deposited crystals were examined using a scanning electron microscope, and

(iv) Deposited crystals and debris from some of the centrifuged samples were analyzed for the presence of different urinary components using X-ray powder diffraction.

The mean dry bulb temperature for the race was 18.4^{o}C (Range 15.8-20.8^{o}C), while the mean humidity was 80% (Range 64-94%).

7.2.3. THE 1985 90 KM COMRADES MARATHON

7.2.3.1. Subjects

The personal details of the runners who took part in this study are given in Table 7.2. All were experienced runners and none had a history of urinary stone disease, unusual diet or excess vitamin C intake.

7.2.3.2. Testing protocol

Nocturnal urine samples were collected in pre-heated thermos flasks on days -10, -7 and -3 prior to the 1985 90 km Comrades marathon and on days +4 and +11 after the race. Analysis of the urine samples was performed as in the previous study. The mean dry bulb temperature for the race was 18.0°C (Range 15.9-19.6°C), while the mean humidity was 57% (Range 42-81%).

7.2.4. THE 1983 201 KM RELAY RACE

The subjects and protocol for this study have been previously discussed (Chapter 3). The urine samples had been stored frozen for approximately one year. They were slowly warmed and then allowed to equilibrate at 37°C. Particle size distribution analysis was conducted as in the previous studies.

7.3. **RESULTS**

7.3.1. PARTICLE VOLUME-SIZE ANALYSIS

Volume-size distribution curves were obtained for all controls and all marathon runners by plotting V_d against d where V_d is the volume of the crystals of diameter d (um). The 15 controls all displayed a major peak in the 3-10 um diameter range while peaks of a very minor nature in the 15-30um diameter range were observed in several of the samples. The mean volume-size distribution curve for the control urine samples at 37°C is shown in Figure 7.1.

The particle volume-size distribution curves for the urines from both groups of marathon runners all displayed a major peak in the 2-5 um diameter range as well as a second peak of significant magnitude in the 15-40 um diameter range (Figures 7.1.-7.3.). This second peak is not as sharp and is spread over the 15-32 um diameter range in the samples from the 42.2 km runners, with maxima around the 20 um range (Figure 7.1.). The bimodal distribution was found both before and after the marathon.

The distribution curves for the urines from the runners who took part in the 90 km marathon show that the second peak is spread over a wider diameter range (15-40 um) in the pre-race urines and over the 18-32 um in the post-race samples.

Maxima are attained at diameters of 32 and 25 um respectively (Figures 7.2. and 7.3.) A histogram of the mean percentage total volume of the larger particles on the various days of the experiment compared to controls is shown in Figures 7.4. The histogram in Figure 7.5. shows the percentage volumes of the differently sized particles in the urines obtained on day +10 after the 42.2 km marathon and the fraction of these which are due to calcium particles (shaded area). Calcium crystals constitute 28% of all the particles in the small diameter range (0-12 um) and 34% of those in the larger range (12-40 um). When only calcium crystals are considered, it is found that 50.4 $\pm$ 8.4% occur in the larger diameter range.

7.3.2. X-RAY POWDER DIFFRACTION

Crystals isolated from the randomly selected urines of six of the 42.2. km marathon runners and one control were subjected to X-ray powder diffraction analysis. The presence of calcium oxalate dihydrate (COD) was established in all 7 samples. In addition, calcium oxalate monohydrate (COM) was identified as a minor component in 4 of the runners' urines. Significant amounts of brushite were found in the control urine as well as in 2 of the runners' samples. Uric acid dihydrate was identified as a very minor component in 3 of the marathon runners' urines.

7.3.3. SCANNING ELECTRON MICROSCOPY AND ENERGY DISPERSIVE X-RAY ANALYSIS

7.3.3.1. Controls

COD crystals, less than 10 um in cross section, were commonly observed in the control urines (Figure 7.6.) while COM (Figure 7.7.) was rare.

7.3.3.2. 42.2 km Marathon Runners

In the marathon runners' urines, much larger COD crystals occurred. These were typically 15-20 um in cross section (Figure 7.8.) although larger ones were often observed (Figure 7.9.). Frequently, 2 or more crystals were found fused together, yielding a "particle" measuring over 40 um in cross section (Figure 7.10.). Rod and plate-like crystals of brushite occurred as randomly deposited entities (Figure 7.11.) and as rosette-like aggregates (Figure 7.12.) of cross section 20-30 um. The presence of calcium and phosphorus in such deposits was confirmed by energy-dispersive X-ray analysis (Figure 7.13.). Another common observation during scanning electron microscope examination of the marathon runners' urinary deposits was that of large globular and irregular particles rich in potassium, chloride, sulphur, phosphorus and sodium as shown in Figures 7.14 and 7.15. respectively.

7.3.3.3. 90 km Marathon Runners

In contrast, very few recognizable crystals were observed in the pre- and post-race urines from the runners who ran 90km. There were occasional large calcium oxalate dihydrate crystals (Figure 7.16.) but these were rare. However deposits of epithelial debris or urinary salts of various morphologies, or both, were common (Figures 7.17.-7.19.). They generally contained only sodium, sulphur and potassium but phosphorus and chloride were also present on occasions.

7.3.4. PARTICLE VOLUME-SIZE ANALYSIS OF URINE SAMPLES FROM THE 1983 201 MILE 24 HOURS RELAY RACE

Previously frozen urine samples from the two runners who took part in the 1983 201 km relay race were also examined for particle volume-size distribution. Volume-size distribution curves for the various days of the study are shown in Figure 7.21. The distribution curves vary considerably but include a large percentage of particles in the diameter range 12-40 um; that is 67.3 $\pm$ 0.4%, 28.2 $\pm$ 19.3%, 50.2 $\pm$ 12.6% and 31.8 $\pm$ 10.3% on the 2 pre-race days, the race day and on days + 1 and + 2 respectively (Figure 7.21.).

7.3.5. THE EFFECT OF FREEZING AND TEMPERATURE CHANGE ON PARTICLE SIZE IN THE THREE CONTROL URINES

The effect of temperature on the distribution curves was studied by repeating analyses for 3 controls at 27°C and 47°C and after freezing at -10°C for 3 weeks. The particle distribution curves (Figure 7.22) shows that whereas initial freezing reduces the number of smaller diameter particles in all the experiments, there is an increase in the number of the larger diameter particles when compared with freshly voided urine analyzed at 37°C. However, only after freezing was this increase significant (Figure 7.23.)

Table 7.1. SUBJECT DETAILS: THE 1984 42.2 KM KELLERPRINZ MARATHON

Subject	Age (yrs)	Height (cm)	Pre-race Weight (kg)	Distance Run per Week (km)	Personal Marathon Record (hrs:min)	Time Recorded (hrs:min)
BM	38	175	70.0	160	2:22	2:29
RR	30	178	78.9	90	3:01	3:01
GI	35	177	75.4	40	2:47	3:05
GG	22	190	75.5	120	2:57	3:24
RvZ-S	40	180	69.0	25	3:05	3:45
AI	40	176	73.0	20	3:24	3:49
TN	35	185	83.0	50	2:50	3:58
MEAN	34	181	75.0	72.1	2:55	3:22
SEM	±2.0	±2.0	±1.9	±20.0	±0:07	±0:12

Table 7.2. SUBJECT DETAILS: THE 1985 90KM COMRADES MARATHON

Subject	Age (yrs)	Height (cm)	Pre-race Weight (kg)	Distance Run per Week (km)	Personal Marathon Record (hrs:min)
GD	30	179	71.0	160	2:26
GG	22	190	76.5	120	2:57
RR	31	178	79.0	100	3:01
MC	25	187	81.0	80	2:45
GI	36	177	74.0	80	2:47
DS	24	172	66.5	110	2:56
BM	39	175	68.0	160	2:22
JH-Z	42	186	74.2	120	3:10
MEAN	31	180.5	73.8	116	2:48
SEM	±2.6	±2.3	±1.8	±11	±0.1

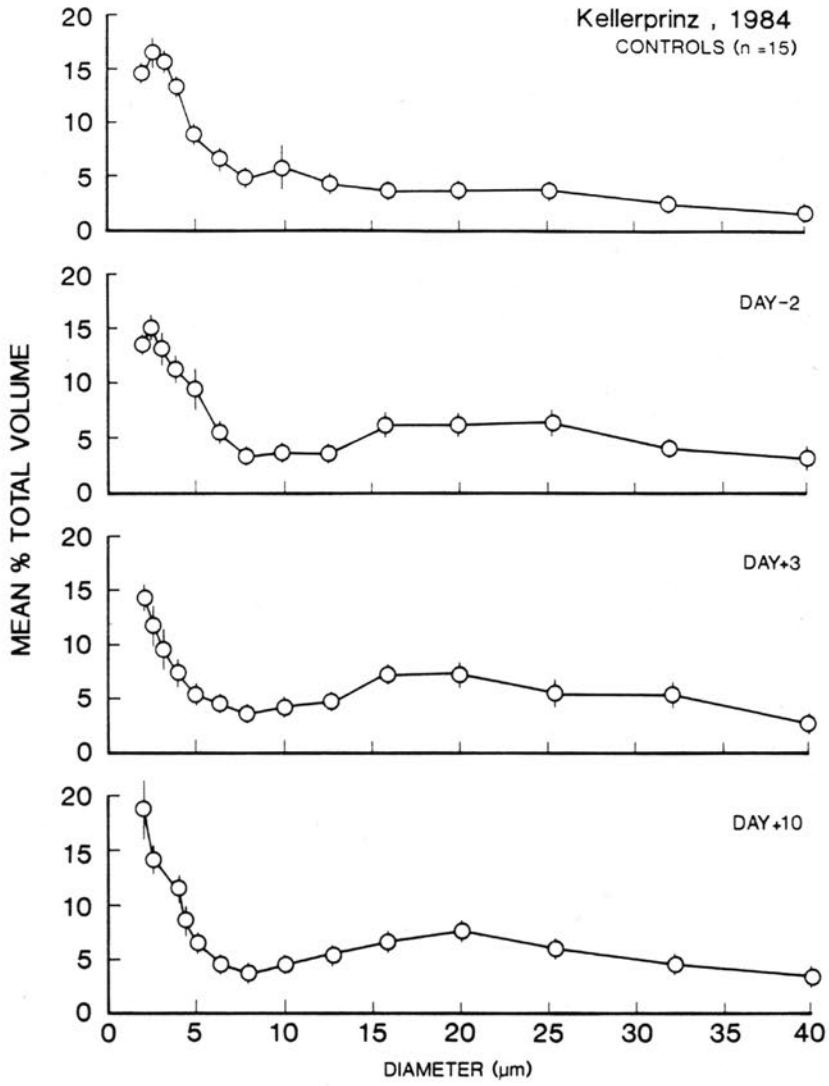

Figure 7.1. Mean volume-size distribution curves (± SEM) for 15 control urines and 7 marathon runners urines on Day -2 and Days +3 and +10 of the 1984 42.2 km Kellerprinz marathon.

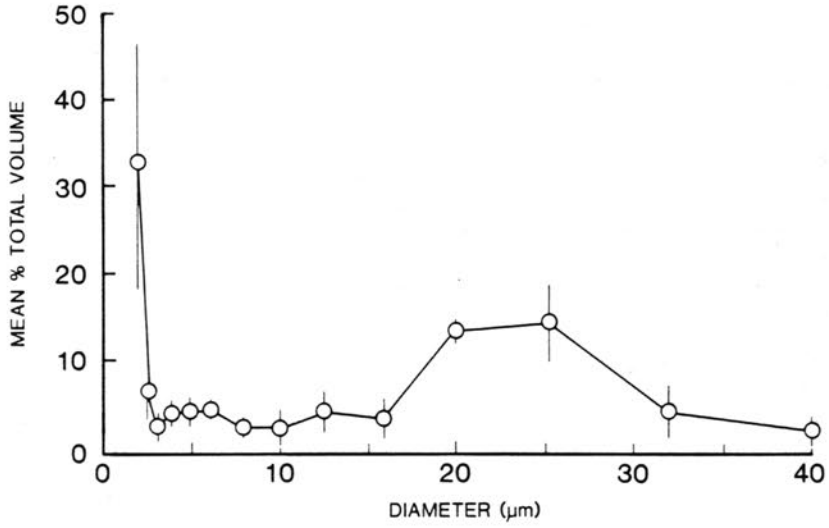

Figure 7.2. Mean volume-size distribution curve (± SEM) for the 7 runners' urine prior to the 1985 90 km Comrades marathon (the mean of Days -10, -7, -3).

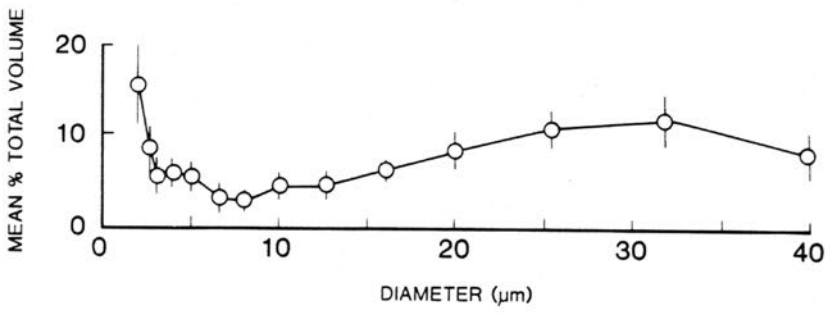

Figure 7.3. Mean volume-size distribution curve (± SEM) for 7 runners urines on Day +11 after the 1985 90 km Comrades marathon.

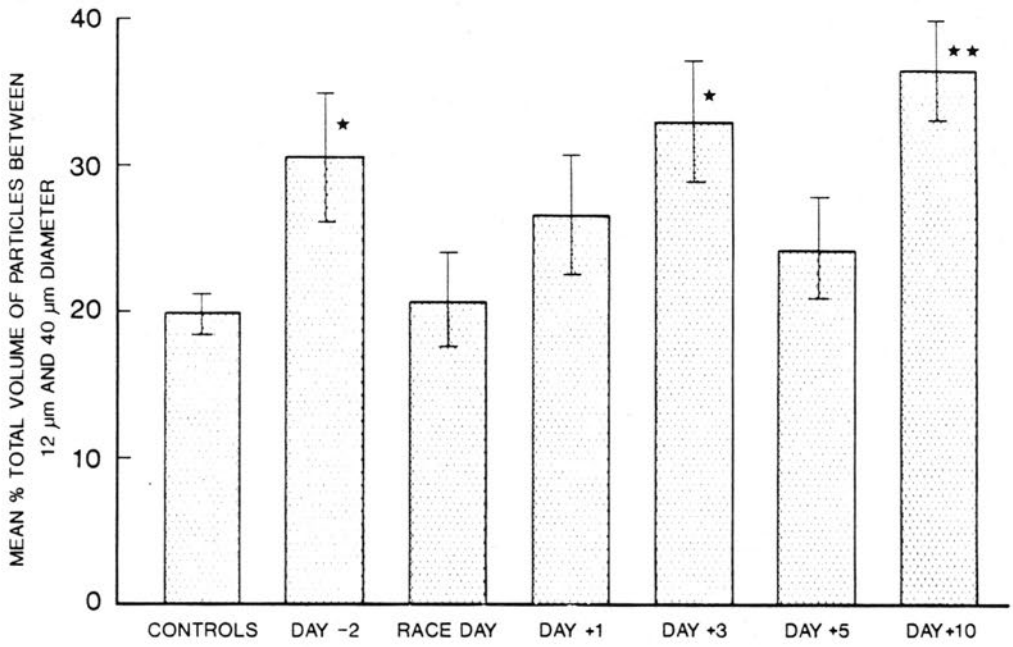

Figure 7.4. Histogram of the mean percentage total volume (± SEM) of the particles in the diameter range 12-40 um for the 42.2 km marathon runners on the various days of the experiment.

* p = < 0.05 compared to the control groups

* * p = < 0.01 compared to the control groups

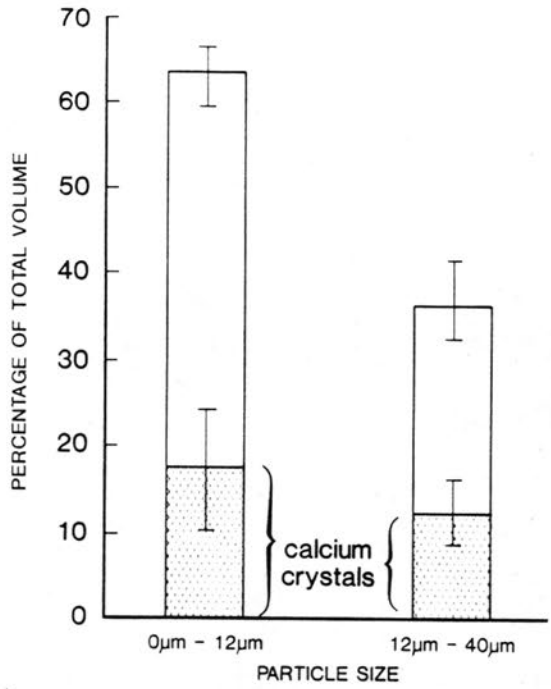

Figure 7.5. Histogram of the mean percentage total volume (± SEM) of all particles in the diameter ranges 0-12 um and 12-40 um in the urine from the 42.2 km marathon runners (Day +10). The shaded areas represent calcium particles.

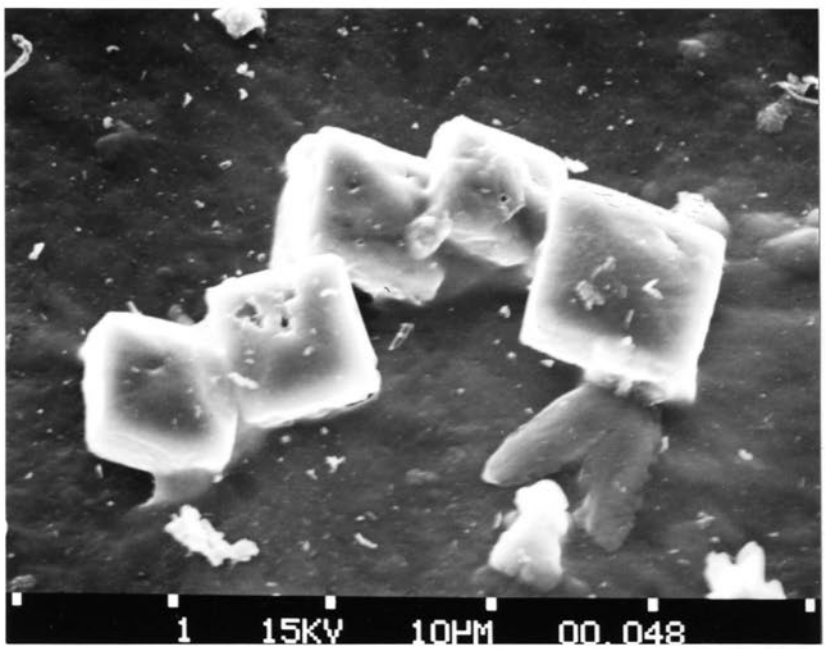

Figure 7.6. Five COD crystals, typical of those observed in the control urines (Note the cross-section dimensions are < 10 um).

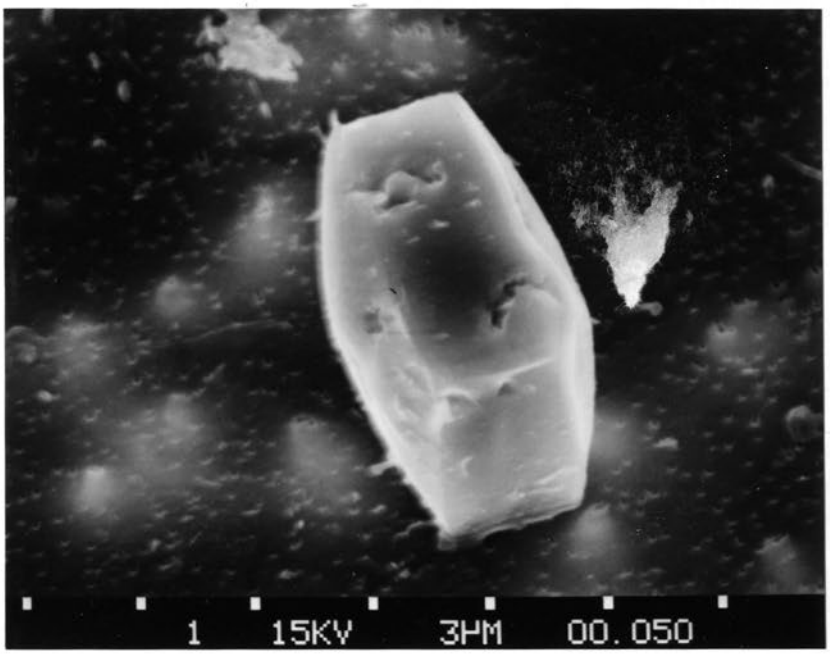

Figure 7.7. COM crystal occasionally observed in the control urines (Note the cross-section < 10 um).

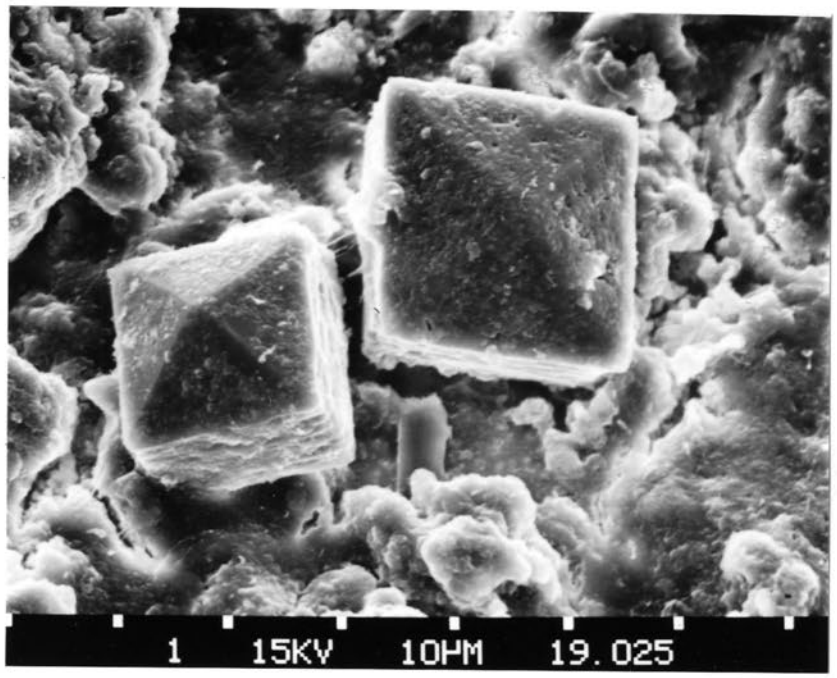

Figure 7.8. COD crystals typical of those observed in the 42.2 km marathon runners' urine (Note the cross-section 15-20 um).

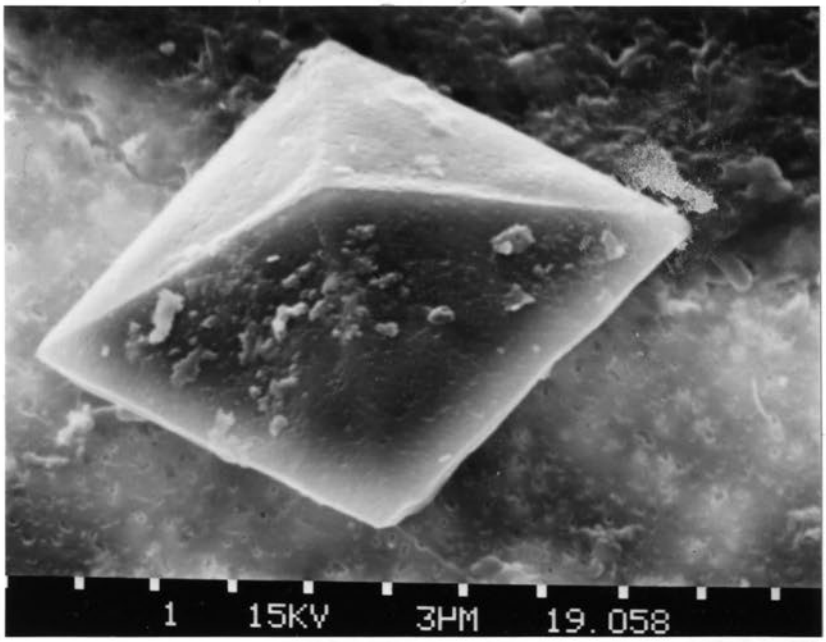

Figure 7.9. Large COD crystal (cross-section > 25 um) commonly observed in the 42.2 km marathon runners' urine.

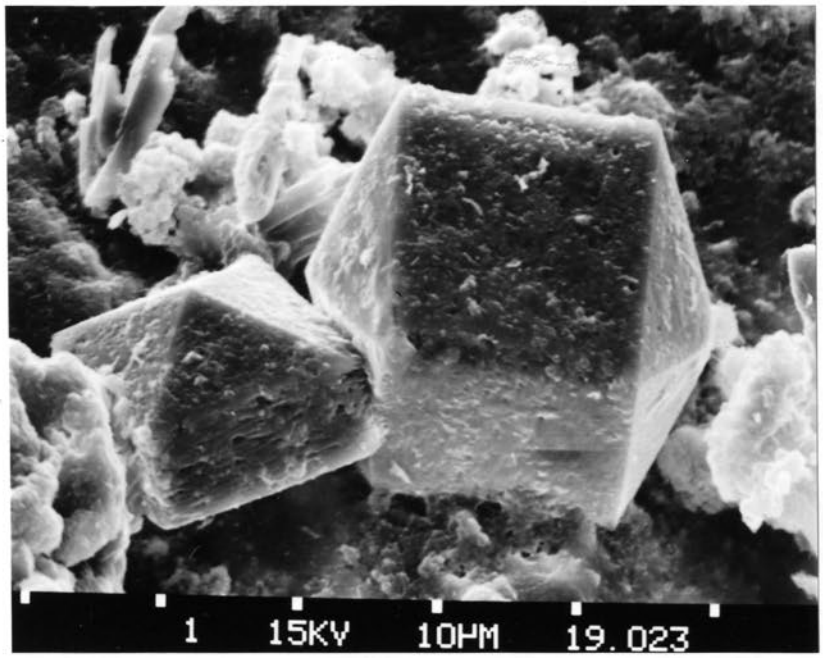

Figure 7.10 Two large COD crystals fused together yielding a 'particle' with a cross-section > 40 um.

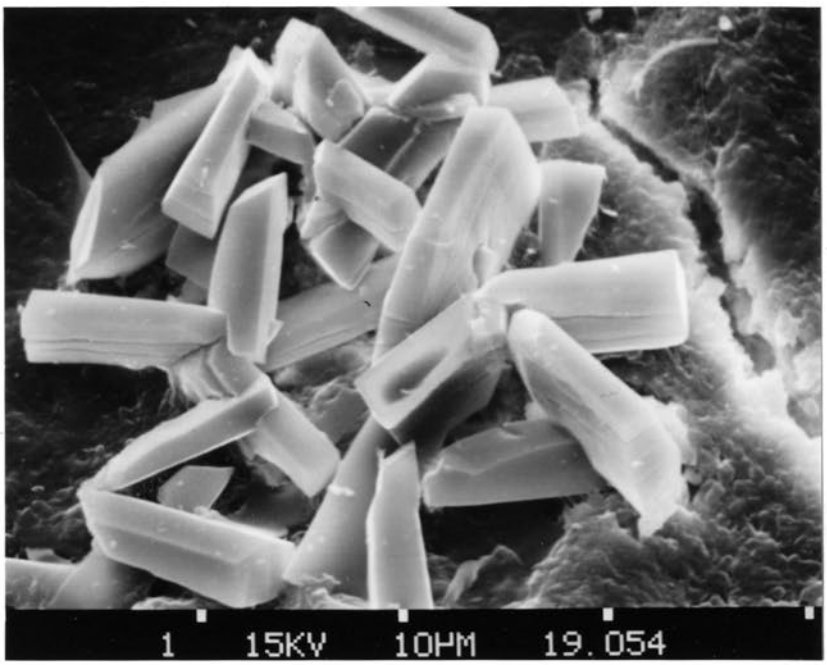

Figure 7.11. Random deposits of brushite crystals observed in some of the 42.2 km marathon runners' urines.

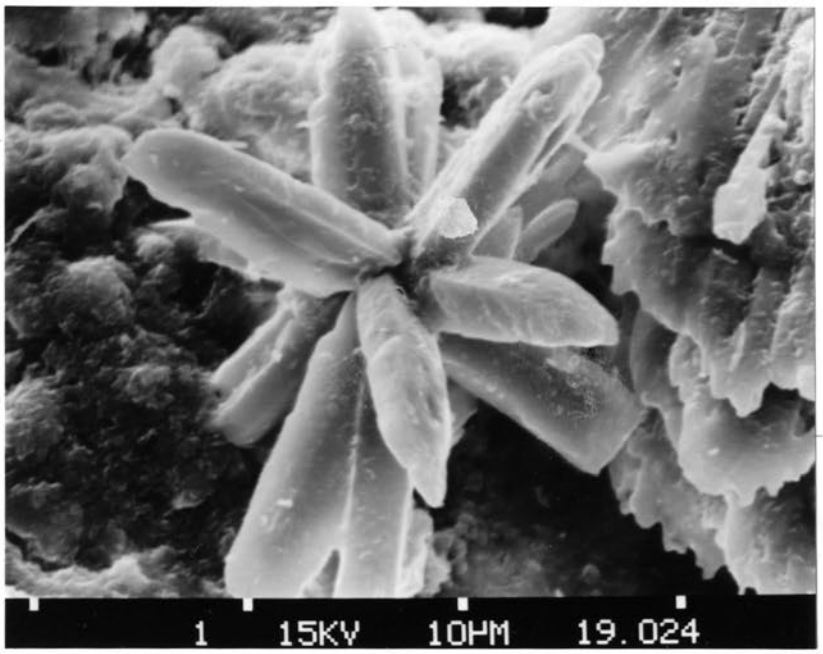

Figure 7.12. Rosette-like aggregates of brushite crystals (cross-section > 20 um).

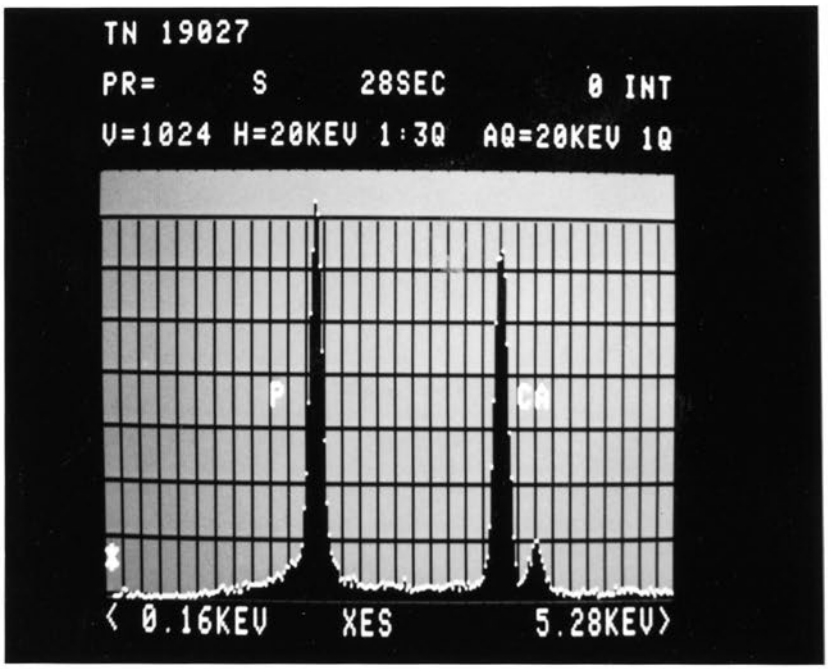

Figure 7.13. Energy-dispersive X-ray analysis spectrum recorded for the deposits shown in Figure 7.12.. The presence of calcium and phosphorus is clearly indicated.

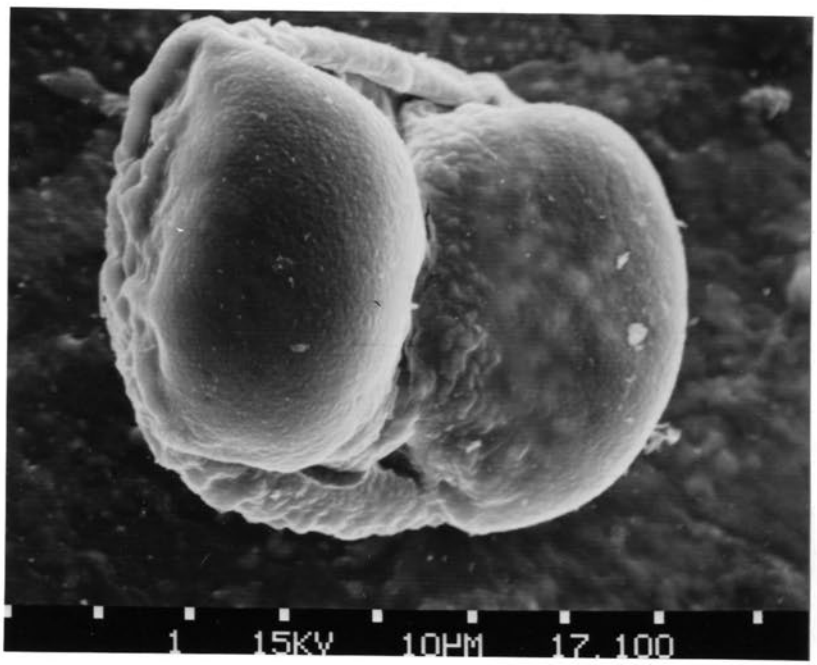

Figure 7.14. Large globular deposit (cross-section - 60 um) frequently observed in the marathon runners' urines (elemental composition potassium, chloride, sulphur, phosphorus and sodium).

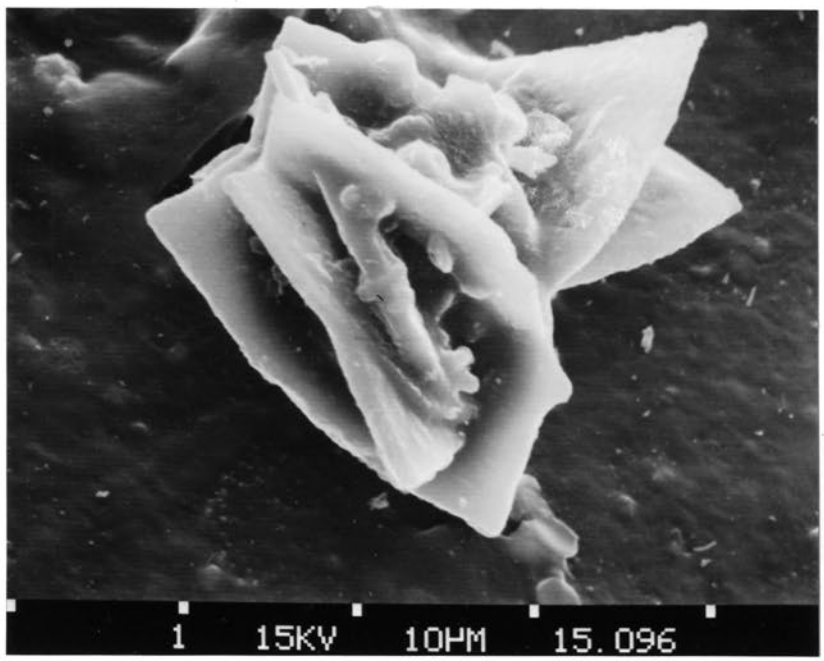

Figure 7.15. Large irregular deposit (cross-section approximately 30 um) frequently observed in the 42.2 km marathon runners' urines (elemental composition calcium, potassium, chloride, sulphur, phosphorus and sodium).

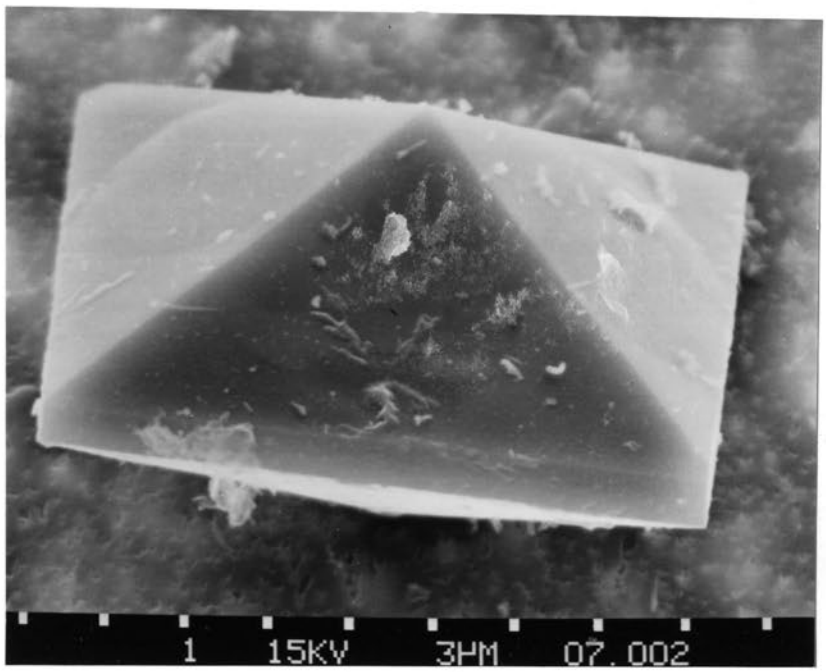

Figure 7.16. Large COD crystal occasionally observed in pre- and post-race urine specimens for the 90 km marathon runners (note cross-section 25 um).

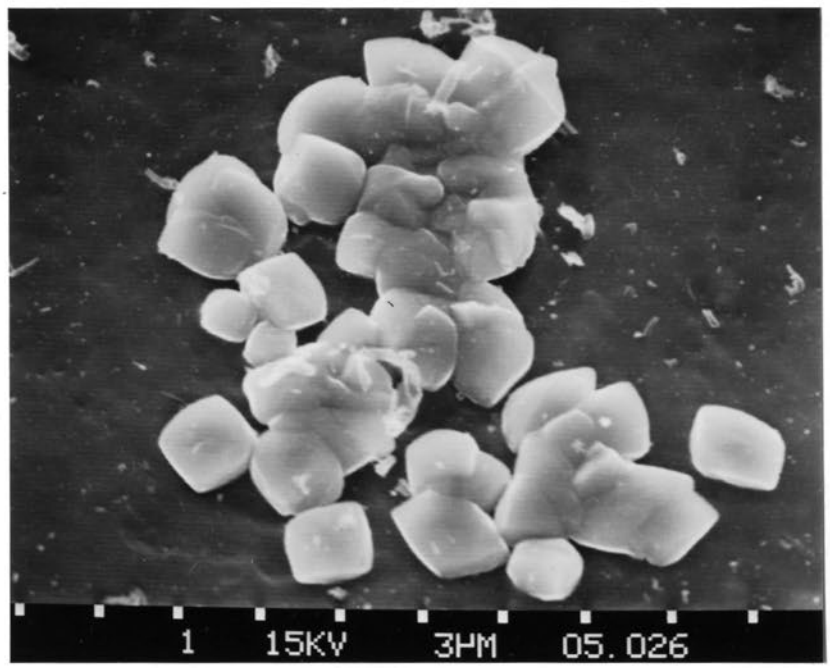

Figure 7.17. Urinary salt deposits observed in the 90 km runners' urine samples; elemental composition sodium, sulphur, potassium and chloride. Note small cross-section - 3 um.

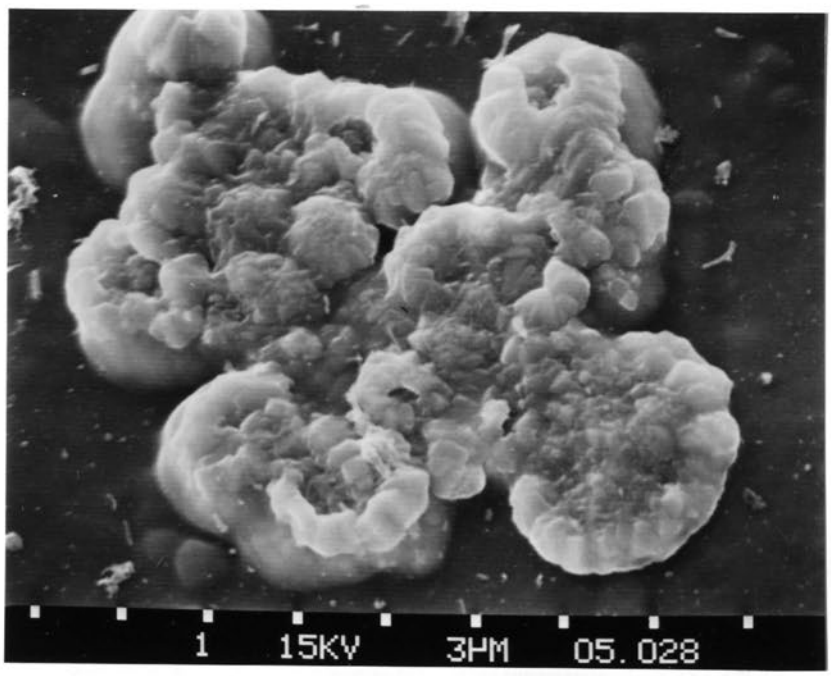

Figure 7.18. Urinary salt deposits and/or epithelial debris typically observed in 90 km marathon runners' urine samples; elemental composition sodium, sulphur and potassium.

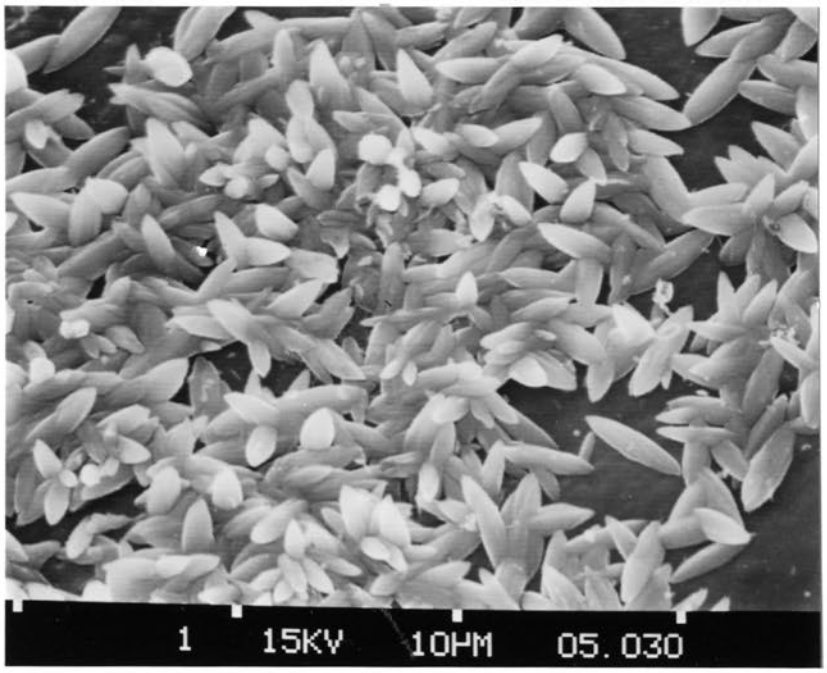

Figure 7.19. Urinary salt deposits typically observed in 90 km runners' urine samples; elemental composition sodium, sulphur, potassium (note small size of individual entities - 5um).

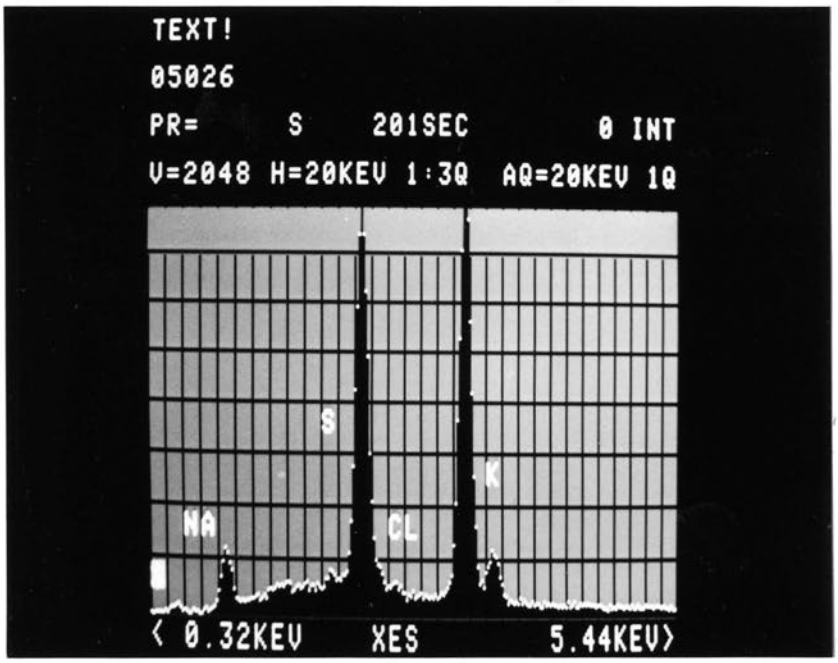

Figure 7.20. Energy dispersive X-ray analysis spectrum recorded for the deposits shown in Figure 7.18.

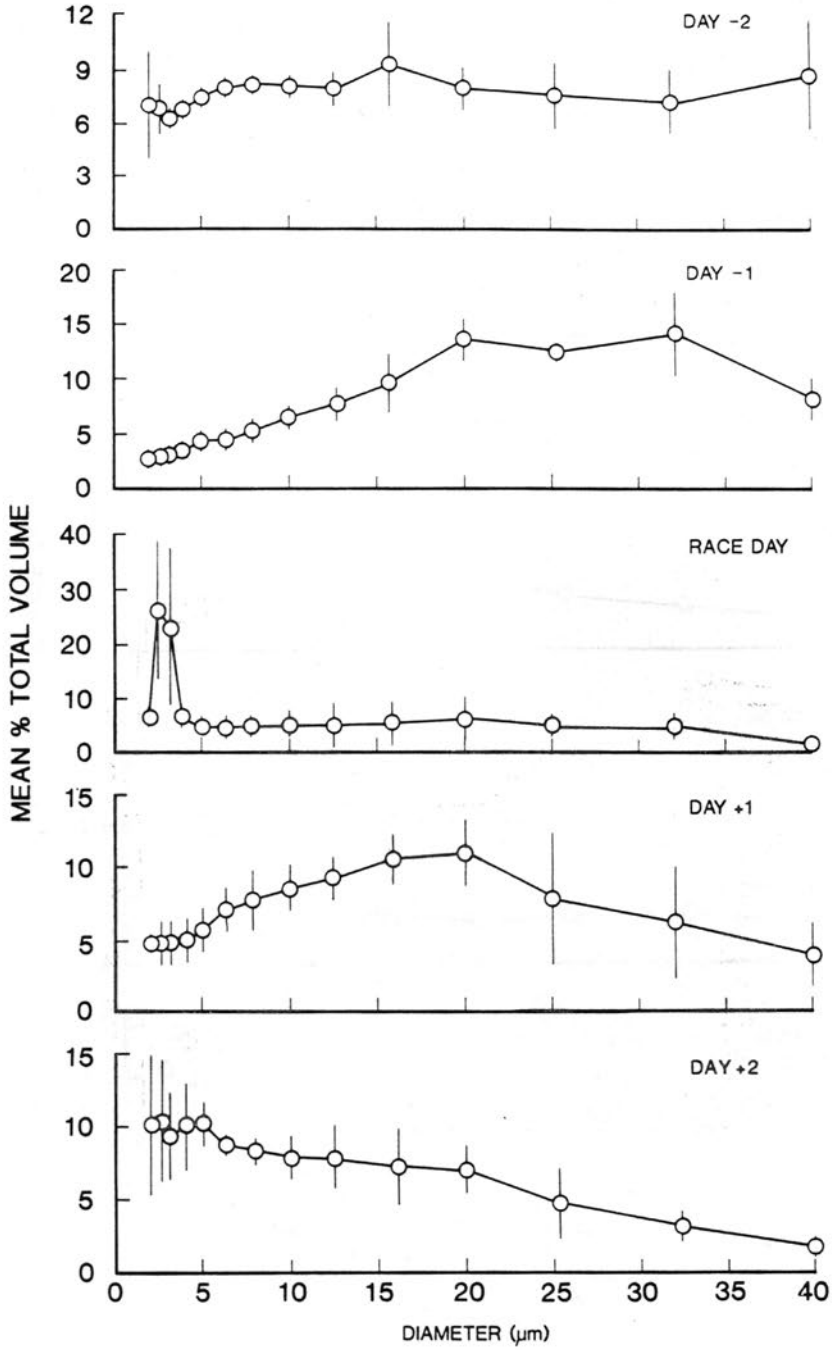

Figure 7.21. Mean volume-size distribution curve (± SEM) for 2 athletes urines before and after the 1983 24 hours relay race. The particle measuring was performed on urine samples which had been stored frozen and were then slowly warmed and allowed to equilibrate at 37°C before particle counting commenced.

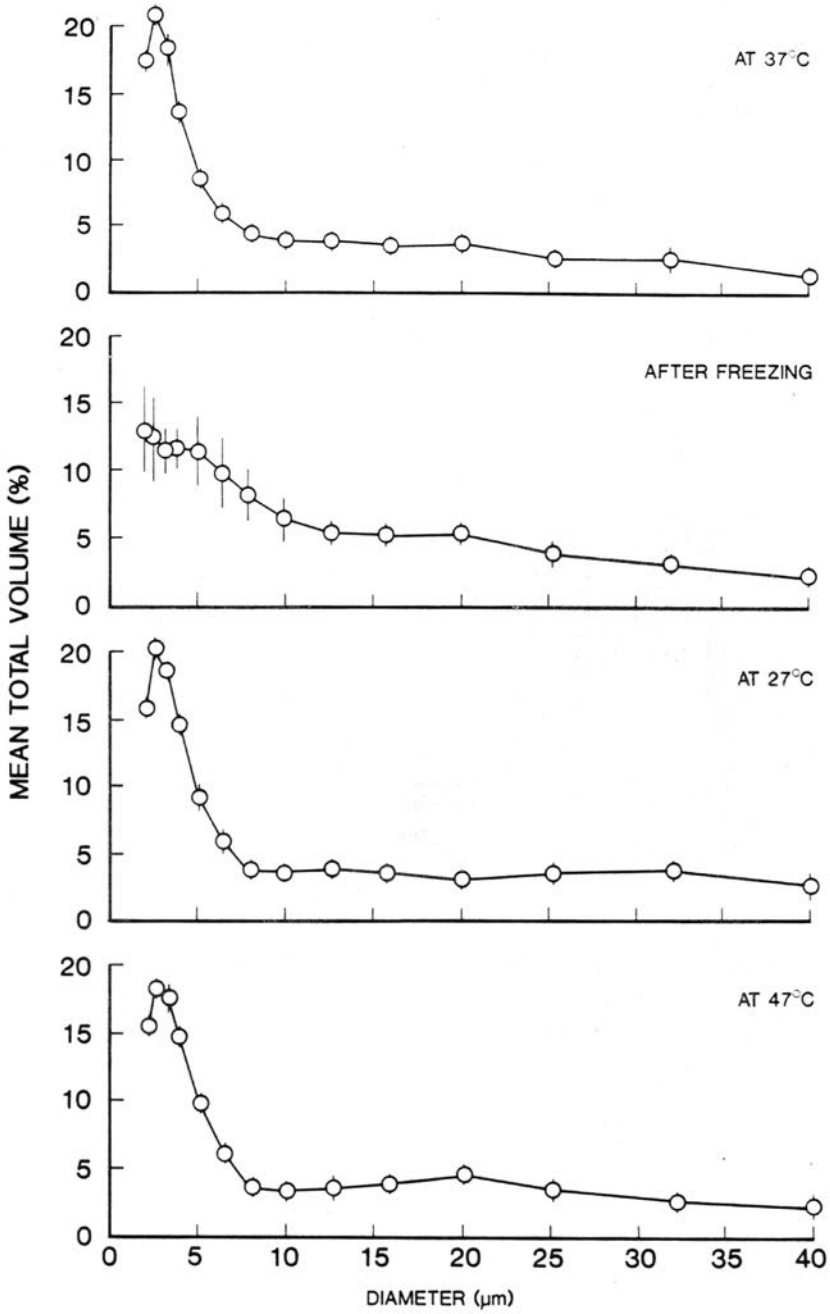

Figure 7.22. Mean volume-size distribution curves for 3 control urines analyzed at 37° C within a few hours of voiding, at 27oC and 47°C and again after freezing at -10°C for approximately 3 weeks. Before particle counting was commenced the frozen samples were slowly warmed and allowed to equilibrate at 37°C.

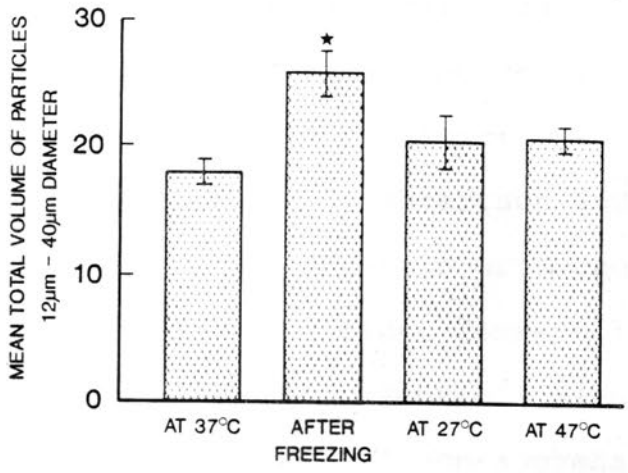

Figure 7.23. Histogram of the mean percentage total volume (± SEM) of particles in the diameter range 12-40 um for the 3 control urines whose volume-size distribution curves are shown in Figure 7.22, at 37°C, 27°C and 47°C and after being stored frozen.

* p = < 0.05 compared with 37°C

7.4. DISCUSSION

7.4.1. CRYSTALLURIA AND RENAL STONE DISEASE

Crystalluria is considered a feature of renal stone disease (Robertson et al 1969) and several studies have shown that there are qualitative and quantitative differences between the crystalluria of recurrent calcium oxalate stone formers and controls (Finlayson 1977; Robertson and Peacock 1972; Werness et al 1981). The crystals produced by controls are small (5 um) while those of stone formers include crystals in the 25 um diameter range. Controls also produce calcium oxalate crystals in the form of non-aggregated monohydrate particles (Robertson et al 1969), while stone formers produce, in addition, large dihydrate crystals which can be present in the form of aggregates of up to 200 um in diameter (Robertson et al 1969).

The particle volume-size distribution profiles for the urines from the control subjects agree with those reported by Robertson and Peacock (1972) in that they are unimodal with the major peak occurring in the small (< 10 um) diameter range (Figure 7.1.).

7.4.2. CRYSTALLURIA AND MARATHON RUNNERS

The particle volume-size distribution profile for urines from marathon runners, both before and after the race, are distinctly different from controls (Figures 7.1.-7.5.). There are 2 peaks, one in the 2-5 um diameter range and a second in the 15-40 um range. This bears a remarkable resemblance to the bimodal distribution reported by Robertson and Peacock (1972) for recurrent idiopathic stone formers.

The identification by X-ray powder diffraction that the crystalline particles in the marathon runners' urines comprise predominantly calcium oxalate dihydrate, with only trace amounts of calcium oxalate monohydrate, also mimics the crystalluric characteristics of the typical stone former (Robertson and Peacock 1972). Yet another feature of the marathon runners' urines which closely resembles that of the typical stone former is crystal aggregation (Hallson and Rose 1976; Robertson et al 1969), which was frequently observed (Figures 7.10. and 7.12.).

It must be remembered that the Coulter Counter does not distinguish between crystalline and non-crystalline material and the "particles" counted could be epithelial debris which have sloughed off during marathon running. Deposits which may be examples of this debris are shown in Figures 7.14.,

7.15. and 7.18. However, particle sizes measured by the scanning electron microscope showed good agreement with the Coulter Counter determinations of calcium oxalate dihydrate crystals as seen in Figures 7.7.-7.11.

In addition, the studies using the complexing agent EDTA with urine samples from Day +10 after the 42.2 km marathon clearly show that a large proportion of the particles present are calcium crystals (34% of these in the larger range (12-40 um) (Figure 7.5.). Our results show that 50.4 $\pm$ 8.4% of the calcium particles are larger than the 12 um threshold value suggested by Robertson and Peacock (1972). Percentages reported for the stone formers lie between 5 and 40% (Robertson and Peacock 1972). This highlights the similarities of the crystalluria found in marathon runners and in renal stone formers.

The bimodal particle size distribution characteristic of the recurrent stone former is observed in the marathon runners' urines both before and after participation in the marathon. This could possibly be because the period immediately preceding a marathon represents the climax of a strenuous and rigorous training schedule during which the above effects of crystal growth and epithelial sloughing could occur.

7.4.3. RENAL STONE FORMATION

There are 3 popular theories of the pathogenesis of stone formation (Pak 1981). Firstly, the precipitation-crystallization theory (Vermeulen and Lyon 1968) proposes that there is a precipitation of salts from a supersaturated urine. Secondly, the matrix theory (Boyce 1968; Malek and Boyce 1977), postulates that crystallization occurs within an organic framework. Thirdly, the inhibitor theory (Fleisch and Bisaz 1964; Howard et al 1967) holds that the absence of inhibitors in the urine leads to stone formation.

Running causes an increase in urine cellular debris (Blacklock 1977; Boileau et al 1980; Dancaster and Whereat 1971) and by providing an organic matrix for crystal deposition (Boyce 1968) could be a factor in the occurence of stones in marathon runners.

A further factor could be dehydration and low urine volume which are risk factors for stone formation in the non-athletic population (Robertson et al 1980). In Chapter 3, however, we have shown that a reduced urine output does not occur as frequently as has previously been believed (Figures 3.1.-3.5.). The presence of various urinary salts (Figures 7.18.-7.20.) is a commonly observed feature of the urine of marathon runners who ran 90 km. There were however few low-solubility urine crystals such as calcium oxalate dihydrate,

and this is unlikely to indicate dehydration. When present the COD crystals (Figure 7.16.) were similar dimensions to those seen in the urine from the runners who ran 42.2 km (Figures 7.6., 7.8, 7.9.).

Renal stone disease can be further classified either as fixed particle disease in which large particles become trapped or as free particle disease in which crystalluric particles are unattached but are prevented by their size from passing through the urinary tract (Finlayson 1974). The fixed particle theory is the more likely as crystal growth rates are probably too low to produce free particle stone disease (Finlayson and Reid 1978).

The sloughing of debris from epithelial walls during marathon running could well produce sites at which calcium oxalate and other crystal particles may become attached and trapped for sufficient time to produce crystal growth particularly if associated with low urine outputs. Because of their smaller size, urinary salts are more likely to pass through the urinary tract unhindered. This is a possible explanation for the presence of urinary salts in the urines from the 90 km marathon runners (Figures 7.17-7.19).

7.4.4. THE EFFECT OF STORAGE ON PARTICLE SIZE

The particle volume-size distribution profiles for the 201 mile relay runners' urines show a high percentage of large particles (Figure 7.21). However these data were obtained from the urine samples which were stored frozen for some months and the profiles have similarities to the distribution profiles obtained from frozen control urines (Figure 7.22.), particularly in the decreased number of smaller particles. It is likely that much of the increase in particle size is due to freezing rather than the marathon race.

It is interesting to note that other workers studying short term storage effects of urine samples at various temperatures showed that no change in mean crystal size occurred in 44% of the specimens (Elliot and Rabinowitz 1980), decreases in mean crystal size occurred in 30% while small increases were registered in the remainder. This is in contrast to our findings (Figures 7.22. and 7.23) which indicate that particle counting should be conducted at 37^{o}C, within a few hours of sample collection and that previously frozen samples should not be used.

The present study shows that marathon runners are at risk for renal stone disease. Possible risk factors are: increased cellular debris which could provide an organic

matrix for crystal deposition and the sloughing of debris from epithelial walls which could provide sites for crystal growth. Dehydration and reduced urine flow are also potential risk factors in marathon runners, although we have previously shown that this is not as frequent a finding as previously believed.

CHAPTER VIII

EVALUATION OF RENAL FUNCTION AND FLUID HOMEOSTASIS DURING RECOVERY FROM EXERCISE INDUCED HYPONATRAEMIA

8.1. INTRODUCTION

Symptomatic hyponatraemia of exercise (serum sodium concentrations < 130 mmol/L) was first reported in 2 athletes who competed in the 1981 90 km Comrades marathon (Noakes et al 1985). Subsequently Godlonton (1985) reported that 9 out of 12 runners who were admitted to hospital after the 1985 90km Comrades Marathon were hyponatraemic. Additional cases have since been reported from North America after marathon running (Nelson et al 1988; Young et al 1987), and ultramarathon races (Frizzel et al 1986; Lind 1988) and after ultratriathlons (Hiller et al 1985, 1986; Novak 1988; O'Toole 1988).

Although this condition is uncommon, and may be present in less than 0.3% of competitors in the Comrades Marathon (Noakes et al 1990), the incidence would seem to be increasing (Frizzel et al 1986). A frequency of 1.5% has been reported in competitors in the Canadian Ironman triathlon (Novak 1988).

The importance of this condition is that it is potentially fatal with grand mal seizures, respiratory failure, pulmonary oedema, coma and profoundly raised intracranial pressure having been reported (Frizzel et al 1986; Laird 1988; Nelson et al 1988; Noakes et al 1985; Young et al 1987). One authority has stated that hyponatraemia has become the greatest risk factor to the health of competitors in prolonged endurance events (Noakes et al 1990).

In spite of the seriousness of this conditon, the pathogenesis is not yet established and its treatment and prevention remains largely empirical. One postulate is that the hyponatraemia of exercise is caused by large sweat sodium chloride losses which are not replaced by athletes who ingest only sodium-free, hypotonic solutions during exercise (Hiller et al 1986; 1987; Hiller 1988; Laird 1988; Lind 1988; O'Toole 1988). Accordingly, this form of hyponatraemia would be associated with either a reduced or a normal extracellular fluid volume.

Others (Frizzel et al 1986; Nelson et al 1988; Noakes et al 1985, 1990; Young et al 1987) have proposed that this condition results from fluid retention in athletes who ingest excessive fluid volumes during prolonged exercise. It has also been suggested that elevated ADH secretion induced by exercise may lead to excessive free water retention in these athletes, leading to hyponatraemia and

hypotonicity (Nelson et al 1988). This proposal does not explain why counter-regulatory mechanisms fail to prevent the development of hyponatraemia.

The most accurate method for determining the pathogenesis of this condition would be to study renal function and fluid and electrolyte balance in athletes as they develop hyponatraemia during prolonged exercise. Yet the extreme infrequency of the condition (less than 60 of 20 000 ultramarathon runners in one study - (Noakes et al 1990)) negates this approach.

Accordingly we chose the more practical approach in which renal function and fluid and electrolyte balance were studied during recovery in eight runners who developed hyponatraemia during and after the 1988 88 km Comrades Marathon footrace, the event in which the condition was first described (Noakes et al 1985). We reasoned that a study of these parameters during recovery would establish which of the competing hypotheses correctly explained the pathogenesis of this condition. For comparison we also similarly studied a group of normonatraemic runners over a similar time period after their aultramarathons.

8.2. METHODS AND MATERIALS

8.2.1. SUBJECTS

Details of the 8 runners who developed hyponatraemia are given in Tables 8.1. and 8.2.

8.2.2. STUDY PROTOCOL

All runners who collapsed during or after the 1988 Comrades marathon run annually between Durban and Pietermaritzburg had blood drawn for the estimation of serum and electrolyte levels and haematocrit using a Novastat Profile 1 analyzer (Nova Biomedical, Waltham, MA). Five of approximately 300 collapsed runners were found to be hyponatraemic (serum sodium levels < 130 mmol/L) and were referred, according to a pre-arranged protocol, to the local hospital (Gray's Hospital, Pietermaritzburg) for evaluation and treatment. One runner's plasma sodium concentration was initially 132 mmol/L. As her condition deteriorated a repeat measurement showed a concentration of 128 $mmol.l^{-1}$ and she was included in the study. Three additional runners admitted themselves directly to the hospital later the same day and were found also to be hyponatraemic. They were included in the study and treated according to the pre-determined protocol.

Sera from these runners were stored frozen at -20°C for subsequent analysis of osmolality and for serum creatinine, urea, chloride, total protein, albumin and aldosterone concentrations and renin activities.

The protocol required that the nature and volumes of all fluids administered either intravenously or orally to the patients were recorded and all urine passed was collected and measured. Urine aliquots were retained and stored frozen for subsequent analysis. Blood samples were drawn at regular intervals with minimal stasis whilst the patients were supine and were analyzed immediately for plasma electrolyte, creatinine and urea concentrations and for haematocrit and osmolality.

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

During hospitalization, a detailed medical and athletic history was taken from each subject. Particular care was taken to determine as accurately as possible, the volumes of fluids the subjects ingested and urinated during the study. For comparison with runners who did not develop

hyponatraemia after ultramarathon races we include selected data from the runners who took part in the 1983 and 1986 56km Two Oceans Marathons and the 1984 Comrades Marathon.

8.2.3. CALCULATIONS

Fluid excess was estimated as the difference between urine output and fluid intake (mainly intravenous fluid). No account was taken of respiratory or sweat losses during recovery even though these can be as high as 50 ml/hr (Ganong 1977). Our estimation of fluid losses from the body during hospitalization are therefore conservative. Sodium deficit or excess was calculated as the difference between sodium intake and urinary sodium excretion. For comparison, the sodium deficit in normonatraemic runners was taken as the difference between the mean 24-hour urinary sodium losses during the pre-race days and the urinary sodium excretion during the 24 hours including the race and the post-race day. Although the runners diets were not controlled during this period, they considered that their sodium intakes had not altered.

Percent changes in plasma volume, serum total protein content and serum albumin content for both hyponatraemic and normonatraemic runners were calculated according to the formulae of van Beaumont et al (1973).

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

8.3. **RESULTS**

8.3.1. RACE DETAILS

The athletes studied competed in the 1988 Comrades Marathon run over 88 km of a hilly demanding course. The mean temperature was 20.9^{o}C (Range during the race 12.5-25.1^{o}C) and the mean humidity was 55% (Range 41-77%).

8.3.2. SUBJECT DESCRIPTIVE DATA

These are detailed in Table 8.1 and 8.2. The subjects comprised 4 males of mean height 1.80 m (range 1.74 - 1.83 m), and mean weight 78 kg (range 73 - 84 kg) and 4 females of mean height 1.59m (range 1.52 - 1.64 m) and mean body weight 53.5 kg (range 50 - 59 kg). The average age of the runners was 41 years (range 35 - 56) (Table 8.1.). All were experienced long-distance runners who had run 15 ($\pm$ 7) (Mean $\pm$ SEM) marathons and 6 ($\pm$ 2) ultramarathons (Table 8.2.). Only one runner (AF) had not previously run an ultramarathon. Six runners completed the full 88 km distance; AF ran 68 and LC 61 km (Table 8.2.). The runners estimated their fluid intakes at between 0.8 and 1.85 L/hr (mean 1.3 $\pm$ 0.1 L/hr) of a cola/water mixture (Na concentration 3.4 mmol/L; (Noakes et al 1985)), or a total of 12.5 $\pm$ 1.6 L of fluid and 42.5 $\pm$ 5.6 mmol of sodium. The

subjects urinated between 1 and 8 times during the race (mean 5 ± 1).

Three of the runners (DC, AF and GC) took non-steroidal anti-inflammatory agents during the race. Runner LC was on 0.1 mg Eltroxin for hypothyroidism and Runner EP was taking Adelphoen-Esidrex (Ciba), one tablet daily. None of the subjects consumed caffeine during the study period after the race.

8.3.3. CLINICAL PRESENTATION

Three subjects (EP, GD, DC) developed grand-mal convulsions and coma. Symptoms in the remainder included weakness, confusion, incoordination and nausea.

Runner EP was the most severely effected. He remained in the Intensive Care Unit for 24 hours and suffered one episode of respiratory arrest. Pulmonary oedema was confirmed radiographically.

All subjects were discharged from hospital fully recovered within 9 to 48 hours.

8.3.4. RENAL FUNCTION AND FLUID AND ELECTROLYTE BALANCE DURING RECOVERY

During recovery the results for the subjects (n = 8) whose mean plasma sodium concentration at the end of the race was 122.4 ± 2.2 mmol/L were significantly different from runners (n = 18) who were normonatraemic at the end of their ultramarathons (mean plasma sodium concentrations 138.2 ± 1.2 mmol/L (Figure 8.2.).

Table 8.3. shows that they excreted a fluid excess of 2.95 ± 0.56 L (Range 1.22 to 5.92 L) during the 15.6 ± 2.1 hours of study while their sodium deficit was 153 ± 35 mmol (Range 24 - 307 mmol). This can be compared with the normonatraemic runners who completed their races in a state of mild dehydration (with a weight loss of 2.08 ± 0.25 kg or 2.7 ± 0.3%) and with a sodium deficit of 187 ± 37 mmol.

Table 8.4. shows serum osmolality, serum total protein andalbumin concentrations at the end of the race and again on recovery, in those subjects who were examined immediately post-race.

Figure 8.1. compares urine output, creatinine, osmolal and free water clearance as well as urine osmolality in the 2 groups during the recovery period (15.6 ± 2.1 hours for the hyponatraemic runners, 17.7 ± 0.5 hours for the

normonatraemic runners). There are significant differences in all these parameters with the subjects showing greatly increased urine output, creatinine, osmolal and free water clearances and a decreased osmolality compared to the normonatraemic runners.

Figure 8.2. shows the mean serum sodium, chloride and potassium concentrations in the 8 subjects when first examined (either in the medical tent or, in 3 patients, on admission to hospital) and again on completion of the study (recovery). These results are compared with those from normonatraemic runners at the beginning and end of a similar time period.

The data from the subjects show that serum sodium and chloride concentrations increase during recovery (from 122.4 $\pm$ 2.2 and 85.6 $\pm$ 3.2 mmol/L to 138 $\pm$ 104.4 $\pm$ 1.8 mmol/L, respectively) whereas serum potassium concentration falls (from 4.0 $\pm$ 0.15 to 3.55 $\pm$ 0.1 mmol/L). There were no significant differences between initial and the recovery serum chloride and potassium concentrations in the normonatraemic runners. In contrast to the finding in the hyponatraemic runners, serum sodium concentrations fell during recovery in normonatraemic runners.

Figure 8.3. which is configured in the same way as was Figure 8.2., shows the mean haematocrit, serum creatinine and urea concentrations. The hyponatraemic subjects were the 5 runners who were first examined at the finish of their races. The subjects' mean haematocrit decreased from 48.2 ± 0.8 to 41.2 ± 1.6% on recovery whereas the mean haematocrit of the normonatraemic runners decreased from 41.7 ± 1.3 to 39.6 ± 1.0%. The subjects' mean serum creatinine concentration at the end of the race was 89.8 ± 8.3 umol/L compared with 104.2 ± 5.6 umol/L in the normonatraemic runners. However the subjects serum urea concentration of 5.7 ± 0.8 mmol/L did not differ from the values of 5.7 ± 0.3 mmol/L measured in the normonatraemic runners.

Serum renin activity and aldosterone concentrations were measured in the 5 runners seen immediately after the race (Table 8.4.). All of the runners had elevated serum aldosterone concentrations while only two had increased serum renin activities.

Figure 8.4. shows calculated percent changes in plasma volume, serum total protein and serum albumin contents in the 5 subjects who were examined immediately after the race. These are compared with changes in 8 runners who remained normonatraemic after the 1986 56km Two Oceans Marathon.

2.4 ± 3.9%, respectively, in the normonatraemic runners.

Table 8.1. SUBJECT DETAILS: THE 1988 88KM COMRADES MARATHON DEMOGRAPHIC DATA

Subject	Sex	Age (yrs)	Height (cm)	Pre-race Weight
EP	M	56	174	73.0
GD	M	35	182	80.0
DC	M	37	183	84.0
AF	M	42	180	75.0
MEAN		41	180	78.0
SEM		±2.5	±2.0	±2.5
CS	F	38	164	59.0
GC	F	35	152	55.0
LC	F	41	157	50.0
CW	F	46	159	50.0
MEAN		40	158	53.5
SEM		±2.4	±2.5	±2.2

Table 8.2. SUBJECT DETAILS: THE 1988 88 KM COMRADES MARATHON RUNNING HISTORY DATA

	Distance Run per Week (km)	No std Marathons Run	No ultra-Marathons Run	Personal Marathon Record (hrs:min)	Best Comrades Time	Time Recorded (Finishers only) (hrs:min)
EP	75	4	1	3:53	-	10:48
GD	30	10	3	3:15	9:22	10:10
DC	75	8	14	3:10	9:27	9:37
AF	90	7	0	4:00	-	-
CS	40	2	1	4:16	10:58	10:58
GC	90	6	4	4:14	10:38	10:40
LC	80	20	6	3:55	10:36	-
CW	110	65	19	3:50	9:00	9:58
MEAN	74	15	6	3:49	-	-
SEM	±9	±7	±2	±0:08	-	-

TABLE 8.3. FLUID AND ELECTROLYTE BALANCE IN 8 RUNNERS DURING RECOVERY FROM EXERCISE-RELATED HYPONATRAEMIA

Runner	Duration of study (hr)	Total fluid intake (ml)	Total urine output (ml)	Fluid excess (ml)	Total sodium intake (mmol)	Total sodium urine losses (mmol)	Total sodium deficit (mmol)	Post-race plasma sodium concentration (mmol/L)
EP	27	6000	10105	4105	780	579	201	113
GD	19.5(13.5)	4100	7430	3330	630	323	307	122
DC	16(10)	3450	9370	5920	390	145	245	113
AF	9	2000	3520	1520	260	62	198	124
CS	12	2000	3460	1460	260	162	98	127
GC	11	1000	3760	2760	130	58	72	124
LC	18(12)	1300	4610	3310	130	106	24	128
CW	12	1000	2220	1220	130	52	78	128
MEAN	15.6	2606	5559	2953	339	186	153	122.4
SEM	±2.1 (13.1 ±2.0)	±628	±1057	±563	±87	±64	±35	±2.2

Runners EP to AF are male, CS to CW are female. For Runners GD,DC and LC the fluid study was continued for 19.5 hours, 18 hours and 18 hours respectively, whereas the sodium study was discontinued after 13.5 hours, 10 hours and 12 hours respectively

TABLE 8.4. SERUM RENIN ACTIVITIES AND ALDOSTERONE CONCENTRATIONS, IMMEDIATELY POST-RACE, IN 5 SUBJECTS WITH HYPONATRAEMIA OF EXERCISE

SUBJECT	EP	DC	AF	GC	CW	MEAN ± SEM
Serum renin activity (ng/mL/hr	11.1	1.26	2.37	8.73	1.85	5.06 ±2.0
Serum aldosterone concentration (ng/L)	384	443	507	303	411	410 ±34

TABLE 8.5. SERUM OSMOLALITY AND SERUM TOTAL PROTEIN AND ALBUMIN CONCENTRATIONS IMMEDIATELY POST-RACE AND ON RECOVERY IN 5 SUBJECTS WITH HYPONATRAEMIA

Subject	Serum osmolality (mosmol/L)		Serum Total protein concentration (g/L)		Serum albumin concentration (g/L)	
	I	II	I	II	I	II
EP	243	275	56	46	39	30
DC	261	289	75	59	50	40
AF	247	280	49	60	33	38
GC	281	286	79	52	45	33
CW	258	292	74	65	45	39
MEAN ± SEM	258 ±66	284 ±3	67 ±6	56 ±4	42 ±3	36 ±2

I - Immediately post-race
II - On recovery

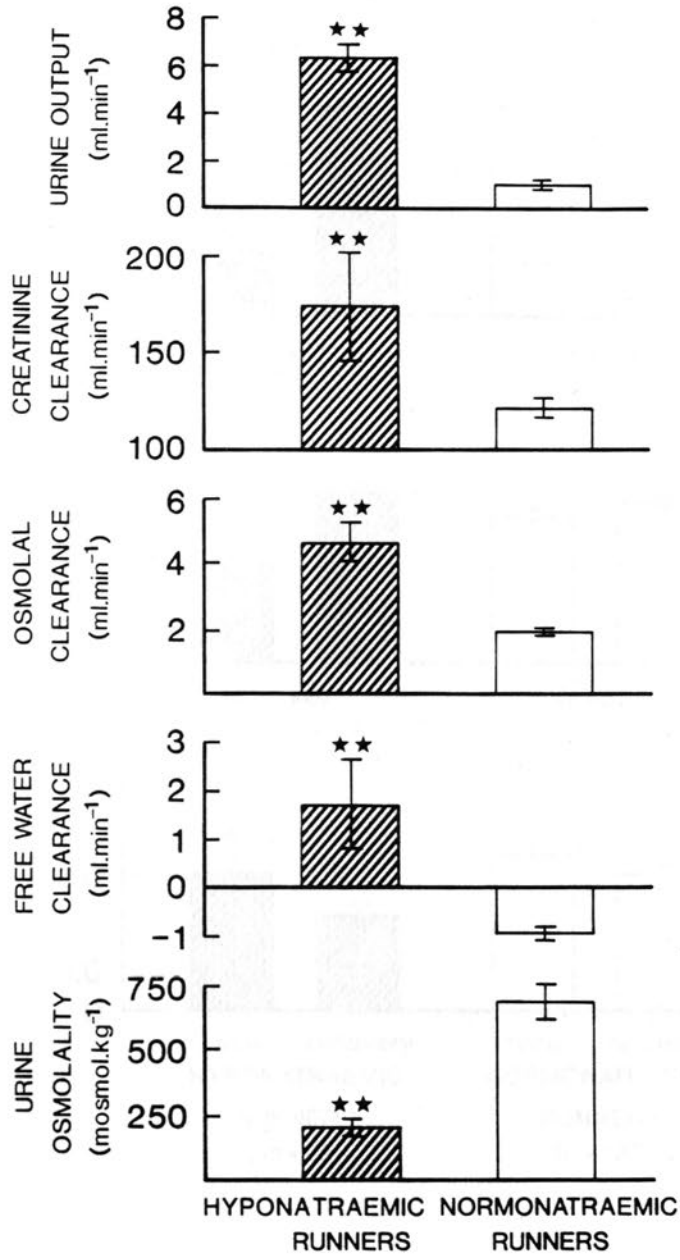

Figure 8.1. Mean (± SEM) urine output, creatinine, osmolal and free water clearance as well as urine osmolality in the 8 hyponatraemic subjects over the study period. The results are compared with 18 normonatraemic runners who were studied over a similar period.

** $p < 0.01$ hyponatraemic runners compared with normonatraemic runners.

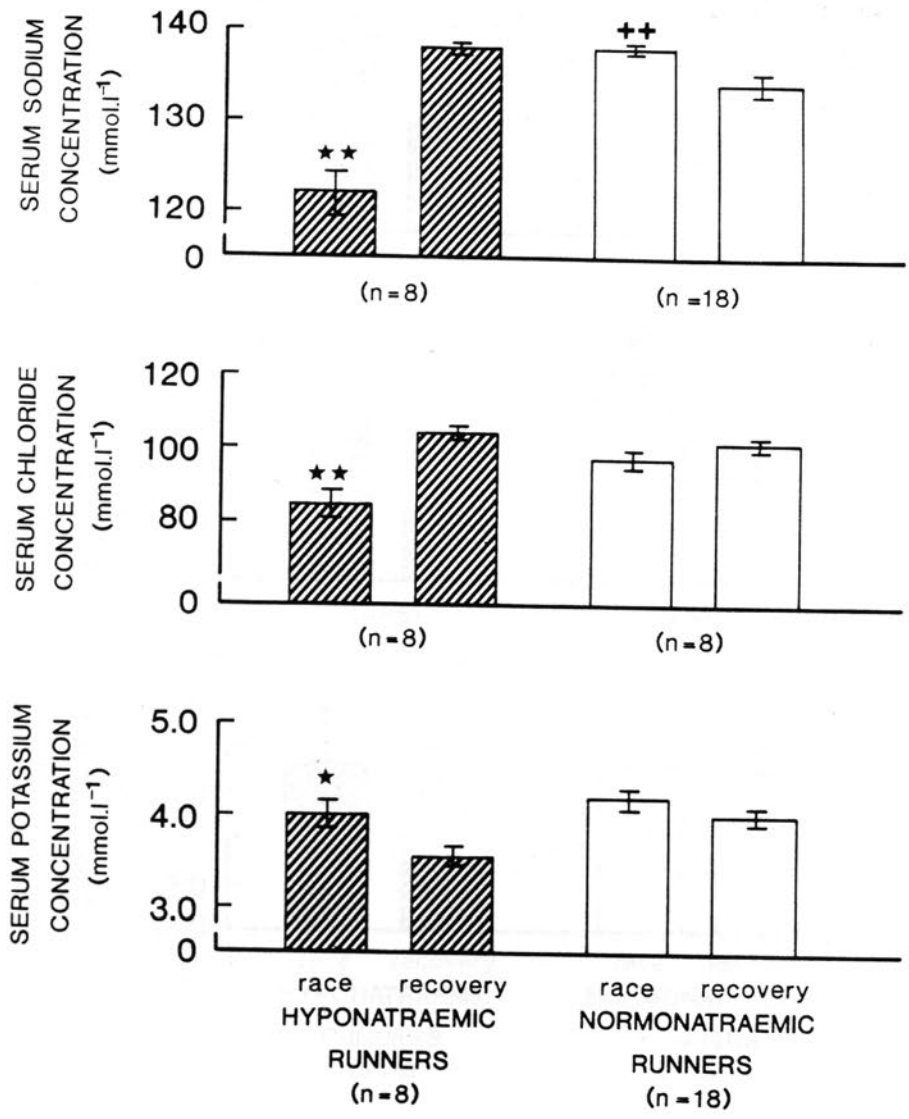

Figure 8.2. Mean (± SEM) serum sodium, chloride and potassium concentrations of hyponatraemic and normonatraemic runners measured at the end of the race in 5 runners and another 3 on admission to hospital, and again on recovery

* * $p < 0.01$ comparing race with recovery in the hyponatraemic runners.

+ + $p < 0.01$ comparing race with recovery in the normonatraemic runners.

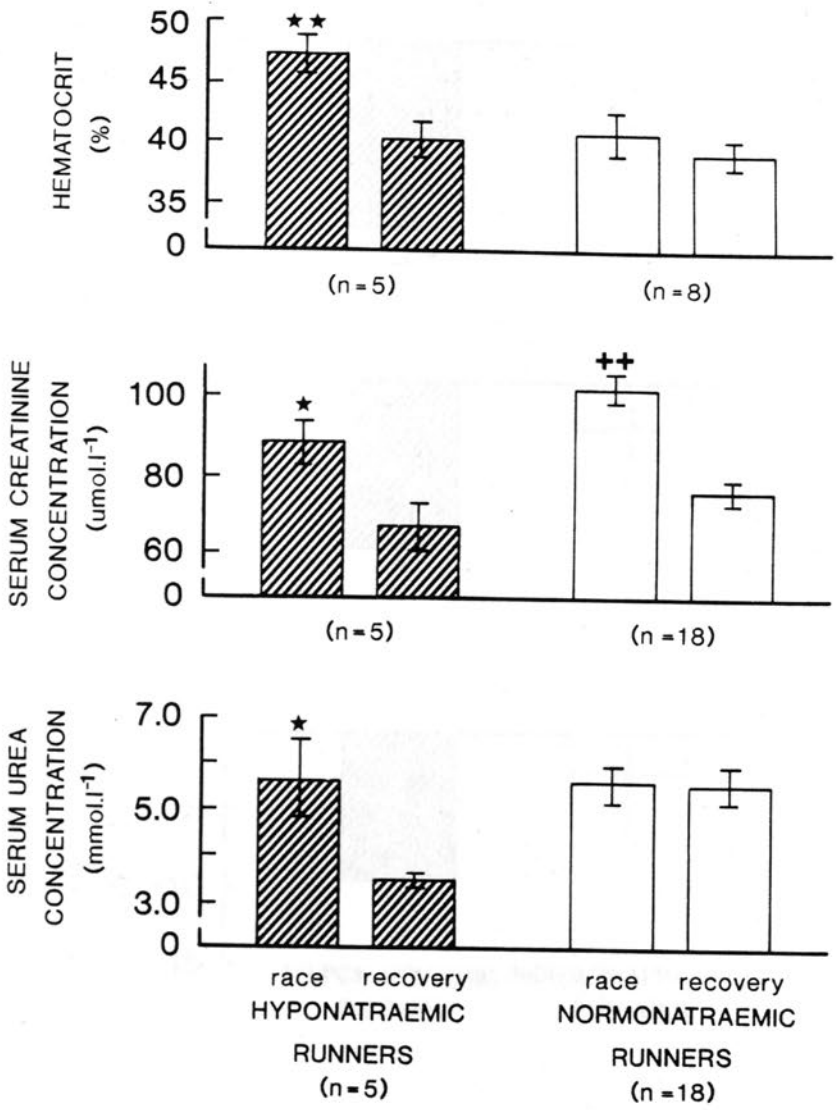

Figure 8.3. Mean (± SEM) haematocrit, serum creatinine and urea concentrations in the 5 hyponatraemic subjects examined at the end of the race and again on recovery, compared with normonatraemic runners over a similar period.

* p = < 0.05

* * p = < 0.01 comparing race with recovery in the hyponatraemic runners.

\+ \+ p = < 0.01 comparing race with recovery in the normonatraemic runners.

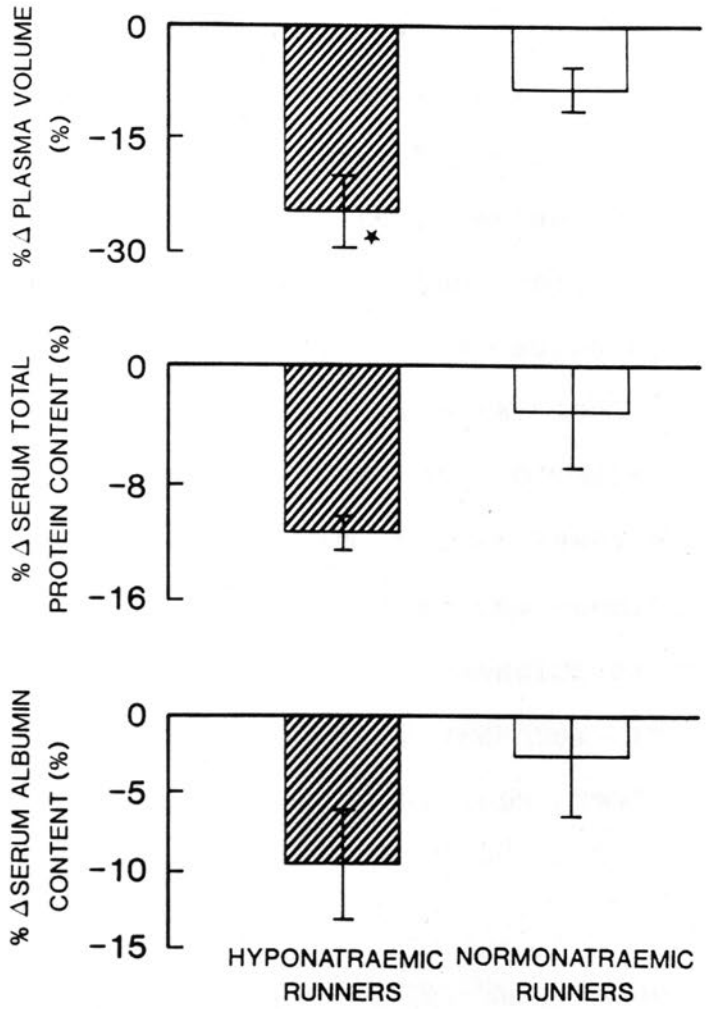

Figure 8.4. Mean (± SEM) calculated percent changes in plasma volume, serum total protein and serum albumin contents in 5 hyponatraemic and 8 normonatraemic runners, measured immediately post-race and during recovery.

* * $p = < 0.01$ comparing hyponatraemic with normonatraemic runners.

8.4. DISCUSSION

The hyponatraemia of exercise is a life-threatening condition (Nelson et al 1988; Noakes et al 1985), the aetiology of which has yet to be established. Two conflicting theories are in vogue. Some authors have postulated that this condition is caused by large sweat sodium chloride losses (Hiller 1988; 1989; Hiller et al 1986, 1987; Laird 1988; Lind 1988; O'Toole 1988) often associated with dehydration (Hiller 1989; Hiller et al 1986); others have proposed that the condition results from fluid retention following the ingestion of excessively large fluid volumes during prolonged exercise (Frizzel et al 1986; Nelson et al 1988; Noakes et al 1985, 1990; Young et al 1987).

This study conclusively resolves this issue. It shows that each of 8 subjects who collapsed with the hyponatraemia of exercise (mean plasma sodium concentration of 122.4 ± 2.2 mmol/L) were fluid overloaded by an amount ranging from 1.22 to 5.92 L (Table 8.3.). These fluid volumes are conservative as no allowance was made for insensible water losses during recovery (Ganong 1987). The subjects conservatively estimated that their fluid intakes during exercise ranged from 0.8 - 1.3 L/hr, compared to maximum values of 0.6 L/hr in normonatraemic runners (Noakes 1990; Noakes et al 1988).

We also found that the subjects' sodium losses (153 ± 35 mmol) (Table 8.3.) were not larger than those of runners who maintained normonatremia during exercise. The normonatremic ultramarathon runners lost 183 ± 37 mmol of sodium while other subjects undergoing prolonged exercise in the laboratory have lost 154.8 mmol of sodium in 4.11 L of sweat (Costill et al 1976). Even higher sweat losses (7.7 ± 0.4 L) have been recorded in normonatraemic Comrades marathon runners (Dancaster and Whereat 1971) suggesting that sodium losses equal to or greater than those measured in the hyponatraemic runners in this study may occur commonly in ultramarathon runners without the development of hyponatraemia. Thus sodium chloride losses alone cannot explain the hyponatraemia of exercise.

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

Finally, hyponatraemic runners initially showed a large post-exercise reduction of up to 24% in plasma volume, compared to normonatraemic runners who either maintain (Figure 5.1.) or show only a modest reduction in plasma volume (Maron et al 1975; Maughan et al 1985; Wells et al

1982) during prolonged exercise. Associated with the marked reduction in plasma volume were large reductions in total plasma protein and albumin contents (Figure 8.4.) and increased serum aldosterone concentration in all runners, and increased serum renin activity in two (Table 8.4.); these latter findings provide additional evidence for a reduced plasma volume in these subjects.

Thus we conclude that the hyponatraemia found in marathon runners results from excessive fluid retention with only mild sodium chloride losses and with no evidence of exercise-induced renal damage. Renal function during the race was, however, clearly inappropriate as indicated by the volume of retained fluid. The retained fluid appears to be distributed mainly into the intracellular volume while there is a reduction in plasma volume. Others have also measured elevated hematocrits in hyponatremic athletes (O'Toole 1988) indicating a reduction in plasma volume.

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

Firstly, although creatinine clearance was elevated during the recovery stage, during the race glomerular filtration rate (GFR) may have been unusually decreased. Marathon running does not necessarily reduce GFR when this is

measured over the duration of a marathon (Figures 3.1., 3.3., 3.4.) but the renal response of these subjects may have been different. However the serum creatinine and urea concentrations measured in the subjects after the race were not greater than those in normonatraemic runners in this study (Figure 8.3.) or in other studies (Dancaster and Whereat 1971; Riley et al 1975). A reduced GFR during the race is therefore unlikely.

Secondly, three of the subjects took non-steroidal anti-inflammatory agents. These can cause a decrease in renal prostaglandin production which can lead to a decline in GFR and accentuate the effects of ADH (Clive and Stoff 1984). There were, however, no significant differences in renal function or fluid balance between this sub-group and the remainder of the hyponatraemic subjects.

Thirdly, in normonatraemic runners plasma volume usually decreases moderately (Maron et al 1975; Maughan et al 1985; Wells et al 1982) or not at all (Figure 5.1.). In spite of gross fluid overload, the subjects in this study failed to maintain a normal plasma volume (Figure 8.4.). The reduced plasma volume would act as a non-osmotic cause for both increased fluid intake and for arginine-vasopressin (ADH) release; the latter would prevent free water clearance thereby compounding fluid retention in athletes stimulated to ingest hypotonic fluids in excess. That ADH secretion

was appropriately suppressed in these subjects during recovery is shown by the positive free water clearance and reduced urine osmolality during recovery (Figure 8.1.); the opposite of the response in normonatraemic runners. The time course of this response followed the rapid normalization of haematocrit and therefore presumably of plasma volume, within the first few hours of collapse (Figure 8.3.). It is of interest to speculate why hyponatraemic runners were unable to maintain plasma volume during exercise.

The most important variable besides extracellular sodium content that influences plasma fluid shifts during exercise is probably transcapillary colloid osmotic pressure (Mohsenin and Gonzalez 1984; Senay 1979; Senay et al 1976). Ingress of protein into the plasma space during exercise acts to maintain plasma volume; thus the reduced plasma volume of hyponatremic runners may have resulted from an inability to mobilize interstitial protein into the vascular space (Figure 8.4.). Under these conditions the excess volume of ingested fluid would be redistributed mainly into the intracellular but also partially into the interstitial space. An expanded interstitial volume would lead to a further reduction in the protein concentration in this space and in the lymph; the latter is believed to be a major source of the intravascular protein influx during exercise (Senay et al 1976).

Non steroidal anti-inflammatory agents have been shown to increase protein loss from the vascular compartments of exercising subjects (Pivarnik et al 1985) and this may have been a factor in the 3 runners who ingested these drugs during the race. The protein losses in these subjects were however, no greater than in the other hyponatraemic runners.

Atrial natriuretic peptide (ANP) increases during exercise (Anderson et al 1986) and may be associated with increased urine sodium losses in normal subjects (Laragh 1985). Whether ANP is a factor in the genesis of the hyponatraemia of exercise is unknown, but the increased aldostrone concentrations in the 5 subjects would not seem to indicate this. The sodium deficits in these subjects, would also not seem to have been excessive. ANP may also increase capillary membrane permeability to plasma proteins (Laragh 1987) and may have been a factor in these subjects, due either to increased rates of ANP secretion or to an increased sensitivity to its actions. Further work is necessary to establish levels of both ADH and ANP in hyponatraemic subjects.

The question as to why the cells of these individuals do not come into osmotic equilibrium with the extra-cellular fluid is of course unanswered by this study. Is there an

inhibition of the enzyme sodium potassium ATPase as has been suggested by other workers (Arieff 1986, 1987) ?

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

This would seem to confirm that the potential dangers of severe dehydration and the need to drink adequately during prolonged exercise have been so well publicized (Noakes et al 1988) that, as a result, some individuals may choose to ingest dangerously large fluid volumes during prolonged exercise. In addition, it is possible that during the later stages of the race, a reduced plasma volume would induce volume-dependent dypsogenic drive thereby sustaining the high rates of fluid intake.

Finally in spite of the moderately low sodium losses in these runners, we would include the hyponatremia of exercise as a form of hyponatremia caused by a low total body sodium content according to the Goldberg classification (Goldberg 1981) but would emphasize that, without the excess fluid

intake, hyponatremia would not have developed. Empirical evidence suggests that a reasonable intake of fluid while exercising prevents the recurrence of hyponatremia in predisposed subjects (Noakes et al 1985). Further work is required to determine whether sodium replacement during endurance events will, in addition, assist in the prevention of this condition as has been suggested (Hiller 1989).

CHAPTER IX

OVERALL SUMMARY AND CONCLUSIONS

9.1. THE EFFECTS OF MARATHON RUNNING

9.1.1. ON URINE OUTPUT, CREATININE CLEARANCE AND RENAL PLASMA FLOW

Traditionally it is believed that marathon running causes a decrease in urine flow and creatinine clearance. Renal plasma flow is also considered to decrease during the race (Neviackas and Bauer 1981) and these changes, when associated with rhabdomyolysis and dehydration can be sufficient to induce acute renal failure. This, however, does not satisfactorily explain the infrequency with which renal complications develop during marathon running.

These studies have shown that, when measured over the period of a marathon, urine output is well maintained (Figures 3.1.-3.5.), as is creatinine clearance (Figures 3.1., 3.3., 3.4.). Creatinine clearance did decrease during a 56km marathon run under warm conditions (Figure 3.2.) and during a 24 hour relay race (Figure 3.5.), but in both of these races, urine output was maintained (Figure 3.2., 3.5.). In none of these studies did the runners complete their races

in a severely dehydrated state as evidenced by the relatively small mean percent body weight losses ($2.6 \pm 0.3\%$). This compares well with another study of 7 marathons during which the weight losses ranged between $1.6 \pm 1.1\%$ and $3.1 \pm 1.9\%$ (Noakes et al 1988).

Further evidence for a maintained renal function during marathon running are the studies on creatinine and urea concentrations. Although the plasma concentrations of both these substances increased during the races (Figures 3.15.-3.17., 3.19.), these increases were caused by an increase in their rates of production (Figures 3.15.-3.17., 3.19.) and not by a decrease in urine excretion (Figures 3.15.-3.18.). Only during the 1983 24 hours relay race (Figure 3.19.) was urine creatinine and urea excretion reduced.

Although RPF was not measured directly, the above studies show that it probably was not greatly reduced during the marathon races.

The classical response to marathon running is, therefore, a maintained renal function as evidenced by unchanged values of RPF, creatinine clearance, urine output and urine urea and creatinine excretion during exercise. This would likely explain why cases of acute renal failure are uncommon amongst marathon runners despite the presence of exercise-

induced muscle damage (Hikada et al 1983; Warhol et al 1985).

During the post-race days there was an increase in GFR as measured by creatinine clearance (Figures 3.1., 3.3, 3.4.). It is proposed that this increase may be due to the release of protein by-products of skeletal muscle damage into blood. Evidence for muscle damage induced by marathon running has been shown by muscle biopsies (Hikada et al 2983; Warhol et al 1985), by increases in serum enzyme activities (Figure 3.12., 3.14.), in plasma CRP concentrations (Figure 3.13.), in serum uric acid content (Figure 3.14.) and increased rates of creatinine production (Figures 3.15.-3.17.). However, as in the case of dietary protein loading (Bosch et al 1983) and amino-acid infusions (Graf et al 1983), both of which also increase GFR, the physiological mechanism is unclear.

9.1.2. ON PROTEINURIA

It has previously been shown that the proteinuria induced by marathon running is caused by an increased glomerular permeability without a significant alteration in renal tubular function (Poortmans and Haralambie 1979; Poortmans and Jeanloz 1968). These studies, in general, agree with these findings (Figures 4.1., 4.3., 4.4.). There are increases in urine $beta_2$-microglobulin excretion (Figures

4.4., 4.5.) but these were usually associated with increases in plasma $beta_2$-microglobulin concentration (Figures 4.1., 4.4., 4.5.) so that renal $beta_2$-microglobulin clearance, a measure of renal tubular dysfunction, was not increased (Figures 4.1., 4.4., 4.5.).

Renal tubular dysfunction can, however, occur during and after marathon running as found in the 1983 Two Oceans Marathon (Figure 4.2.). As mentioned, this race was run under warmer conditions than the others, and was also the only race in which the creatinine clearance decreased below pre-race levels (Figure 3.2.). One of the runners (AI - Table 3.2.) manifested a 42-fold increase in renal $beta_2$-microglobulin clearance on Day 1 and is discussed later. It should be noted that 2 out of 27 runners where renal tubular function was studied developed some degree of renal tubular impairment (Chapter 6). Neither case would normally have been reported, but whether this indicates a greater incidence of renal tubular change than is normally anticipated, is uncertain.

The increased glomerular permeability after short-term exercise has been shown to remain for approximately 4 hours (Poortmans et al 1989). These studies show an increased urine total protein excretion 1 and 4 days after the marathon had finished (Figures 4.1., 4.5.). Further work, using the measurement of renal albumin clearance, is

required to confirm whether this response is due to the delayed onset of increased glomerular permeability.

9.1.3. ON RENAL ELECTROLYTE HANDLING

A transient impairment of the renal concentrating capacity has been described after long-distance ski-racing (Refsum and Stromme 1975, 1977). This was not a feature of the marathon races that we studied. Urine osmolality was only decreased during one race (Figure 3.3.) and the osmolal clearance decreased only during the two longest races (Figure 3.4., 3.5.). During the majority of the races urine osmolality and osmolal clearance remained within the pre-race range (Figure 3.1.-3.5.).

Urine sodium excretion was, however, decreased for between 24-48 hours after the race (Figure 3.8., 3.10.) while significant increases in PRA occurred in 2 of the 3 races that were studied (Figure 3.11.).

These studies also confirm the finding that exercise does not have a consistent effect on renal potassium excretion (Castenfors 1967; Kachadorian 1972). Viru and Korge (1971) have shown an increase in urine potassium excretion after a standard marathon and have suggested that a maintained urine excretion may indicate an exhausted, collapsed runner. These studies show that only during one race (Figure 3.9.)

was urine potassium excretion increased. None of our runners collapsed or were excessively fatigued; thus our findings do not support this hypothesis.

9.1.4. ON PLASMA VOLUME

Traditionally it is believed that marathon running induces a decrease in plasma volume as has been recorded after several marathons (Maughan et al 1985; Myhre et al 1982, 1985; Wells et al 1982) where plasma volume decreased by between 5.4% and 27.4%).

In contrast, and in agreement with some of the changes noted by Maughan et al (1989), our studies show that plasma volume was well maintained after a 56km marathon (Figure 5.1.). Similar findings have previously been reported (Costill 1972; Maron et al 1975; Poortmans and Haralambie 1979).

It is likely that the different plasma volume responses depend on the amount of protein entering the vascular compartment (Figure 5.2.) as discussed by Senay and Pivarnick (1985). The distance and intensity of exercise may be a critical factor determining plasma volume changes as plasma volume expansion has been recorded after longer-distance events (Pugh 1969a,b; Refsum et al 1973).

The associated race-induced decrease in urine sodium excretion (Figure 3.8.) must be a contributory factor in maintaining plasma volume.

As previously reported by Maron et al (1977) and Robertson et al (1988) plasma volume expands during the post-race recovery period (Figure 5.1.), initiated by protein influxes into the vascular compartment (Figure 5.2.) and associated with increases in plasma sodium content (Figure 5.2.).

Repeated exercise causes an increase in plasma volume (Convertino et al 1980; Dressendorfer et al 1981). The plasma volume expansion on Day 6 after the marathon (Figure 5.1.) with an increase in serum albumin content and a maintained serum sodium content (Figure 5.2.) may be due to a number of mechanisms initiated by the runners recommencing gentle exercise.

Whether the increase in plasma sodium content (Figure 5.2.) indicates an increase in the total body content of sodium as has been shown after consecutive days of exercise (Williams et al 1979) is not proven by these studies. However, during the post-marathon days there was a tendency for increases in urine output (Figure 3.1.), osmolal clearance (Figure 3.1., 3.2.) and urine sodium excretion (Figure 3.8.). This may indicate fluid and sodium retention. There was a slight

increase in body weight during the post-race days but these changes were not significant.

9.1.5. ON BLOOD PARAMETERS

During the days after a marathon a decrease in the red cell count can occur (Figure 5.4.). This is due to the plasma volume expansion that occurs at that time (Figure 5.1.).

The marathon itself induces a leukocytosis (Figure 5.4.) with no correlation between the leukocyte increase and fitness, training distance or time recorded.

In conclusion: These studies show that the traditional belief regarding the effects of marathon running on renal function are incorrect. This belief is that long-distance running is associated with a decrease in RPF and GFR, but the findings of this thesis suggest the opposite. In addition an impairment of the renal concentrating capacity, reported after ski-racing was not usually found after marathon running. The maintained RPF and renal function explains why acute renal failure is uncommon marathon runners. However, renal tubular dysfunction may be more common than generally believed.

Similarly, a decrease is the plasma volume does not necessarily occur during ultra-marathon running, although it is the more usual response during standard 42.2km marathons. A greater or lesser influx of albumin into the vascular compartment is the likely explanation for the differences in plasma volume response.

An increase in renal glomerular permeability does, however, occur after marathon running, but an increase in urine $beta_2$-microglobulin excretion is usually, but not always associated with an increase in plasma $beta_2$-microglobulin concentration. Temporary renal tubular impairment was observed in this study after a 56km marathon, run in warm conditions, where a decrease in creatinine clearance occurred, but no other signs of renal impairment were noted.

During the post-race days an increase in GFR is shown to occur and may be associated with increased efflux of by-products of skeletal muscle damage into plasma. A plasma volume expansion also occurs during this time, associated with an influx of albumin and electrolytes into the vascular space. It is important that cognisance is taken of the plasma volume expansion and that the total content of plasma constituents be measured before conclusions are made regarding post-marathon biochemical changes.

9.2. THE PATHOLOGICAL EFFECTS OF MARATHON RUNNING

9.2.1. ACUTE RENAL FAILURE

As previously discussed, these studies have shown that urine output, creatinine clearance and almost certainly RPF appear to be well maintained during marathon running, in contrast to the more generally held belief that renal function is impaired during prolonged exercise. This finding would also explain why acute renal failure occurs so infrequently during marathon running although the incidence would appear to be increased in ultramarathon runners.

However renal damage can occur as is reported in the study of Runner A during and after a 90km marathon (Chapter 6). Renal damage was shown by the following; a 50-fold increase in renal $beta_2$-microglobulin clearance (Figure 6.1.); oliguria during and immediately after the race (Figure 6.3.); and a decreased post-race creatinine clearance (Figure 6.3.). Unlike the other runners, Runner A drank little during the race and became dehydrated (an 11% body weight loss). This severe dehydration was almost certainly a major initiating factor for the acute renal injury.

A further milder case of tubular dysfunction is also reported in Chapter 6. Runner AI had a 42-fold increase in renal $beta_2$-microglobulin clearance on Day 1 after a 56km

marathon (Figure 6.7.). In contrast to Runner A, this athlete was well hydrated (Table 6.1.) and there were no other signs of renal dysfunction. A race-induced rhabdomyolysis as a result of inadequate pre-race training was considered to be the major factor in this case.

In conclusion: Acute renal failure is uncommon after marathon running in spite of exercise-induced muscle damage. This thesis has shown the reason for this. When renal failure does occur in athletes, it cannot be due to exercise alone and must be due to other additional factors. Two of these factors, dehydration and excess muscle damage are described. The use of analgesics and anti-inflammatory drugs may be important in the genesis of renal failure among runners. However the incidence of drug use has not been reported.

9.2.2. RENAL STONE FORMATION

This study suggests that marathon runners may be at risk for renal stone formation as was suggested by the original survey of Milvy et al (1981). The studies of crystalluria before and after 2 marathon races (Chapter 7) show that the urine of marathon runners shows the same characteristics as those found in idiopathic renal stone formers and which differ from control subjects. These differences are: (i) an increased excretion of larger crystals (15-32 um in

diameter) in addition to the normal excretion of small urinary crystals (2-5 um in diameter) (Figure 7.1.-7.5.) (ii) an increase in the numbers of calcium oxalate dihydrate crystals (Figure 7.6., 7.8., 7.9.), (iii) the occurrence of crystal aggregates (Figure 7.10., 7.12.).

Possible reasons for this crystalluria are: (i) an increased cellular debris which could provide an organic matrix for crystal formation (Figure 7.14., 7.15., 7.17-7.20.), or (ii) the sloughing of debris from epithelial walls may produce sites at which calcium oxalate particles could become attached and grow.

These studies also show that particle counting should be conducted at 37^{o}C and within a few hours of sample collection (Figures 7.21.-7.23.) as storage and temperature change alters crystal size.

In conclusion: Marathon runners are, to some extent, at risk for renal stone formation. This is shown by the similarities between their crystalluria and that of idiopathic stone formers.

9.2.3. THE HYPONATRAEMIA OF EXERCISE

In spite of the seriousness of this condition (Nelson et al 1988; Noakes et a; 1985), prior to the completion of this study, the aetiology was uncertain and two conflicting hypotheses had been advanced (Frizzel et al 1986; Hiller 1988, 1989; Noakes et al 1985; 1990).

This study of eight runners who developed hyponatraemia during or after the 1988 Comrades Marathon conclusively resolves this conflict and shows that:

(i) The hyponatraemia in these athletes was caused by fluid overload (conservatively estimated at between 1.22 and 5.92 L) (Table 8.3.).

(ii) The sweat and urine sodium losses during the race were not excessive (Table 8.3.) and are comparable with runners who do not develop hyponatraemia.

(iii) Functionally the renal response during the recovery phase was normal as indicated by the elevated urine output and creatine clearance (Figure 8.1.). Serum creatine and urea concentrations at the end of the race were also similar to normonatraemic runners (Figure 8.3.).

(iv) At the end of the race, in spite of the fluid overload there was a reduction in plasma volume (up to 24%) (Figure 8.4.) as shown by haematocrit measurements (Figure 8.3.) and inferred by serum aldosterone concentrations and serum renin activity (Table 8.4.).

(v) There was a decrease in plasma total protein and albumin content compared with normonatraemic runners (Figure 8.4.), and finally:

(vi) Fluid shifts occurred after the race as fluid moved into the vascular compartment as shown by a decrease in haematocrit measurements (Figure 8.3.).

The reason for the inappropriate renal function during the race is, however, still uncertain. The reduced plasma volume may have acted as a non-osmotic cause for ADH release (Goldberg 1981), or the subjects may be unduly sensitive to this hormone. The GFR during the race would seem to have been maintained as indicated by the normal post-race serum urea and creatinine concentrations.

In addition, renal function in the sub-group of runners with hyponatraemia who took non-steroidal anti-inflammatory agents during the race was not different from that of those who did not. These drugs could play a role in the genesis of hyponatraemia by decreasing renal prostaglandin production (Clive and Stoff 1984) or by increasing vascular

protein loss (Pivarnik et al 1985). The role, if any, of ANP in the genesis of this conditon requires further study.

Finally, the excess fluid intake by these subjects may have had both behavioural and physiological causes.

In conclusion: These studies have shown that hyponatraemia in the group of ultramarathon runners who were studied is not caused by a sodium deficit with associated dehydration. The hyponatraemia induced by marathon running is caused by fluid overload with normal sodium losses and an inability to excrete this fluid excess while running. The reason for this inappropriate renal response is unclear but is almost certainly not due to renal damage. The large decrease in plasma volume must, however, play a role in the genesis of this condition.

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