MEDICAL GRAND ROUNDS

SELF-INDUCED RHABDOMYOLYSIS

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INTRODUCTION

The last time the general topic of rhabdomyolysis was presented at Grand Rounds was 1977. A table prepared to display the causes of rhabdomyolysis was presented at that time. It was organized on the basis of etiology related to abnormalities of energy production by muscle cells, whether acquired or hereditary as well as other tangible causes of skeletal muscle necrosis such as infectious agents or myotoxins. An update of that table has been prepared (Table I) since during the past 10 years there have been a large number of case

TABLE I

CAUSES OF RHABDOMYOLYSIS

I. INCREASED ENERGY CONSUMPTION

1. EXERCISE STRESS
2. AMPHETAMINE, LSD, COCAINE
3. DELERIUM TREMENS
4. CONVULSIONS
5. HIGH VOLTAGE SHOCK
6. TETANUS
7. SUCCINYL CHOLINE
8. FEVER
9. MALIGNANT HYPERPYREXIA
10. EXERCISE INDUCED HEATSTROKE
11. HEAT CRAMPS
12. DYSTONIA
13. MALIGNANT NEUROLEPTIC SYNDROME
14. THYROID STORM

II. DECREASED ENERGY PRODUCTION-GENETIC

A. AFFECTING CARBOHYDRATE METABOLISM
1. MYOPHOSPHORYLASE DEFICIENCY
2. α-GLUCOSIDASE DEFICIENCY
3. AMYLO-1, 6-GLUCOSIDASE DEFICIENCY
4. PHOSPHOHEXOISOMERASE DEFICIENCY
5. PHOSPHOFRUCTOKINASE DEFICIENCY
6. ? CYTOCHROME DISTURBANCES
7. DIABETIC ACIDOSIS
8. NONKETOTIC HYPEROSMOLAR COMA
9. MYOADENYLATE KINASE DEFICIENCY
10. PHOSPHOGLYCERATE KINASE DEFICIENCY
11. PHOSPHOGLYCERATE MUTASE DEFICIENCY

B. AFFECTING LIPID METABOLISM
1. CARNITINE DEFICIENCY
2. CARNITINE PALMITYLTRANSFERASE DEFICIENCY

C. VARIOUS MUSCULAR DYSTROPHIES

D. MISCELLANEOUS
- LACTATE TRANSPORTER DEFECT

III. ↓ ENERGY PRODUCTION ACQUIRED

1. K-DEFICIENCY
   (a) ↓ GLUCOSE OXIDATION
   (b) ↓ GLYCOGEN FORMATION
   (c) ↓ INSULIN RELEASE WITH HYPERGLYCEMIA
2. ETHANOL
3. MYXEDEMA
4. HYPOTHERMIA, FROSTBITE
5. HYPOPHOSPHATEMIA
6. DIABETIC KETOACIDOSIS

IV. ↓ OXYGENATION

1. ↓ MUSCLE BLOOD FLOW
   (a) K-DEFICIENCY
   (b) McARDLE'S SYNDROME
   (c) POSTURAL VASCULAR OCCLUSION
   (d) ARTERIAL EMBOLISM
   (e) PROLONGED SURGERY - (OPEN HEART)
   (f) VENA CAVA LIGATION
   (g) CONGESTIVE HEART FAILURE
2. CARBON MONOXIDE
3. SHOCK
4. TRAUMA
   (a) CRUSH SYNDROME
   (b) CONGA DRUMS
   (c) FIREARM RECOIL
   (d) KARATE
   (e) ICE-SKATING
   (f) JACK HAMMER
5. SICKLE CELL TRAIT
6. GENERALIZED SPONTANEOUS ARTERIAL THROMBOSIS

V. PRIMARY MUSCLE INJURY

1. POLYMYOSITIS
2. DERMATOMYOSITIS
3. TRAUMA, CRUSH
4. BURNS

VI. INFECTIOUS

1. GAS GANGRENE
   - CLOSTRIDIA WELCHII
   - PASTURELLA MULTOCIDA
2. TETANUS
3. LEPTOSPIROSIS
4. MYCOPLASMA PNEUMONIA
5. COXSACKIE INFECTION
6. SHIGELLOSIS
7. HERBICOLA LATHYRI BACTEREMIA
8. REYE'S SYNDROME
9. SEPTIC SHOCK
10. MYXOMA VIRUS
11. PSEUDOMONAS BACTEREMIA
12. ACQUIRED IMMUNODEFICIENCY SYNDROME
13. KLEBSIELLA MYOSITIS
14. E. COLI BACTEREMIA
15. MICROAEROPHILIC STREPTOCOCCUS
16. TOXIC SHOCK SYNDROME
17. STAPHYLOCOCCAL BACTEREMIA
18. INFLUENZA A
19. INFLUENZA B
20. ROCKY MOUNTAIN SPOTTED FEVER
21. ECHOVIRUS 9
22. KAWASAKI DISEASE
23. LEGIONNAIRES' DISEASE
24. EPSTEIN-BARR VIRUS
25. PNEUMOCOCCAL BACTEREMIA
26. SECONDARY SYPHILIS
27. BRUCELLA MELITENSIS
28. PICORNAVIRUS INFECTION

VII. MISCELLANEOUS

A. VENOM
1. SNAKE BITE (SEA SNAKE, RATTLESNAKE)
2. HORNET
3. HOUSEHOLD BROWN SPIDER
4. YELLOW JACKET

B. DRUGS
1. HEROIN
2. BARBITURATES
3. PROPOXYPHENE
4. METHADONE
5. GLUTETHEMIDE
6. AMPHETAMINES
7. PLASMOCID
8. LICORICE (GLYCYRRHIZATE)
9. CARBENOXOLONE
10. AMPHOTERICIN-B
11. DIAZEPEM
12. CODEINE
13. EPSILON AMINOCAPROIC ACID
14. PEANUT OIL (ARACHIDONIC ACID)
15. PHENCYCLIDINE
16. PHENYTOIN
17. CLOFIBRATE
18. LITHIUM CARBONATE
19. HALOPERIDOL
20. STRYCHNINE
21. METHYLSALICYLATE
22. METHYLPHENIDATE
23. LOXAPINE
24. COMBINED POISONING WITH ACETOAMINOPHEN AND SALICYLATES
25. RADIOGRAPHIC CONTRAST MEDIA (UROGRAFIN)
26. AMOXAPINE
27. VINCRISTINE (?)
28. QUINIDINE
29. CIMETIDINE
30. TRIETHYLENE TETRAMINE
31. LABETALOL
32. SOTALOL
33. PROPRANOLOL
34. PENICILLAMINE

C. OTHER
1. QUAIL INGESTION
2. ISOPROPYL ALCOHOL
3. ETHYLENE GLYCOL
4. HAFF DISEASE
5. "CALCIPHYLAXIS" (AZOTEMIC HYPERPARATHYROIDISM)
6. ACUTE SCHIZOPHRENIA
7. HYPERNATREMIA
   - EMETINE
8. ACUTE HYPONATREMIA
9. INSOMNIA
10. 2, 4-DICHLOROPHENOXYACETIC ACID
11. ACUTE INTERMITTENT PORPHYRIA
12. NONKETOTIC HYPEROSMOLAR COMA
13. GLUE SNIFFING (TOLUENE)
14. YELLOW PHOSPHORUS POISONING
15. IPECAC POISONING
16. MERCURIC CHLORIDE POISONING

reports as well as formal papers dealing with causes and mechanisms of muscle cell necrosis or rhabdomyolysis.*

Rhabdomyolysis is an extremely important clinical condition. It is very common, has a multitude of causes and perhaps of most importance, it is often associated with serious morbidity or mortality. If a person knew nothing about Internal Medicine and scanned general medicine textbooks for the topic of rhabdomyolysis, it would be quite logically assumed that this entity is not one of great importance. In our two major textbooks, Cecil or Harrison's Textbooks of Medicine, the discussion on rhabdomyolysis is covered in less than one page. The same textbooks contain numerous examples of diseases that are seldom seen such as primary hyperparathyroidism, that contain discussions in excess of 10,000 words. While long and detailed exposure of rare diseases is important and understandable, to short change a condition such as rhabdomyolysis is unfortunate because physicians do not always appreciate the gravity of this illness and the seriousness of its complications.

In this Grand Rounds, I intend to emphasize self-induced rhabdomyolysis. Initially, I would like to review some important physiologic changes that are brought about by physical conditioning that in turn are thought to reduce ones susceptibility to rhabdomyolysis. This will be followed by several relevant case presentations. Next, several case presentations will be shown that represent maneuvers utilized by competitive runners to improve their performance that unfortunately backfire and cause potentially disastrous consequences. The next will be the interesting issue that women almost never develop rhabdomyolysis with exertion. This will be followed by the apparent hypersusceptibility to rhabdomyolysis and a number of other vascular occlusive events seen after exercise in patients with sickle cell trait. Finally, mention will be made of rhabdomyolysis and other associated disasters seen in a young man with rattlesnake bite and another in a young man who smoked "crack" - as examples of generalized, myotoxin-induced rhabdomyolysis.

Table II lists a number of complications of competitive exercise that may occur either during or immediately after its completion. Most of these, with a possible exception of water intoxication, are less likely to occur in an individual who has undergone satisfactory training. Yet, it is to be emphasized that anyone can develop rhabdomyolysis of massive degree and every other abnormality listed on this table despite his or her status of training if they push themselves to the point of collapse.

TABLE II

IMMEDIATE COMPLICATIONS OF COMPETITIVE EXERCISE

1. CARDIAC ARRHYTHMIAS	13. GASTROINTESTINAL HEMORRHAGE
2. SUDDEN DEATH	14. HYPOGLYCEMIA
3. MYOCARDIAL INFARCTION	15. DECREASED LACTATE UTILIZATION
4. VASCULAR COLLAPSE	16. DIARRHEA
5. RHABDOMYOLYSIS	17. SALT DEPLETION
6. HYPERKALEMIA	18. WATER DEPLETION
7. HYPERPHOSPHATEMIA	19. WATER INTOXICATION
8. HYPOCALCEMIA	20. CONVULSIONS
9. HYPERURICEMIA	21. DISORIENTATION
10. ACUTE RENAL FAILURE	22. FOCAL CEREBRAL DYSFUNCTION
11. HEMATURIA	23. HEATSTROKE, HYPERTHERMIA
12. SPLANCHNIC ISCHEMIC	24. HEMOLYSIS

*The specific entries in this table do not carry references. These are all based upon published reports which are available from me [if you can find me].)

I. THE STATUS OF TRAINING AND THE SUSCEPTIBILITY TO RHABDOMYOLYSIS

Exercise training represents a fascinating series of adaptations brought about by methodically pushing ones self toward higher and higher levels of performance. A trained person can run faster, run longer, move more weight, generate less heat and develop fewer of the complications of physical work than before. Training raises the threshold for clinically relevant exertional rhabdomyolysis, but unfortunately, it is not totally protective. Training does not appear to provide protection against other types of injury seen in the competitive long distance runner, such as disseminated intravascular coagulation or apparent bowel ischemia.

In metabolic terms relevant to skeletal muscle there are three critical adaptations that must occur to facilitate training.

1. Increased capacity for fuel delivery.
2. Enhanced fuel storage.
3. More efficient fuel utilization.

IMPROVED FUEL DELIVERY TO CELLS

A. Circulatory Component

Perhaps the most important single determinant in one's ability to train is the adaptability of the cardiovascular system. A number of studies have clearly shown that the maximum cardiac output during exercise becomes substantially higher after training (1). The heart becomes modestly hypertrophied, slightly dilated, and its resting rate is considerably lower. The circulatory volume increases as much as 25% over values in the untrained state. These changes are measurable within several days following initiation of training and are characterized by an overall increase in blood volume, a disproportionate rise in plasma volume, and increase in the circulating mass of albumin (2), (since serum albumin and total protein concentrations remain unchanged), and a smaller increase in red cell mass. Characteristically, a highly trained runner has a hematocrit that is slightly less than it was in the untrained state. There is also a measurable increase in the number of capillaries surrounding each skeletal muscle fiber (3). The net effect is increased muscle cell perfusion capacity. Inspection of a highly trained and physically conditioned man or woman shows a person with distended veins corresponding to their increased blood volume. Such changes are apparent whether the person is an athlete or one who performs hard physical labor each day to make a living.

The purpose of physiological hypervolemia with training is clearly evident. For example, during hard work there occurs massive shunting or displacement of blood to those organs performing the work and to those organs that provide fuel for the work. For example, muscle blood flow at rest is extremely low; perhaps only 1-2 ml/min/100g. During hard work, it may rise to values approaching 40 mL/ 100 g of muscle/minute. When one considers that nearly 40 or 50% of our total body mass is skeletal muscle, and if one is performing a type of work that employs virtually the entire muscle mass, the amount of blood volume diverted to skeletal muscle must be enormous.

There also occurs a direct loss of water from arterial blood into working muscle cells. There is good evidence that intracellular osmolality rises during physical work due to formation of osmotically active substances in the muscle cell as a result of metabolism. One can show that during initial contractions of a muscle that there occurs a loss of plasma water that at least initially may amount to about 10% of muscle cell volume (4). In support of this, muscle swelling or total muscle volume increases during work over and above its content of blood. This cellular swelling rapidly reaches a plateau because of Starling forces in capillary blood, tissue pressure and a resulting increase of plasma tonicity about the muscle fiber.

It is critical that blood flow be maintained in vital organs during physical work although they don't directly participate in the work. For example, hepatic blood flow must be sustained during exercise, since if it fell, lactate and other metabolites such as alanine destined to return to the liver could not be utilized to maintain glucose output. Actually, total blood flow to the liver does decline somewhat, but with the help of glucagon and epinephrine, both released during exercise, its net output of glucose rises (5). Continued blood flow to the liver stands in sharp contrast to alterations of blood flow to other abdominal viscera during exercise. Exercise, especially when conducted in the heat, demands severe reductions in blood flow to "non-essential" vascular compartments. These reductions of flow are mediated by vasoconstriction that appears to result from the action of norepinephrine (6). Major reductions or perhaps even frank elimination of blood flow may occur in areas such as the kidney (7), the gut and perhaps the spleen. (The latter mechanism is not nearly so important in man as it is in the dog. Resting dogs may have enormous spleens. During exercise, the spleen constricts and results in a massive autoinfusion of blood so as to maintain blood volume in more critical beds). The vascular pools that obviously must maintain substantial blood flows during exercise include the brain, the heart and lung, the liver and skeletal muscle. In their respective vascular beds, on-going metabolism releases vasodilator substances which overcome the vasoconstrictor effects of norepinephrine (6). If heat is being generated and stored when work is performed in a hot environment, skin blood flow must increase accordingly to facilitate heat loss.

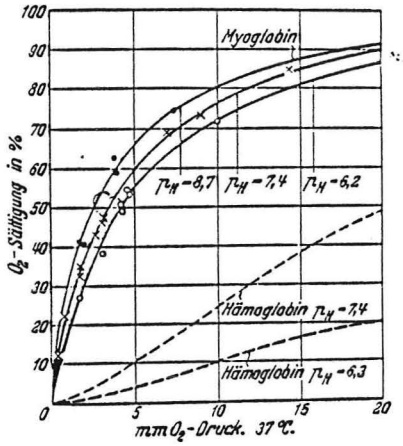
The increase of circulatory volume necessary to sustain blood flow to critical vascular beds during hard work, especially work in the heat, requires retention of water and salt along with increased synthesis of proteins, especially albumin. Salt and water retention occur in response to activation of the renin-angiotensin system, increased aldosterone production and increased secretion of anti-diuretic hormone (8). Other hormones are also "over-produced" in response to exercise training. One is growth hormone, which also has the capacity to increase retention of salt and water (9). However, the dominant hormones appear to be renin, angiotensin II, aldosterone and ADH.

B. Increased Oxygen Delivery

In addition to mechanisms that increase the capacitance and volume of the circulatory system, other important changes occur that facilitate increased delivery of oxygen. Increased blood volume and increased red cell mass both help maintain oxygen delivery to working tissue. Some investigators have also described an increase in the content of 2, 3-diphosphoglycerate in red cells (10). This substance, produced only in the red cell, facilitates oxygen dissociation from hemoglobin. There also occurs an increase in myoglobin content of

skeletal muscle cells (11,12) so as to provide increased delivery of oxygen to mitochondria that in turn sustains production of ATP. The major functional difference between hemoglobin and myoglobin are the different P-50 values. The P-50 is the oxygen tension of blood at 37° when 50% saturated. The value for hemoglobin is 26 mmHg. In sharp contrast, the P-50 for myoglobin (see Figure 1), is about 3 mmHg (13). Although the total amount of oxygen bound to

Figure 1



37° C. ●: p_H = 8,7. ×: p_H = 7,4 ○: p_H = 6,2.

myoglobin is small in terms of total oxygen consumption during exercise, the low P-50 implies that the major function of myoglobin is to release oxygen under conditions of extreme hypoxia so that ATP production can proceed. It also means that myoglobin has an intense affinity for "low" oxygen tensions, such as that existing in venous blood. Thereby, it serves as an oxygen shuttle to deliver oxygen to mitochondria that could otherwise escape (14). The effect of myoglobin is highly important in oxidative types of muscle fibers such as the heart and red (Type II) muscle. In these fibers, damage is closely related to inadequate resynthesis of ATP, which in turn is related to local hypoxia. Of interest, most forms of rhabdomyolysis, and especially exertional rhabdomyolysis, predominantly damage red muscle fibers. Myoglobin content, which usually averages about 0.3% of wet weight of skeletal muscle, may nearly double as the result of intense prolonged endurance training. This would explain why trained muscle fibers become red since the redness is the result of myoglobin content.

IMPROVED FUEL STORAGE

One of the biochemical hallmarks of physical training is an increase in muscle glycogen content. In the untrained state, muscle glycogen content is about 1% wet weight. Training may increase this value to 2 or 3% (15). Manipulations of the diet in conjunction with training may further increase this value up to 5% wet weight (16). Glycogen is the most important fuel under conditions of ischemic exercise. It is not possible to sustain maximum work after glycogen stores become depleted. Under conditions of maximum work, oxygen delivery to skeletal muscle becomes inadequate to maintain the required quantity of ATP solely by oxidative metabolism. As a result, glycogen is split into glucose and because of hypoxia, each millimole of glucose when metabolized to lac-

tate results in the production of 1 mmol of ATP. Even though glycogen content of skeletal muscle increases three-fold to five-fold as the result of training, the major adaptation to training for sustained submaximal work such as that performed by a long distance runner must be an increased oxygen delivery and increased oxidative capacity of skeletal muscle cells to produce ATP. Although glycogen metabolism dominates as the energy source in the early part of a race, eventually as glycogen disappears, the major fuel becomes fatty acids.

In contrast to changes of glycogen content in response to training, lipid content of skeletal muscle tissue also increases substantially as the result of exercise training. Morgan and his associates (17) studied this response in muscle biopsies obtained from the quadriceps muscle from individuals who exercised daily on a bicycle odometer for a period of four to six weeks. The human volunteers for these studies exercised their right leg while the left leg rested. Biopsies were obtained from both legs in serial fashion so that each individual served as the control. After this period of time, there was an average change of total phospholipid content of skeletal muscle from 45.98 to 53.33 mmol/g dry weight. In some individuals, there was a rise from 33 to 58 mmol. Phosphatidylcholine rose in the exercised leg from 23.55 to 28.60 mmol/g. Cholestrol did not change. However, triglycerides rose from 27.6 to 50.5 mm/g dry weight. When these quantities are expressed in terms of potential caloric yield, exercise training resulted in about a 10% increase in fuel from stored triglycerides in muscle cells as the result of training.

IMPROVED FUEL UTILIZATION

Mitochondrial mass and individual size of mitochondria both increase in oxidative type muscle cells as a result of exercise training (18). There is also a corresponding increase in the content and activity of oxidative enzymes (19). Structurally, some white fibers (Type I or glycolytic) become red fibers (Type II, oxidative) and thereby increase the capacity for ATP production (20).

Increased capacity for oxidative metabolism as a result of training has several important salutory effects. Compared to glycolysis, metabolism of glucose through oxidative pathways yields approximately 19 times more ATP. Since metabolism and heat production are interdependent, it follows that more efficient metabolism of glucose via oxidative pathways would produce less heat per mole of ATP produced. It is noteworthy that heat per se reduces the maximum capacity for physical performance and imposes a greater risk for rhabdomyolysis (21). Kozlowski and others (22) studied dogs exercising on a treadmill under controlled work loads at an ambient temperature of 20.0°C (68°F). When exercised to exhaustion, muscle temperature (quadriceps femoris) averaged 43.0°C (109.4°F) and rectal temperature 41.8°C (107.2°F). Imposition of cooling while performing work at the same capacity reduced muscle and rectal temperatures to average values of 41.8°C (107.2°F) and 40.8°C (105.4°F), extended their endurance by 45 per cent, reduced lactate elevation from 3.4 to 3.0 mmol/L, prevented the decline in muscle ATP content by about 25% and reduced the rate at which glycogen declined.

That trained athletes become less heated for a given quantity of work compared to their untrained state is unquestionable. For example, an untrained but otherwise healthy young man who runs a 500 meter race may develop a rectal temperature of 103° or 104° upon completion (temperatures of 109°F without complications have been reported)(8). After a period of brisk training for the same event, and under the same environmental conditions, if he runs 500 meters

at exactly the same speed as before, his rectal temperature may be no more than 99 or 99.5°F. Three important adaptations result in less heating. First, less heat is produced because of improved biochemical efficiency. Second, because of training, he sweats more effectively. Third, he has a larger blood volume, and because of improved cardiovascular performance, he can deliver more blood to his skin where its heat can be dissipated to the environment. The best evidence suggesting that such an individual displays improved oxidative efficiency is gained by measuring the anaerobic threshold. The anaerobic threshold is expressed as the rate of ventilation compared to the rate of oxygen consumption (23). These are usually linear. The point at which ventilation begins to outstrip oxygen consumption reflects one's maximum capacity to provide energy by oxidative metabolism. In the untrained state, the curve breaks at a lower oxygen consumption. Trained persons also show a lower lactate threshold, defined as the level of physical activity (expressed as O_2 consumption) at which arterial lactate concentrations in blood begin to rise. For any given work unit, the net level of lactate production will be less with training (24). This implies that more of a trained persons' energy production occurs as a result of converting glucose and fatty acids to CO_2 and water.

One of the perplexing adaptations that occurs in response to physical conditioning is an increase of electrical transmembrane potential difference of skeletal muscle cells. In our own studies, dogs and humans showed a substantial increase of resting membrane potential of skeletal muscle cells (25). Table III

TABLE III

RESTING MUSCLE MEMBRANE POTENTIAL

	MEDICAL STUDENTS	LONG DISTANCE RUNNERS
	n=7	n=5
AGE	21-24 YRS.	17-18 YRS.
	EM	EM
	90.2	101.4
	89.6	98.8
	92.1	97.5
	92.8	95.7
	93.0	104.3
	94.1	
	90.0	
AVERAGE	91.7	99.5
STD. DEV.	1.7	3.4

illustrates the values for resting membrane potential in highly trained, competitive long distance runners from Texas Christian University compared to an age-matched group of medical students who were active but relatively untrained. One teleological reason for this change might be that hyperpolarization of muscle cells could promote more rapid cellular uptake of potassium ions released during exercise, and thereby reduce the risk of exercise hyperkalemia. In fact, one can demonstrate in exercise-trained animals that potassium uptake by skeletal muscle cells is accelerated. On the other hand, it is also possible that muscle cell hyperpolarization could enhance glucose transport capacity. It has been shown by several investigators that insulin causes electrical hyperpolarization of muscle cells (25a,25b). Zierler examined the possibility that hyperpolarization per se could somehow be responsible for glucose transport mediated by insulin. Employing patch clamp techniques, he showed that hyperpolarization in the absence of insulin promoted glucose uptake in skeletal muscle cells (26). Training results in a slight reduction of baseline insulin levels (27). However, glucose transport or glucose disappearance rates following insulin administration to trained individuals shows that training enhances

insulin-mediated glucose transport by 250 to 500% (28). In normal subjects, as well as in trained subjects, exercise causes a reduction of insulin release from the pancreas and a reduction of insulin levels in plasma (29). Insulin is not necessary for glucose uptake by skeletal muscle cells during exercise. In fact, it is important that insulin levels fall during exercise so as to permit continued glucose availability to the brain. Perhaps this explains why fatty acids are the favored fuel for muscle metabolism during sustained moderate exercise (30).

Besides increased capacity for fuel delivery, enhanced fuel storage and more efficient fuel utilization, a number of other events occur that reflect a higher threshold against development of rhabdomyolysis. These include (1) increased activity (25) and probably density of Na, K-ATPase activity in muscle cells probably for the purpose of ameliorating exercise-induced hyperkalemia, (2) because transport capacity for sodium ions is also increased, electrogenicity would correspondingly rise so as to facilitate non-insulin-mediated glucose uptake, and because some Na^+ is exchanged for H^+, (3) a reduction of metabolic acidosis after a given unit of exercise. Net acid (H^+) production would be substantially less if ATP is produced by oxidative (metabolites are CO_2 and H_2O) rather than glycolytic (Lactate + H^+) pathways, (4) if intracellular acidosis is reduced, the rate of substrate flow through the glycolytic pathway will be more rapid since relative acidosis will not reduce phosphofructokinase activity (31). The effect of Na:H exchange by mitochondria has not been examined to determine the effects of training. Resiliency of the sarcolemma may also improve since it can be shown that training reduces myoglobin release or myoplasmic enzyme release after exercise (32,33).

Despite the influences of training, a highly conditioned individual can push himself to higher levels of performance, implying greater levels of exertion and when performing at peak levels for a sufficient period of time, can still develop rhabdomyolysis with all of its complications in an identical manner to a person who is less well trained. Thus the protection produced by decreased lactic acid accumulation, a higher anaerobic threshold, decreased release of muscle enzymes after exercise, or decreased release of myoglobin into the circulation after a given athletic event, reflects resistance to injury only for that particular level of performance at which training was aimed.

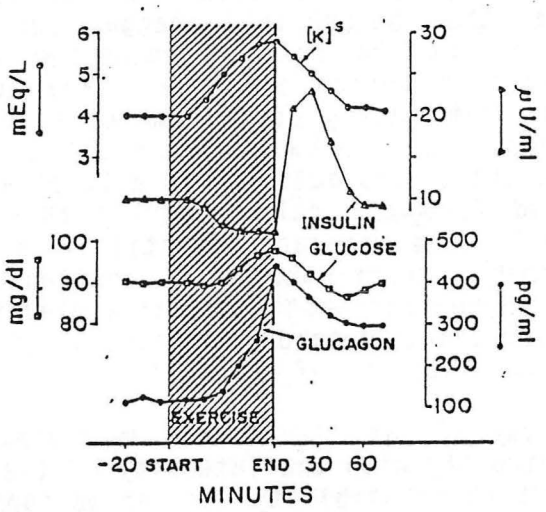
THE STATUS OF TRAINING AND BASAL METABOLISM

Some avid runners believe that so long as they remain in peak condition by running that virtually any type or amount of food can be consumed without the hazard of gaining weight. In terms of the law of mass action, such a notion would appear preposterous. Yet there is increasing evidence that it is true. At least it may be true in certain circumstances.

It is well known that exercise elevates the resting metabolic rate to a level required for the work being performed. However, the interesting point to be made is that increased energy consumption persists up to 12 to 18 hours following completion of high intensity exercise (34). If less intensive exercise is conducted, recovery of the basal metabolic rate to the normal baseline occurs rapidly. It was demonstrated (35) that if exercise were preceded by a meal or under conditions of insulin administration, the resting metabolic rate after exercise was intensified. Thus, it has been postulated that post exercise hypermetabolism might somehow involve insulin.

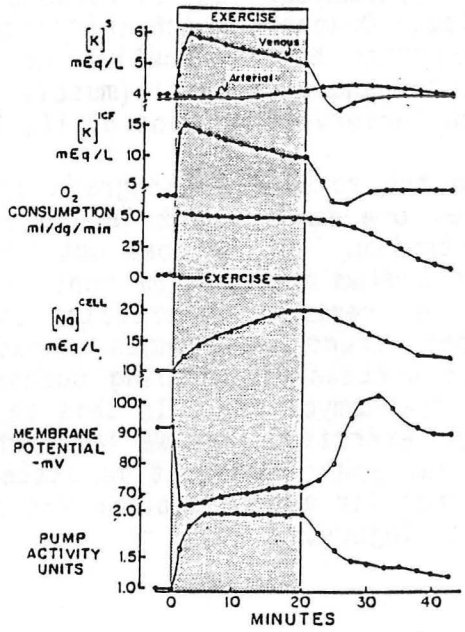
Figure 2 shows that although insulin-secretion is suppressed during exercise, it may increase sharply upon completion of exercise. Since this apparently does not occur as a result of hyperglycemia, it has been postulated that exercise-induced hyperkalemia may be the insulinogenic factor under such circumstances. Thus, upon completion of exercise, insulin through its action on sodium and potassium exchange would constitute a physiological mechanism to speed up recovery from hyperkalemia.

Figure 2



At this point, I would like to propose a hypothetical explanation for sustained post exercise hypermetabolism. Figure 3, represents a number of events

Figure 3



that occur in muscle during and immediately following exercise produced by stimulating the intact gracilis muscle of the dog (36). The top portion of this figure illustrates net release of potassium from contracting muscle fibers into the interstitial fluid (ICF) which is reflected by leakage into capillary blood and then into venous blood, so called "exercise hyperkalemia". This hyperkalemia persists throughout the period of exercise. Since potassium concentration in this range exerts potent vasodilator properties , interstitial hyperkalemia is thought to play a role in facilitating increased muscle blood flow during exercise. Adenosine release during exercise also appears to play an important role in maintaining vasodilatation. In the lower mid portion of the figure is illustrated the sequential changes of intracellular sodium concentration. Sodium enters the cell as potassium escapes. The membrane potential becomes depolarized during exercise. The activity of the sodium-potassium pump increases immediately during exercise, probably in response to the increase of intracellular sodium concentration. Upon completion of exercise, as the pump continues its activity at a level above the resting value, sodium is slowly cleared from the cell. During this process, potassium is pumped back into the cell. The membrane potential recovers and in fact, overshoots temporarily, probably corresponding to continued potassium uptake and hypokalemia. Note that oxygen consumption remains elevated in the muscle cells presumably reflecting increased metabolic activity of the pump required to remove sodium ions from the interior of the cell.

It seems very likely, at least in my view, that post-exercise hypermetabolism varies directly with the intensity of the exercise performed and in fact, if one considers the possibility that exceptionally strenuous activity leads to cellular injury, which in this case would imply an ongoing sodium leak, then it would be necessary that the muscle cell work harder to expel sodium ions and in the process, show a sustained increased oxygen consumption or heat production so long as this abnormality persists. In fact, if one administers insulin after exercise (35) or norepinephrine (37), the period of hypermetabolism is exaggerated and prolonged. It is well known that insulin increases sodium permeability in muscle (25b). In a human subject, it would be interesting to determine if post-exercise hypermetabolism corresponded to the level of CK enzyme release during exercise. Ouabain, which specifically blocks Na, K-ATPase activity, eliminates post-exercise hypermetabolism in the dog (36). It also seems likely that cardiac output and peripheral (muscle) blood flow must also be sustained at higher levels to subserve the needs of the hypermetabolic muscle.

The notion expressed in the foregoing paragraph probably fits in with the concept that to train muscle, one must induce injury first. "One can't train without pain" is probably a truism. If one does not train sufficiently so that muscle is injured and permit sodium and calcium ions to enter, there is probably no mechanism to destroy and restructure proteins to facilitate the process of hypertrophy or induce other structural changes characteristic of the trained cell. This would imply that successful training pushes muscle cell injury to the verge of overt injury or rhabdomyolysis. In this sense, the CK release that occurs in normal persons after exercise which we label rhabdomyolysis is clearly physiological. It also implies that the putative state of hyperphagia without fear of becoming fat demands regular exercise of sufficient violence to maintain a persistent state of cellular injury.

II. EXERTIONAL RHABDOMYOLYSIS

A. WHITE COLLAR RHABDOMYOLYSIS

Exertional rhabdomyolysis is most commonly seen in intelligent, educated persons such as physicians, medical students, businessmen, school teachers, preachers and in others whose work schedule permits considerable time for running. None of these individuals perform particularly hard work during the day and for this reason seem to have enough energy to run several miles each day or several days of each week. In contrast, exertional rhabdomyolysis seldom occurs in blue collar people such as carpenters, plumbers, dockworkers, farmers, construction workers or other manual laborers. They work so hard during the day that they do not feel "up to" running after work. Exertional rhabdomyolysis likewise almost never occurs in alcoholics, bartenders, policemen or taxi cab drivers because they are more interested in other commitments than running.

Many episodes of white collar rhabdomyolysis follow participation in a competitive run. Commonly, the victim will be in reasonable physical condition but not at the level necessary to keep up with an accomplished pacesetter. The history is often stereotyped. They begin a race that usually is scheduled for 10,000 meters or more or perhaps even a marathon. Between the 5th and the 10th mile, they wander off the course and appear pale. Upon examination, very little is evident except disorientation, a slightly depressed blood pressure, a moderate heart rate and fever of 101° to 103°F. The absence of hyperthermia and the presence of pallor and sweating clearly eliminate heatstroke as a diagnosis. Hyperventilation may be a prominent finding. Laboratory findings at this stage usually disclose hypernatremia, mild hyperkalemia, hyperphosphatemia mild to modest lactic acidosis, hyperuricemia, and modest elevation of CK. As a rule, improvement occurs rapidly upon infusion of fluids and the lactic acidosis vanishes. Early on, the urine usually shows some formed elements such as red cell casts and granular casts (athletic pseudonephritis), a 1+ or 2+ reaction for protein and a positive dipstick test for heme pigment, which is presumably myoglobin. The serum is never discolored. The specific gravity for the urine at this stage will commonly be in the vicinity of 1.018 or higher.

The patient usually deteriorates by the next day. Frank oliguric acute renal failure, florid rhabdomyolysis, hypocalcemia, and all of the signs of disseminated intravascular coagulation may appear. Acute respiratory distress syndrome may occur in severe cases. Disseminated intravascular coagulation (DIC) is a universal finding and in some patients may completely overshadow a relatively minor degree of rhabdomyolysis. Usually, the DIC is at its worst on the 3rd to the 5th day and if the patient does not bleed severely, spontaneous improvement occurs by the 10th to the 14th day. Bleeding may be so severe that fresh frozen plasma is required. Fortunately, the youth and stamina of most patients who develop this illness probably accounts for the fact that most recover.

Table IV lists laboratory values anticipated in a typical competitive runner who develops exertional rhabdomyolysis.

TABLE IV

BIOCHEMICAL FINDINGS IN ACUTE RHABDOMYOLYSIS

1. HEME PIGMENT IN URINE (MYOGLOBIN IN PRESENCE OF CLEAR SERUM
2. ELEVATION OF SERUM CPK OR ALDOLASE
3. DISSEMINATED INTRAVASCULAR COAGULATION
4. HYPERKALEMIA
5. HYPOCALCEMIA
6. HYPERPHOSPHATEMIA
7. HYPERURICEMIA
8. HIGH CREATININE: BUN RATIO
9. HYPOALBUMINEMIA

Although white collar rhabdomyolysis is most apt to occur in warm or hot weather, a good number of cases have occurred under rather modest conditions. The mechanism to explain disorientation and pallor that occur while running is not at hand. Although there might be a decrease in cardiac output and in turn decreased cerebral perfusion, physical findings of pulmonary edema have not been described in such cases. Perhaps vasodilatation becomes so pronounced in the peripheral circulation (muscle) so as to reduce venous return, and in turn, cardiac output. Usually there is nothing in the past history of these individuals that would predict such an event except the possibility that they are inadequately trained to perform at the level required for competitive running. Under conditions of non-competitive running, such an individual would likely stop, rest and recover. However, in a competitive race, the zeal to win or the shame of quitting apparently provide the drive that appears to be the coup de grace.

Some patients with white collar rhabdomyolysis die. The following case is representative:

> A 34 year old white man, a community leader, was an avid runner who had successfully participated in long distance competitive runs on many occasions. He participated in a 10,000 meter race sponsored for charity purposes in the spring of 1986. The dry bulb temperature had been recorded at the unusual level of 87° which was inordinately hot for this part of the United States. The humidity was also said to be high but no value was obtainable. He had completed a 10,000 meter run three days before the event. Whether he did this for the purpose of unloading or whether he consumed a high carbohydrate diet was unknown. He had nearly completed the race when he fell. He managed to get up and struggle across the finish line, collapsed again, and became unresponsive.

Apparently no treatment was given at the site of the event. He arrived in the local hospital admitting room about 15 to 30 minutes following his collapse. He was unresponsive, showed a blood pressure of 60/0 and a rapid thready pulse. His temperature was not taken. Because an observer felt that he might have struck his head on the ground after his first collapse, he was immediately taken to the CAT scan lab that resulted in a two hour delay of further treatment. The CAT scan of his head was within normal limits. His initial laboratory data were as follows:

Laboratory Data Case 1.

A. 45 MINUTES POST COLLAPSE

BLOOD	Na^+	145 mEq/L	BUN	10 mg/dL	
	K	5.8 "	Cr_{+2}	2.5 "	
	Cl	102 "	Ca^{+}	10.4 "	← very bad prognostic sign.
	HCO_3	< 8 "	Alb	1.7 G/dL	
	Anion Gap	> 25 "	Gluc	259 mg/dL	
	CK	37,000 IU/L	Uric	17.0 "	
	HCT	26 vol%	Plat	88,000/mm	
	PT	28 secs.	PTT	> 180 secs.	
			FSP	> 1:160	

When he returned to the intensive care unit, the patient remained comatose and in shock. By this time he was noted to be bleeding from multiple sites and oozing from sites of venipuncture. His pupils were assymetric. A blood smear showed fragmented red cells. At this time, his rectal temperature was found to be 106°F and later 107°F. Over the course of the next few hours, the patient received 21 units of fresh frozen plasma and 18 U of packed red cells. This along with large volumes of saline in an attempt to maintain blood pressure lead to massive anasarca. Before death, his serum potassium rose to 6.8 mEq/L, his sodium fell to 126 mEq/L and his serum glucose had declined to 35 mg/dL.

Some remarkable findings are presented by the above case. Once again, the event appeared to be precipitated by a desperate effort to win just before the end of the race. This is a common occurrence in such cases and may explain why so many of them demonstrate horrible degrees of acute lactic acidosis. If this patient had undergone carbohydrate loading, his potential for lactic acid formation could have been increased enormously because of the load of muscle glycogen created by this maneuver. The last ditch effort to win could be responsible for releasing huge quantities of catecholamines which in turn could aggravate lactic acidosis. Epinephrine promotes glycolysis. Lactic acidosis of this degree can depress myocardial contractility (38). Splanchnic ischemia could also materially contribute to the lactic acidosis.

The admitting laboratory data are especially interesting in

this patient. Besides the pronounced lactic acidosis, it is noteworthy that his serum creatinine was 2.5 mg% in the face of a BUN of 10 mg%. Hypercreatininemia suggests rhabdomyolysis that was proven by the elevated CPK. Very likely, rhabdomyolysis is also responsible for the disproportionate elevation of uric acid concentration. Purine precursors released from injured skeletal muscle as well as other organs result in marked overproduction of uric acid (39). Perhaps most interesting was the patient's low value for serum albumin measured on his first blood sample. Two weeks before this patient collapsed he had undergone his annual physical examination. His serum albumin measured at that time was 4.5 g/dL. Hypoalbuminemia before fluid administration is thought to represent evidence of massive capillary destruction resulting in leakage of albumin into the interstitium of not only skeletal muscle but probably other organs. It seems that since the patient's hematocrit and hemoglobin were also normal four weeks before the race that he had also leaked a substantial amount of red cells or in fact destroyed them by some mechanism within the first minutes of his injury. The fact that he developed pronounced DIC, as mentioned previously, is seen in all patients with exertional rhabdomyolysis or exertional heatstroke. However, I have never seen such a pronounced example of DIC as that which occurred in this patient.

B. Acute Water Intoxication in Marathon Runners

Acute hyponatremia has been reported to cause rhabdomyolysis (40,41). Such cases have occurred in persons with associated illnesses. However, increasing numbers are appearing in long distance runners who, realizing that water deficits impair performance and prevent heat dissipation, over-zealously replace their water losses during the race. Although the following case reports did not include data on muscle enzymes, there appears to be no question that rhabdomyolysis occurred because of physical findings. I know of several unreported instances of marathon-associated water intoxication complicated by frank rhabdomyolysis with myoglobinuria. Of interest, only one case (41), developed acute renal failure. This negative relationship suggests once again that hydration protects against acute tubular necrosis. Of course, acute symptomatic water intoxication is a poor substitute for acute renal failure.

Frizzell and his associates (42) described self-induced symptomatic water intoxication in a medical student and a 45 year old physician who were participating in an ultramarathon sponsored by the American Medical Joggers Association in Chicago. The dry bulb temperature was 89°F. The wind velocity on the Chicago lake front was only 20 mph and consequently a bit calm for that city. An ultramarathon is a competitive run extending more than 50 miles. In this case, the two individuals ran 50 and 62 miles respectfully. The runners stopped at each first aid station along the course and consumed fluids that contained

mostly all water and a very small amount of sodium. A glance at Table V shows that the net fluid consumption by these two persons was 20 and 24 L with respective sodium intakes of 196 and 110 L, representing a markedly hypotonic fluid intakes of 9.8 and 5.5 mEq/L, respectively.

Table V—Profiles of Two Runners

Characteristics	Runner 1	Runner 2
Age, yr	24	45
Height, cm (in)	178 (70)	193 (76)
Weight, kg (lb)	74 (165)	81 (180)
No. of marathons	4	14
Best performance	2:54	3:21
No. of ultramarathons	15	1
Estimated fluid intake, L	20	24
Estimated sodium intake, mEq	196	110

For short periods of time, some individuals can produce 3 liters of sweat per hour. This rate cannot be sustained without endangering life. Studies conducted on military recruits training in hot climates have shown that sweat volumes commonly equal 10 L/day and in some individuals may amount to 12 L/24 hrs. These individuals participating in the ultramarathon ran for 8 - 10 hours. Fluid losses in marathon runners (26 mi.) who do not consume fluids during the race may amount to about 1.1 liters per square meter per hour (43), or about 4-6 liters during the race. In the ultramarathon runners described in these reports, net fluid intake greatly exceeded fluid losses. Of great interest, neither of the runners developed symptoms of water intoxication until the race had been completed. The medical student became stuporous and disoriented five minutes after finishing the race. The 45 year old physician became disoriented 30 minutes after completing the race. Their respective serum sodium concentrations were 123 and 118 mEq/L. Their laboratory values are shown in Table VI.

Table VI—Results of Hospital Admission Blood Chemistry Tests of Two Runners Following an Ultramarathon Run

Test	Reference Range	Runner 1	Runner 2
Sodium level, mEq/L	135-148	123	118
Potassium level, mEq/L	3.5-5.3	3.6	3.8
Chloride level, mEq/L	98-109	83	91
Osmolality, mOsm/L	280-295	250	248
Glucose level, mg/dL	70-110	99	153
Serum urea nitrogen, mg/dL	8-22	9	10
Carbon dioxide level, mEq/L	23-31	22	20
pH	7.35-7.45	7.30	7.56

The medical student had a convulsive seizure and within 24 hours, recovered mental function after treatment with hypertonic salt solution. The physician,

whose serum sodium was lower, completely recovered within 3 hours following administration of 3% sodium chloride solution (this may illustrate the benefits rather than the detriments of treating acute symptomatic hyponatremia with hypertonic salt. Both individuals showed normal brain CAT scans).

Competitive participation in an ultramarathon in hot weather for many hours demands marked diversion of blood volume to the skin and skeletal muscles to permit survival. Yet, life also depends upon continuing perfusion of vital organs such as the brain, the lung and the liver. This means that vasodilatation, especially in muscles and skin, must be counterbalanced by vasoconstriction in less vital areas. Otherwise, fatal hypovolemic shock would ensue. It has been shown that blood flow to the kidneys is virtually zero during strenuous exercise in hot weather (7). This has two important implications: First, there is no urine formation because GFR and renal blood flow are immeasurably low, and second, in the absence of glomerular filtration, excess water intake cannot be excreted. Because of a marked reduction in blood flow to the gut, there can be very little if any avenue for absorption of fluids taken by mouth. Rowell and his associates (5,44) have shown that splanchnic blood flow falls markedly in trained runners in relatively brief periods of time if they exercise at fifty percent of their maximum oxygen utilization. Studies of experimental animals show that the reduction of splanchnic blood flow, measured by techniques employing a flow-sensitive transducer around the superior mesenteric artery, does not occur in the presence of α-adrenergic blockade (6). Almost assuredly, professional participants in such demanding events as the 10 K race, marathon or ultramarathon, especially in hot weather, must perform at this level or higher to be competitive. Thus, it seems reasonable to assume that if there is no blood flow to the mesenteric circulation to dissipate concentration gradients, diffusion must become so limited that absorption must cease. This would explain why the two individuals described above showed no symptoms until the race was essentially finished. Upon completing the race, blood flow to the gut must become re-established permitting sudden absorption of fluid retained. Other ultramarathon runners who have consumed large volumes of fluids during the race experience sudden, massive diarrhea shortly after completing the race. This pattern suggests that ingested fluids remain within the lumen of the gut during the run and when mesentric blood flow is restored after the race, peristalsis returns and expels the gut contents. Another interesting observation possibly related to splanchnic ischemia during competitive runs is the fact that 20 per cent of these individuals develop guaiac positive stools (45), in fact, (if more sensitive tests are used) 80% are positive. Some experience frank bleeding (46) and in those who dedicate themselves to frequent long distance runs, iron deficiency is common (47). In fact, iron deficiency becomes worse in avid female runners than men, and its degree in both sexes varies directly with the frequency and duration of running each day. Lower gastrointestinal bleeding in the runner has been ascribed to "bouncing of the bowel" in the pelvis causing traumatic leakage of blood. Nausea, vomiting, and cramps during a marathon are well known among competitive runners. However, such findings in conjunction with absorption difficulties, and investigative evidence for splanchnic ischemia point to bowel ischemia and blood loss as the likely mechanism. A quote (46) from Derek Clayton, made immediately after winning the world marathon in 1979, is pertinent:

> "Two hours later, the elation had worn off. I was urinating quite large clots of blood, and I was vomiting black mucus and had a lot of black diarrhea. I don't think too many people can understand what I went through for the next 48 hours." (Runner's World, May 1979, p. 72).

It is noteworthy that the American Medical Joggers Association race guidelines recommend that runners consume 300 to 360 mL of fluid at each station along the course of a marathon. Since there is a water station each mile, this amounts to a total of 15 to 18 L for 80 kilometers (50 miles) or 18 to 22 L for 100 kilometers (62 miles). It is unfortunate that more members of this association are not fluid and electrolyte specialists since such quantities will almost certainly induce water intoxication. As a precaution, some authors now recommend that scales be used to record weights and thereby determine actual fluid loss during the course of a race. Even using weight loss as an index, there is no certainty that a runner could absorb the fluid lost as sweat. The only maneuver that would consistently work would be to have someone infuse hypotonic saline intravenously. This would be clearly impractical. One questions why would anyone in their right mind attempt to run 60 miles or indeed 100 miles on a day when the temperature is nearly 90°.

A report by Noakes and his associates (48) dramatize the foregoing comments on impaired capacity to absorb fluids by the gut during competitive running and the sudden rather massive absorption of fluid from the gut after running is completed, apparently when gut bloodflow has resumed. In reporting four cases of water intoxication, the first case is particularly interesting. This was a 46 year old woman competing in an 88 kilometer ultramarathon in South Africa. After 30 kilometers of the marathon, she suddenly developed watery diarrhea. Up to this point, she had consumed 2.5 L of dilute Coca-Cola. She continued to pass diarrheal stools and after consuming a total of 6 L of fluid, by 70 kilometers, she became exhausted, mentally confused and was forcibly withdrawn from the race. During transportation to a hospital, she suffered a grand mal seizure. She was comatose and showed persistent fasciculations. A chest x-ray demonstrated pulmonary edema and slight enlargement of the heart. She also showed marked nuchal rigidity and generalized muscular hypertonia. Both eyes were deviated to the left and the right pupil was dilated and unresponsive to light. She showed bilateral papilledema. Her serum sodium was 115 mEq/L. Treatment with saline was followed by complete recovery within 48 hours. Since then she has completed several marathons. This case illustrates the possibility that fluids cannot be absorbed normally during severe exercise but once bloodflow is apparently reestablished, absorption can occur very rapidly so as to result in water intoxication. Diarrhea is well known among long distance runners and also tends to occur more commonly upon completion of the race. In two other patients who developed water intoxication described by Noakes and his associates (48), symptoms of acute water intoxication appeared five hours after running and in another patient one hour after running. Their fourth case was a 29 year old woman competing in a triathlon, which is composed of a 6 kilometer swim, a 100 kilometer bicycle ride, and a 42 kilometer marathon. She consumed an enormous amount of water during the first two phases of the triathalon so that she was only able to complete 14 kilometers of the marathon. Her weight was 57 kg. She had ingested 8 L of fluid during the race.

The fundamental explanation for water intoxication in all of these individuals is overzealous hypotonic fluid replacement. Although it has been shown that a highly trained, heat acclimatized healthy man may produce up to 3 L of sweat per hour, in reality, very few people can accomplish this feat and under most circumstances, the salt losses associated with such sweat rates would become disabling. Most individuals produce about 1 L or perhaps 2 L of sweat per hour. This implies that even if a person attempts to replace water losses, it may be impossible to absorb such quantities because of the disturbances of gut blood flow during exercise. During hard work, norepinephrine release is

sufficient to induce vasoconstriction in every organ. The fact that blood flow to the heart, lungs and muscle increases, is ascribed to release of certain metabolic products into the interstitial fluid of those particular sites that require vasodilatation. It has been shown that metabolic products of working cells, e.g. K^+, CO_2, lactate or adenine nucleotides, exert sufficient vasodilatory properties to overcome the vasoconstrictor properties of norepinephrine (44). Where metabolism is not necessary, such as the kidney and the gut, vasoconstriction prevails. This explains why gut blood flow and renal blood flow become virtually unmeasurable during hard work, especially if it is conducted under conditions of high temperature.

C. Exertional Rhabdomyolysis in Patients with Sickle-Cell Trait

Twelve young men with proven sickle-cell trait have been described who developed exertional rhabdomyolysis. I know of an additional four cases that have been unreported. Almost all of these have been unusually severe in a sense that they present with extreme lactic acidosis and in some instances, other potentially fatal complications such as necrotic bowel or spinal artery occlusion with transverse myelitis. Two interesting cases are herewith presented:

Case 1. The patient is a 17 year old black football player with known sickle cell trait (HbAS). He died five hours after a six mile run. During the run, he developed severe abdominal pain, complained of painful cramps in his legs and collapsed. On a previous occasion, he had collapsed after running, showed severe lactic acidosis and a drop in his hematocrit and hemoglobin from normal values to 15 per cent 5 g/dL respectfully. His serum was clear and no findings suggestive of hemolysis were observed. He recovered from this episode and over the course of a year, his hematocrit rose spontaneously to 49%. Following the event preceding his death, his hematocrit and hemoglobin again plunged to similar values. He showed no evidence of bleeding. He had a very high CPK and a serum myoglobin concentration of 46 mg/dL. His urine was black. Chemical measurements showed that the urinary pigment was all myoglobin. His autopsy showed hemorrhagic necrosis of skeletal muscle, engorged lungs, engorged abdominal viscera and a normal spleen. Apparently this young man succumbed from acute sequestration of red cells in addition to rhabdomyolysis. Splenic sequestration has been previously described in patients with hemoglobin SC but not in those with sickle cell trait (49).

Case 2. A 21 year old black enlisted man was undergoing air assault training at Ft. Campbell. He collapsed following the second of two, two mile runs. The temperature and humidity on that day, March 29, 1985 were 70°F and 55% respectively. When the man was first examined, he was unresponsive, his rectal temperature was 106°. He awoke with cooling and showed a blood pressure of 100/0. His laboratory data showed a mixed metabolic and respiratory acidosis with a pH of 7.1. His urine was Coca-Cola colored and showed a positive test for myoglobin. His serum potassium was 8.5 mEq/L.

Despite resuscitative efforts, the young man remained oliguric, hypotensive and complained of marked abdominal

pain. His blood pressure fell to 60/0 and his temperature remained at 99°. He showed persistent tachycardia. His abdomen was extremely tender and showed board-like rigidity. He was oozing blood from his nose and mouth and showed laboratory findings characteristic of disseminated intravascular coagulation. During the first 24 hours in the hospital, his creatine kinase rose to 150,000 IU/L, his serum calcium was 7 mg/dL, his potassium was 7 mEq/L and phosphorus 9 mEq/L. He developed an anterior tibial compartment syndrome bilaterally which required fasciotomy.

In attempts to insert an arterial cannula for dialysis, it was noted that his muscle blood flow and arterial blood flow were both markedly reduced. Because of his rigid abdomen with absent bowel sounds, a laporatomy was performed. His entire bowel showed signs of infarction from the stomach to the cecum. Later that day, the patient became paraplegic. Death occurred 30 hours after onset of the illness. The patient's hemoglobin type was SA.

In a review dealing with death associated with rhabdomyolysis and acute tubular necrosis in patients with sickle cell trait published in 1984 (50), Diggs describes several pieces of information of potential importance. In a review of autopsy material on sudden deaths in basic military recruits between the years of 1946 and 1951, 27 were patients with sickle-cell trait. In another review of sudden deaths occurring in basic training between the years 1951 and 1971, 24 additional deaths were recorded in patients with sickle-cell trait. More recently Posey and associates published data in abstract form on basic training deaths occurring between the years of 1977 and 1981 (51). Sixty-one deaths occurred during this period of time of which 57 were sudden. Seven of these occurred in young men with sickle-cell trait; each was associated with exertion. The incidence of sudden death in persons having normal hemoglobin is 0.31 per 100,000 trainees. In persons with sickle-cell trait, the death rate was 8.36 per 100,000 per year. These authors conclude that the 27 fold greater incidence of sudden death among young men with sickle-cell trait imposes a much greater risk in this particular group of persons.

Some of the patients described above clearly had heatstroke associated with exertional rhabdomyolysis during heavy physical exertion in hot weather. On the other hand, some cases have occurred in young men exerting themselves in temperatures no higher than 62°F. The pronounced lactic acidosis seen in some of these young men suggests an undue amount of skeletal muscle hypoxia or, in addition to skeletal muscle hypoxia, a major contribution of lactate perhaps from an ischemic bowel or an ischemic liver (52). Bloody diarrhea, massive necrosis of the bowel and transverse myelitis have also been associated events in some cases (50). In some, there has been pronounced bilirubinemia with SGOT or SGPT enzyme elevations exceeding CPK values. Such evidence clearly points to major visceral arterial occlusion as well as rhabdomyolysis. The hazards of this illness imposed by high altitudes is well known (53-55).

Although much has been written on the morbidity and complications of sickle-cell trait, studies aimed at detecting abnormal responsiveness to exercise in such individuals have up to this point yielded little relevant information. Dr. Idell Weisman, who supervises a pulmonary laboratory at the William Beaumont Army Hospital in El Paso, located there because it is 5,000

feet above sea level, has shown that young men with sickle-cell trait develop up to 25% sickling in vivo when working at 4000 meters above sea level. They also show hypoxia and lactic acidosis. Such findings have not been observed during work at lower altitudes (56). A study conducted by Robinson and his associates (57) examined exercise capacity in black men with sickle-cell trait men whose age ranged between 15 to 25 years to determine their exercise capacity. Sixteen such subjects were compared to matched young men without sickle-cell trait. There was no difference in exercise capacity, oxygen consumption, heart rate, or their electrocardiograms. Although one might postulate that if similar studies were conducted under conditions of heat stress and dehydration, and if the degree of exertion were pronounced as it often is in the competitive athlete, that differences would become apparent. Yet, the overall incidence of exertional rhabdomyolysis and the associated destructive complications remains rare in terms of the total number of young men with sickle cell trait who participate in competitive sports. Obviously, thousands of black athletes with sickle-cell trait have successfully competed in major athletic performances repeatedly without complications. Perhaps those individuals who develop such complications must have either defects in their red cells or other tissues that favor development of this syndrome. Although its cause is unknown, it would seem prudent to ensure that black athletes with sickle-cell trait avoid hypoxia and make every attempt to maintain hydration and salt balance during athletic events and if possible, either avoid such activities or take special precautionary measures during hot weather. It should be clearly appreciated that rhabdomyolysis has not been a substantial complication in patients with SS Disease. One study attempted to implicate non-traumatic rhabdomyolysis as a cause of renal injury in two patients with sickle cell crisis (58). In these patients, total CK values were only 470 and 290 IU/L. Such trivial values are substantially lower than those seen in patients with rhabdomyolysis and myoglobinuria precipitating acute tubular necrosis.

D. Rhabdomyolysis in Women: An Exceptionally Rare Event

Rhabdomyolysis associated with septic shock, electrolyte disturbances, mineral deficiencies, drug abuse or alcohol appears to occur with equal frequency in both men and women. However, exertional rhabdomyolysis is virtually unheard of in women. This is interesting because an ever-increasing number of women are participating in competitive endurance races and although women may become unstable while running (as witnessed by the world watching television during the last Olympics), there are no reports of clear-cut exertional rhabdomyolysis in ladies. A complicated case of exertional rhabdomyolysis and heatstroke was recently reported by Pattison and his associates from Tucson (59).

> A 25 year old woman from Virginia was vacationing in the Grand Canyon in the month of September. She maintained a state of hydration equal to other members of her party. However, after walking down into the canyon for a period of four hours, she suddenly collapsed and became unconscious. She was noted to have moist but warm skin. Her fellow hikers immediately carried her further into the canyon and immersed her into the Colorado River. Four hours later she was evacuated by helicopter to a hospital and was noted to have a temperature of 104°. Cooling was effected with ice packs during transportation to the hospital. Her initial laboratory data are shown in the following Table. It is remarkable that

Laboratory Data. Lady in Grand Canyon

WBC	23,300/mm^3	PT	24.2 secs	Na	147	BUN	21
Hb	16.4 g/dL	PTT	42.4 secs	K	3.0	Cr	3.2
Hct	50.8 vol%	FSP	elevated	HCO_3	10	Uric	20.1
Platelets	< 5000/mm	Urine-casts, red cells				CPK	1,600,000 IU/L

she showed findings almost identical with horrible cases of white collar rhabdomyolysis in men characterized by profound DIC, and a CPK value of 1.6 mIU. She went on to develop the purpuric manifestations of thrombocytopenia and a muscle entrapment syndrome involving the anterior tibialis muscle in her left foot. Hemodialysis was required because of acute renal failure with anuria for six weeks. One year later, her serum creatinine was 1.3 mg/dL. Her foot drop disappeared.

An explanation for the virtual absence of exertional rhabdomyolysis in women is not apparent. Some studies of body heat accumulation during work in hot environments seems to indicate that women are able to cool themselves more effectively than men in terms of quantity of work produced per body surface area or in terms of body weight (60-62). It has been shown that men sweat more voluminously than women for a given degree of heat stress and in addition, men demonstrate greater evaporative sweat losses than women under comparable conditions (63). Under carefully controlled conditions of work, it can also be shown that when women are pre-ovulatory, body heating is less than men. This is no longer true in the post-ovulatory phase of the menstrual cycle (63). Supportive evidence for this observation has been published on oophorectomized rats given estrogens (64).

The possibility exists that the woman with rhabdomyolysis described above was potassium deficient because hypokalemia in a patient with severe rhabdomyolysis, oliguria and metabolic acidosis is distinctly unusual. Hyperkalemia is the rule under such conditions. It seems possible that potassium deficiency might have impaired muscle blood flow during exercise and lead to inordinate heat buildup, and contributed to the development of rhabdomyolysis (65).

There have been several interesting studies showing differences in CPK release in men and women following exercise. Table VII is taken from a paper by Shumate and his associates (66) comparing the effect of 120 minutes of half

Table VII

Sex differences during exercise

	Men (Mean ± SD)	Women (Mean ± SD)	$p(\sigma^{\prime} > \varphi)$
Increase in serum lactate (mM)	5.4 ± 1.8	5.4 ± 1.6	< 0.4
Work load: body mass (kpm:kg)	8.9 ± 2.3	10.0 ± 1.9	< 0.8
Baseline CK (before exercise) (mU/ml)	122 ± 109	72 ± 23	< 0.3
24-hour CK (after exercise) (mU/ml)	664 ± 646	152 ± 111	< 0.01
Δ CK (24-hour - baseline)	541	81	< 0.01
24-hour: baseline CK	9.69	2.13	< 0.02

maximal exercise on a bicycle ergometer. Blood sampling was conducted before, during, immediately after and for 72 hours after the exercise. Maximum exercise capacity was determined before the study was accomplished. Lactate levels in venous blood were not different. Baseline CPK values were higher in men, perhaps reflecting a larger muscle mass. Twenty-four hours after exercise, men showed an average CPK of 664 IU/L compared to 152 IU/L in women. Speculating about this difference, the authors cited a greater penetrance of disease manifestations in males with X-linked muscular dystrophy. They also point out that diethylstilbestrol reduces CK in Duchenne dystrophy patients, implying that estrogens may be a "CPK-protective" factor. They also point out that since an elevated CPK is expected in men following exercise of the intensity applied in their study, which is equivalent to recreational forms of exercise, a similar elevation in a women following should alert one to the existence of a myopathic process.

Nicholson and associates (67) studied the effect of aerobic exercise on serum CPK activity in 15 young women. Their average CPK activity was 77 IU/L and rose to a mean value of 681 IU/L. Most of these subjects noted muscle pain. These investigators pointed out that aerobic exercise at least partially consists of mixtures of concentric and eccentric muscle contractions. Concentric contractions refer to muscle shortening such as that performed while stepping up. In contrast, eccentric exercise is that characterized by stepping down in which a muscle is absorbing energy while lengthening. Several studies have pointed out that eccentric muscle contractions are more likely to result in pain and stiffness. Newham and coworkers (68) examined the effects of eccentric exercise in 8 normal men and 8 normal women. They examined CPK levels after prolonged exercise patterned after the Masters two step test. The test was standardized by adjusting the level of the step to 110% of the lower leg length. The study was conducted so that the quadriceps muscle of one leg contracted concentrically by stepping up while the contralateral leg was used in stepping down, thus representing eccentric muscle contractions. Steps were conducted at 15 cycles per minute. Figure 4 illustrates the response to these studies. All

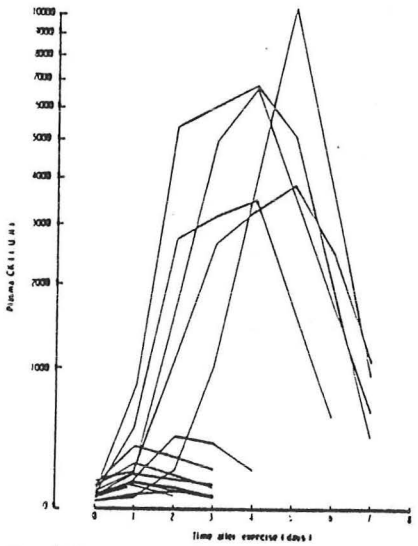


Figure 4 Plasma creatine kinase in 13 normal subjects after stepping for 20 minutes. Note the two groups of response, those showing smaller increases peaked at 1–2 days after exercise while the larger responses peaked at 4–5 days.

of the subjects showed a small CPK rise immediately after the exercise which continued to rise for the first 24 hours. Seven of the subjects showed a return of CPK to normal within this time. However, five of the subjects showed a sizable rise of CPK up to 10,000 IU/L that occurred several days after the exercise. Of interest, four of those showing the delayed peak were women. Additional studies were conducted on three men who performed the step test until fatigued. The results of this study are shown in Figure 5. One of the individuals showed

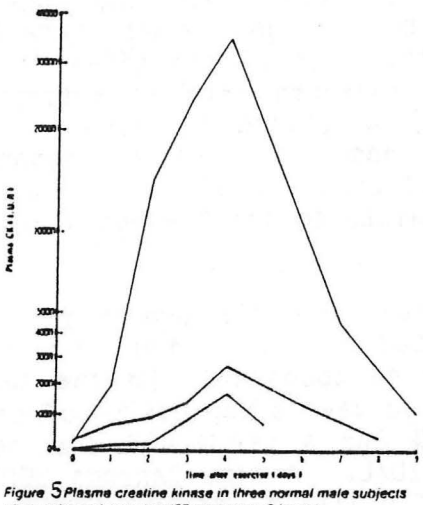


Figure 5 Plasma creatine kinase in three normal male subjects after prolonged stepping (50 minutes to 2 hours).

a marked delay in response of CPK that approached 40,000 IU/L. Muscle pain and tenderness in all of these subjects was noted only in muscles used for eccentric work, implying the quadriceps and gluteal muscles of the leg used in stepping down and the calf of the contralateral leg strained by stepping down onto pointed toes. Friden and associates (69) examined morphology of muscle from normal persons following downhill running and observed extensive areas of z-line streaming compatible with early rhabdomyolysis. Evidence that rhabdomyolysis is worse in experimental animals after downhill running has also been published (70). In this light, it is perhaps interesting and noteworthy that the case of the women with exertional rhabdomyolysis was walking <u>down</u> into the Grand Canyon while her episode occurred.

III. <u>MASSIVE RHABDOMYOLYSIS ASSOCIATED WITH TOXINS OR DRUGS</u>

One of the hallmarks of exertional rhabdomyolysis in an otherwise healthy person is the physical finding that the muscle injury is usually limited to those muscles used during the exercise. Thus, a long distance runner who develops exertional rhabdomyolysis usually shows pain, stiffness, swelling and weakness involving the muscles of the leg, the buttocks or perhaps the lower abdomen

but usually not muscles of the upper extremities. In contrast, myotoxin-associated rhabdomyolysis may involve all muscles. Two examples of such syndromes follow:

A. Rhabdomyolysis with Rattlesnake Venom

> A 26 year old man was admitted to the University of Texas Medical Branch in Galveston following a bite on his index finger by his pet rattlesnake! He had been drinking beer during the evening and upon returning home decided to remove the snake from its cage. Since there was no immediate reaction at the site of the bite, it was assumed that the venom was injected into an artery or a vein. Within a few hours, he became extremely ill, lethargic and was taken to a hospital. He was hypotensive upon arrival with a blood pressure of 80/60. An appropriate anti-venom was administered intravenously and a dopamine infusion was begun.
>
> The patient's initial oliguria progressed to absolute anuria that persisted for a period of 7 days before small amounts of urine appeared. On the second day of the illness, he showed severe depression of serum calcium from 8.6 to 4.5 mg% and a serum CPK that was approximately 2.5 million IU/L. A simultaneous SGOT value was 17,820 U. Frequent dialysis was required. Because of diaphragm weakness and hypoxia he had to be placed on a respirator. By the fourth week, the patient had entered a frank diuretic phase. By this time he had lost 53 lbs. Two months later his serum creatinine was 0.9 mg% and his blood urea nitrogen 9 mg%. His creatinine clearance at that time was measured at 108 cc/minute.

This is a remarkable case because as far as I know it represents the first case of rhabdomyolysis, myoglobinemia, hemoglobinemia and frank myoglobinuria resulting in acute renal failure from a rattlesnake bite. Several cases have been described in the past of rhabdomyolysis and acute renal failure from bites of the common seasnake (enhydrina schistosa) (71), a condition that can be reproduced by injecting the venom into mice (71). A report from Brazil describes two patients with rhabdomyolysis, myoglobinuria and acute renal failure following invenomation by the South American rattlesnake which closely resembles rattlesnakes found in Southern United States (72). However, except for direct tissue destruction at the site of invenomation, which obviously includes rhabdomyolysis, generalized rhabdomyolysis has not been described except in the single report above and the case described from Galveston. Most cases of rattlesnake bite associated with acute renal failure have occurred in the wake of hemolysis and hemoglobinuria. It is well known that rattlesnake venom contains mixtures of neurotoxins and hemolytic toxins. The patient described above showed virtually generalized paralysis requiring respiratory support. Whether this was a neurotoxic effect or the result of generalized muscle destruction cannot be discerned. Nevertheless, he showed generalized muscle swelling and tenderness suggestive of global muscle necrosis. The fact that he recovered after a period of four weeks appears more compatible with muscle injury than nerve injury. To my knowledge, this is the highest value for CPK in a patient with rhabdomyolysis ever recorded. A value almost as high, 2.1 mIU/L

was measured in a patient managed by Dr. Jack Coburn in Los Angeles who developed rhabdomyolysis as a result of injecting ritalin (73).

B. Rhabdomyolysis Following Cocaine Overdose

Some patients with rhabdomyolysis associated with narcotic overdose, especially heroin, clearly develop muscle necrosis because of prolonged compression and ischemia of a limb secondary to coma. However, other cases fit the theory that these drugs may also be primarily myotoxic, since rhabdomyolysis may be severe and generalized, apparently involving all muscles, and occur in persons who have not become comatose.

An illustrative case of generalized rhabdomyolysis, intestinal infarction and transverse myelitis following a cocaine (crack) overdose was recently seen in Parkland Memorial Hospital. This case is especially interesting because it resembles some cases of sickle cell trait with rhabdomyolysis, intestinal infarction and transverse myelitis.

> A 23 year old white man with a history of cocaine (crack) abuse was admitted to Parkland Memorial Hospital. Two years previously he had undergone evaluation for ventricular bigeminy. Before this admission, he was observed by the police to be smoking "crack". While attempting to escape, he collapsed. The distance he ran was unknown. The patient stated that his legs became so weak that he fell. He also complained of severe pain in his legs. The paramedics recorded a systolic blood pressure of 90-110 mmHg, a pulse of 130-140/min, a respiratory rate of 30/minute. His temperature was normal.
>
> Physical examination on admission showed an alert and oriented young man with a blood pressure of 160/70 mmHg, pulse 108/min. and respirations of 28/min. Cardiac examination showed a summation gallop and a systolic ejection murmur along the left sternal border. The abdomen was rigid, diffusely tender and showed no bowel sounds. There was no rectal sphincter tone. Peripheral pulses were bounding and symmetrical. Both legs were paralyzed. Deep tendon reflexes were absent. There was no response to pain. He was thought to have a sensory level at T-10. He had been anuric since admission.
>
> Pertinent laboratory findings on admission showed hyperkalemia (6.7 mEq/L, Na 141, Cl 104, HCO_3 7, phosphorus 14.0, calcium 6.6 mg/dL, creatinine 2.2, CPK 4780 IU/L, LDH 512, lactate 22 mmoles, and WBC 18,000 with a left shift). Platelets were normal. Arterial blood showed a pH of 7.11, pCO_2 27 and pO_2 97 mmHg. X-rays of the thoracolumbar spine were normal. An electrocardiogram showed effects of hyperkalemia.
>
> The patient quickly became unresponsive as his blood pressure fell to 50/0. He required saline, dopamine and bicarbonate to maintain his blood pressure. Hemodialysis was begun for hyperkalemia. Eventually, distal pulses in the legs were

lost because of compression by edema fluid. A peritoneal lavage revealed grossly necrotic bowel and foul fluid. The patient expired. His CPK before death 13 hours after admission had rise to 170,000 IU/L. A section of muscle removed after death showed gross rhabdomyolysis. Cocaine and ethanol (82 mg/dL) were identified in a blood sample.

Unfortunately, a complete autopsy was not performed on this young man. Since he showed no clear-cut findings of aortic rupture or dissection, which have been reported in fatal cases of poisoning with cocaine, crack or amphetamine (74), we must assume that intense vasoconstriction resulted in mesenteric infarction, transverse myelitis and rhabdomyolysis. One can also assume that ischemia of the spinal cord probably resulted from spasm or occlusion of the artery of Adam-Kiewicz (75).

In high concentrations, cocaine prevents re-uptake of norepininephrine by preganglionic sympathetic nerves. Re-uptake of norepinephrine normally stops α-adrenergic stimulation (76). In the presence of cocaine, the vasoconstriction action of circulating norepinephrine will be markedly accentuated.

Extremely high levels of norepinephrine can depolarize cells and by mechanisms not clearly understood, facilitate release of Ca^{++} ions from the sarcoplasmic reticulum of skeletal muscle cells (77,78). High levels of cytoplasmic Ca^{++} in muscle cells (79) and endothelial cells (80), can initiate a cascade of events that culminate in cell destruction or lysis.

Drugs abusers commonly blend cocaine or crack with phencyclidine, heroin, amphetamines or strychnine (81). Each of these drugs, independently, can cause rhabdomyolysis. Since ethanol was also found in the blood of this young man, ethanol potentiation of cellular toxicity is an additional consideration (82).

Convulsive seizures may also occur in patients with cocaine or crack overdose. That a convulsion may precipitate severe rhabdomyolysis, especially in a person with pre-existent muscle injury, is well-established.

CONCLUSION

Exertional rhabdomyolysis may be a relatively bland disorder, especially in an individual who simply runs but is not subjected to additional physical stresses such as volume depletion or heat. However, if the latter factors coexist, the resulting mandatory diversion of blood away from the splanchnic circulation results in the ominous complications of (a) mounting lactic acidosis since the poorly perfused liver can't metabolize lactic acid produced by muscle, (b) ischemic intestinal infarction, (c) ischemic renal failure and (d) refractory shock. Disseminated intravascular coagulation is always present and accounts for major morbidity in this disease.

Successful treatment for patients with massive rhabdomyolysis, especially when associated with hyperthermia, is prompt recognition, prompt cooling and circulatory stabilization with appropriate fluids. The problem posed by case number one, (the man who collapsed after a 10 K race), viz., that of hypoalbuminemia unexplained by dilution, reflects macromolecular loss through injured endothelium. This finding resembles the person with a severe thermal

burn. In burn patients, endothelial injury may increase the normal extravascular leak of albumin enormously from about 5% per hour (83) to values approaching nearly 50% of the circulating protein in blood per hour.

It was noteworthy that this patient's blood pressure did not stabilize despite administering huge quantities of colloid, in fact, such treatment resulted in progressive, severe edema. The rationale of administering hyperoncotic colloid to burn patients (and patients such as this) has been challenged because the rate of albumin egress from the vascular space is such that it causes major collections of fluid in the extravascular space (84). Indeed, it has been pointed out by those who manage thermal injuries that the best results follow resuscitation with solutions containing sodium chloride. It has been recommended that if colloid is to be administered to such patients, its concentration should not exceed the prevailing level in the patient's plasma.

If one important point from this Grand Rounds sticks in your memory, I hope it will be the one concerning the unappreciated high frequency of intestinal ischemia and/or necrosis in patients with this syndrome. This may occur in normal persons driving themselves to win a long-distance competitive race, it may appear in patients with sickle-cell trait - possibly because of intravascular sickling, and it may occur in individuals who potentiate their own norepinephrine effect by using other vasoconstrictors such as cocaine or amphetamines. It is interesting to note that in a paper describing five patients admitted to Parkland Memorial Hospital with shock and massive rhabdomyolysis following intravenous pheumetrazine or metamphetamine published by Kendrick and his associates (85), each patient also complained of cramps, abdominal pain and diarrhea. Perhaps of more interest, massive quantities of saline were used and each of the five patients survived. The only colloid administered was to the 5th case who received blood for hemorrhage from DIC. Patients seldom die of rhabdomyolysis alone, especially if its immediate complications such as hyperkalemia, are properly managed. They most often die of other complications, such as dead bowel, DIC or refractory shock.

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