MEDICAL GRAND ROUNDS

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RHABDOMYOLYSIS AND MYOGLOBINURIA

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INTRODUCTION

Rhabdomyolysis is defined as an injury of the skeletal muscle cell allowing its contents to escape so that they are identifiable in either plasma or urine. These contents are usually enzymes [creatine phosphokinase (CPK), aldolase, glutamic oxaloacetic transaminase or lactic dehydrogenase], myoblobin or electrolytes (PO_4, ^{--}K). It may be deceptively subtle or massive. It does not necessarily imply necrosis, which is an irreversible process, since apparently, reconstruction of affected muscle cells may occur.

Myoglobinuria means myoglobin in the urine. As will be pointed out in some detail, myoglobinuria usually occurs with rhabdomyolysis but is often missed.

The recognized diseases and conditions associated with rhabdomyolysis are increasing rapidly. Table I is a revision from an earlier publication (1) and hopefully includes all recognized causes of rhabdomyolysis to date.*

The causes of rhabdomyolysis are categorized on the basis of etiology. There is mounting evidence that any process interferring with delivery, storage or utilization of energy by the muscle cell may lead to injury or necrosis.

In each of these categories, a relationship is easily conceivable between deranged energy metabolism and cellular injury, whether injury is induced by unmeetable energy demands such as in violent, exhaustive exercise, a biochemical disturbance or by simple ischemia. In the following presentation, an attempt will be made to highlight certain of these interrelationships as well as the complications of rhabdomyolysis.

HISTORICAL BACKGROUND OF MYOGLOBINURIA

The earliest reference to myoglobinuria is somewhat uncertain but nevertheless titillating. It concerns rhabdomyolysis and myoglobinuria resulting from ingestion of quail. Several authors contend that this may have been responsible for large numbers of deaths among the Israelites during the Exodus (2-4). The diet of the Israelites consisted largely of quail. The quail had very likely fed on hemlock seeds during their migration westward across the Gulf of Agabah to the Sinai Peninsula. Modern observations have shown that when sensitive persons consume quail whose diet has been hemlock seeds, there occurs within hours intense muscular pain and paralysis of those muscles being used. Myoglobinuria follows. Sergent (3) was able to reproduce the syndrome in dogs by allowing them to eat quail fed on hemlock seeds.

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*References for each entry in this table are not necessarily included in the bibliography but might be available if requested.

TABLE 1
CAUSES OF RHABDOMYOLYSIS

I. INCREASED ENERGY CONSUMPTION

1. EXERCISE STRESS
2. AMPHETAMINE, LSD
3. DELERIUM TREMENS
4. CONVULSIONS
5. HIGH VOLTAGE SHOCK
6. TETANUS
7. SUCCINYL CHOLINE
8. FEVER
9. MALIGNANT HYPERPYREXIA
10. EXERCISE INDUCED HEAT STROKE
11. HEAT CRAMPS

II. DECREASED ENERGY PRODUCTION-GENETIC

A. AFFECTING CARBOHYDRATE METABOLISM
   1. MYOPHOSPHORYLASE DEFICIENCY
   2. α-GLUCOSIDASE DEFICIENCY
   3. AMYLO-L, 6-GLUCOSIDASE DEFICIENCY
   4. PHOSPHOHEXOISOMERASE DEFICIENCY
   5. PHOSPHOFRUCTOKINASE DEFICIENCY
   6. ? CYTOCHROME DISTURBANCES
   7. DIABETIC ACIDOSIS
   8. NONKETOTIC HYPEROSMOLAR COMA

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

VARIOUS MUSCULAR DYSTROPHIES

III. ↓ ENERGY PRODUCTION ACQUIRED

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

V. PRIMARY MUSCLE INJURY

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

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)
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

VI. INFECTIOUS

1. GAS GANGRENE
2. TETANUS
3. LEPTOSPIROSIS
4. VIRAL INFLUENZA
5. COXSACKIE INFECTION
6. SHIGELLOSIS
7. HERBICOLA LATHYRI BACTEREMIA
8. REYE'S SYNDROME
9. SEPTIC SHOCK
10. MYXOMA VIRUS
11. PSEUDOMONAS BACTEREMIA

VII. MISCELLANEOUS

A. VENOM
1. SNAKE BITE
2. HORNET
3. HOUSEHOLD BROWN SPIDER

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)

C. OTHER
1. QUAIL INGESTION
2. ISOPROPYL ALCOHOL
3. ETHYLENE GLYCOL
4. HAFF DISEASE
5. "CALCIPHYLAXIS" (AZOTEMIC HYPERPARATHYROIDISM)
6. ACUTE SCHIZOPHRENIA
7. HYPERNATREMIA
8. INSOMNIA
9. 2,4-DICHLOROPHENOXYACETIC ACID

The anology between those recent small outbreaks of rhabdomyolysis and myoglobinuria following ingestion of quail and the deaths of many Israelites being led from Egypt by Moses is based upon the following information from the Old Testament (Numbers 10, 36 to 11,34).

Numbers 10,36 to 11,34

"The foreign elements among the Israelites were so greedy for meat that even the Israelites lamented again, "Would that we had meat for food! -- we see nothing before us but this manna." (Numbers 11,4-5). In vengeance, the Lord promised them meat," -- and you will eat it, not for one day, or two days, or five, or ten or twenty days, but for a whole month -- until it comes out of your very nostrils and becomes loathesome to you--" But Moses said "The people around me include 600,000 soldiers; yet you say I will give them meat to eat for a whole month" In response to Moses doubt that there could never be enough sheep or cattle to fulfill such a promise, the Lord said "you shall see now whether or not what I have promised you takes place."

There arose a wind sent by the Lord, that drove in quail from the sea and brought them down over the camp site at a height of two cubits (4 feet) from the ground for the distance of a day's journey all around the camp. All that day, all night, and all the next day the people gathered in the quail. Even the one who got the least gathered ten homers of them. (A homer is about 12 bushels). Then they spread them out all around the camp. But while the meat was still between their teeth, before it could be consumed, the Lord's wrath flared up against the people, and he struck them with a very great plaque. So that place was named Kibroth-hattaavah, because it was there the greedy people were buried."

In 1881, Fleischer described "a new" form of hemoglobinuria associated with muscular exertion and striking changes in the urine (5). Inami (6) described an earlier experience by Hackradt suggesting that myoglobinuria may be linked to acute renal failure. Long before these reports, veterinarians had clearly recognized the association of myoglobinuria and renal failure in horses with exertional rhabdomyolysis, referred to as the "tying-up syndrome", "Monday morning Sickness" or "Azoturia". Indeed, they were the first to demonstrate that myoglobin was rapidly excreted into the urine after intravenous injection and that this produced urine exactly like that of the sick horses (7).

The first description of the clinical features and later the first clearcut pathophysiological relationship between crush injury, myoglobinuria and acute renal failure must be credited to Bywaters (8). The following is a quotation from his first paper in which he described four cases:

"The patient has been buried for several hours with pressure on a limb. On admission he looks in good condition except for swelling of the limb, some local anesthesia and whealing. The hemoglobin, however, is raised, and a few hours later, despite vasoconstriction, made manifest by pallor, coldness and sweating, the blood pressure falls. This is restored to the pre-shock level by (often multiple) transfusions of serum, plasma, or occasionally, blood.
Anxiety may now arise concerning the circulation in the injured limb, which may show diminution of arterial pulsation distally, accompanied by all the changes of incipient gangrene. Signs of renal damage soon appear, and progress even though the crushed limb be amputated. The urinary output, initially small, owing perhaps to the severity of the shock, diminishes further. The urine contains albumin and many dark brown or black granular casts. These later decrease in number. The patient is alternately drowsey and anxiously aware of the severity of his illness. Slight generalized edema, thirst, and incessant vomiting develop, and the blood pressure often remains slightly raised. The blood urea and potassium, raised at an early stage, become progressively higher, and death occurs comparatively suddenly, frequently within a week. Necropsy reveals necrosis of muscle and in the renal tubules, degenerative changes and casts containing brown pigment."

The foregoing description of the crush syndrome with myoglobinuria and acute tubular necrosis has undergone little if any revision or significant additions in the following 35 years. The importance of Bywaters observations was two-fold, first--he clearly described the relationship between trauma and acute renal failure, and second, he recognized that myoglobin might be implicated in the pathogenesis of acute renal failure.

THE FATE OF MYOGLOBIN IN THE CIRCULATION

Myoglobin is normally absent in serum. Once present, its half-life varies considerably but is usually between 1-3 hours in man. Anywhere from 1-6 hours are required for complete disappearance from plasma (9). Concentrations of approximately 100 mg/dL are necessary to produce visible staining in either plasma or urine (10). Experimentally, when large quantities of myoglobin are injected, it is almost completely excreted into the urine (7). This accounts for the clinical observations that grossly visible heme pigment in the urine is probably myoglobin if the serum is clear, but likely hemoglobin if the serum is stained red or pink. When milligram quantities of labelled myoglobin are injected, only traces appear in the urine, the remainder is metabolized to bilirubin (11)*

The renal threshold for myoglobin in the dog is 21 mg/dL (12,13). In man, the concentration above which all myoglobin would be excreted is 23 mg/dL (10).

*Protoporphyrin IX is the prosthetic group of both hemoglobin or myoglobin.

This means that myoglobin is bound to serum proteins, but the binding sites are not saturated until concentration exceeds the total binding capacity. At lower concentrations about one-half the myoglobin is unbound, thereby accounting for the observation that myoglobin may be found in the urine even though its concentration in plasma is less than 23 mg% (10).

Although I have not been able to find a case, it is remotely possible that in a patient without renal function that sufficient myoglobin could accumulate to stain the plasma pink. To accomplish a plasma concentration of 100 mg/dL would require enormous muscle destruction. The distribution space of myoglobin appears to be about 28.5L in a normal person (9). Therefore, to produce staining of this volume would require elaboration of 28,500 mg of myoglobin. If normal muscle contains 4 mg myoglobin per gram, this would require destruction of 7.1 Kg of muscle. The same quantity of muscle would normally contain 800 mEq of potassium. This would probably cause such fulminating hyperkalemia that death would occur before the plasma myoglobin concentration ever reached visible levels.

Wheby, Barett and Crosby (14) attempted to identify the protein which binds myoglobin. It is not haptoglobin. It has equal affinity for hemoglobin, myoglobin and hematin. In patients with chronic hemolytic disease, this protein disappears from the blood but only after disappearance of haptoglobin. The protein appeared to be an $\alpha 2$ globulin based upon information obtained by electrophoresis.

In contrast to the theoretically enormous quantity of myoglobin release necessary to produce visible staining of plasma, comparatively little may be required to produce visible myoglobinuria.

Figure 1 contrasts the physical properties of myoglobin and hemoglobin that are relevant to this discussion.

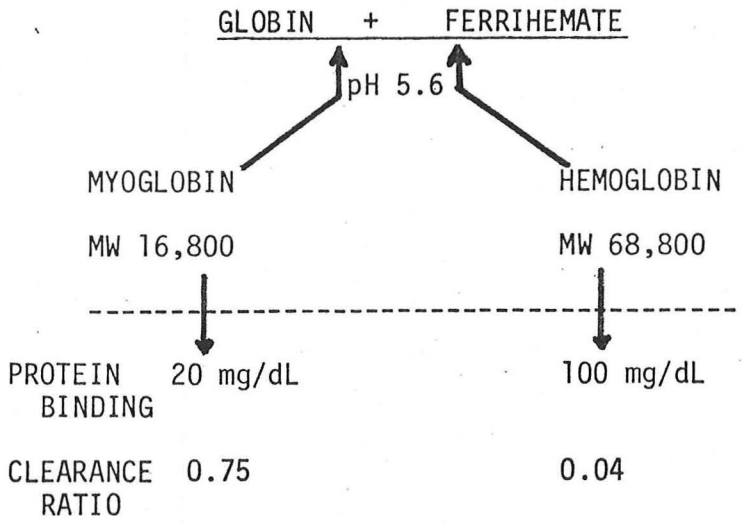

FIG. 1

A variety of tests are available to identify myoglobin in the urine. These are reviewed by Kagen (10). The benzidine, guaiac or orthotolidine (dipstick) tests will detect extremely small concentrations of myoglobin with comparable sensitivity to that obtainable by immunodiffusion (15). The latter procedure employs an antibody against human myoglobin prepared in the rabbit. It is sensitive to concentrations as low as 5-10 μg/ml. Using this method, urine myoglobin concentrations up to 2000 mg/dL have been observed (16).

Before any myoglobin can appear in the urine, it appears to be necessary that the plasma level exceed 1.5 mg/dL (10). Again, assuming a distribution volume of 28.5 Liters and a muscle myoglobin content of 4 mg/gm, about 102 gm of muscle must be destroyed for sufficient myoglobin release to attain the renal threshold. Once the renal threshold has been exceeded, the variables affecting the chance of seeing gross myoglobinuria are (1) the plasma concentration of myoglobin above the renal threshold, (2) the extent of myoglobin-binding in plasma (3) glomerular filtration rate and (4) the urine flow rate.

To examine the effect of these variables, Table II illustrates the interaction between various plasma levels of myoglobin, the quantity filtered by the glomerulus (which is probably equal to the quantity excreted), the quantity of muscle which must be lysed to free this quantity of myoglobin, and when, in terms of urine flow, the pigment will be visible.

TABLE II.

$[Mb]^P$ mg/dL	L^{Mb} mg/min	Q^m gm	$[Mb]^\mu$ mg/dL URINE FLOW (ml/MIN): 0.3	0.5	1.0	5.0	10.0
2.5	0.38	178	127	76	38	7	4
5.0	1.31	356	437	262	131	26	13
10.0	3.18	712	1060	636	318	64	32
20.0	6.94	1425	2313	1389	694	139	69

$[Mb]^P$ represents plasma myoglobin in gm/dL.
L^{mb} represents the filtered load of myoglobin. It is calculated by:

$$L^{mb} = [Mb]^P \div 1.5 \times 0.01 \text{ GFR} \times 0.5 \times 0.75$$

(1.5 = renal threshold for myoglobin; 0.5 the fraction of myoglobin not bound to serum proteins at the respective concentration which is filterable and 0.75, the clearance ratio).

Q^m = quantity of muscle destroyed;
$= [Mb]^P \times 28.5 \text{ L} \times 10 \div 4$. (See text for explanation of numbers).
Mb^μ = concentration of myoglobin in urine.

In this table, it is assumed that GFR is 100 cc/min. The urine flow of 0.3 ml/min represents a realistic value observed in men working in the heat; 1.0 ml/min is representative of optimal hydration and 10 ml/min represents intense diuresis. The enclosed values under $[Mb]^{u}$ represent visible myoglobinuria. At a urine flow of 0.3 ml/min and minimal rhabdomyolysis, visible myoglobinuria will occur. In contrast, substantial rhabdomyolysis may fail to produce visible myoglobinuria when urine flow rates are high. These data illustrate that myoglobinuria is commonly seen in patients with exertional rhabdomyolysis because of their tendency to excrete a highly concentrated and scanty urine.

Using the same calcuations, Table III shows why visible myoglobinuria is much less likely when the GFR is 50 ml/min.

TABLE III.

$[Mb]^{p}$ mg/dL	L^{mb} mg/min	Q^{m} gm	$[Mb]^{u}$ URINE FLOW (ml/MIN) 0.3	0.5	1.0	5.0	10.0
2.5	0.19	178	63	38	19	3.8	1.9
5.0	0.66	356	220	132	66	13.2	6.6
10.0	1.59	712	530	318	159	31.8	15.9
20.0	3.47	1425	1157	694	347	69.4	34.7

These calculations predict that minor rhabdomyolysis in a patient with a GFR of 50 ml/min would probably never produce visible myoglobinuria. At a urine flow rate above 1.0 ml/min, rather massive rhabdomyolysis would be required to produce visible myoglobinuria.

Finally, the quantity of myoglobin in muscle can have an important effect on the appearance of myoglobinuria. Thus, it has been shown that myoglobin content of muscle rises with training. Therefore, myoglobinuria will be more pronounced in a healthy, trained person with rhabdomyolysis than it would be in a patient with chronic disabling disease although the quantity of muscle damaged may be the same. This difference in muscle myoglobin content may well explain why acute renal failure is much more likely to occur in a healthy individual who at the time rhabdomyolysis occurs, has excellent renal function.

NEPHROTOXICITY OF MYOGLOBIN

In their original observations on clinical crush injury, Bywaters and his co-workers observed an apparent association between renal failure and excretion of an acid urine (8,17). They subsequently examined the potentially harmful consequences of myoglobin on renal function in the rabbit. They showed that two factors were important for induction of acute renal failure in the model; hypovolemia mediated by vascular compression of the hind leg and any measure acting to acidify the urine (18). They as well as others (19-21) observed that myoglobin infusions without such interventions were generally innocuous. It was concluded therefore that a low intratubular pH was a prerequisite for experimental myoglobin nephrotoxicity. Corcoran and Page (22) confirmed this finding and also showed that dehydration and a concentrated urine potentiated the effects of aciduria per se on myoglobin nephrotoxicity. At or below a urine pH of 5.6, both myoglobin and hemoglobin dissociate into ferrihemate (23) and their respective globin moieties. Evidence that ferrihemate might be the toxic component of myoglobin has been elicited by several investigators (21,22,24). The relative nephrotoxicity of ferrihemate is dose-related (22).

A general plan of a more recent study by Braun and his associates (24) is illustrated in Figure 2. Using this model, subcutaneous injection of 50% glycerol at a dose of 1.0 ml/Kg body weight into either a rabbit or a rat which

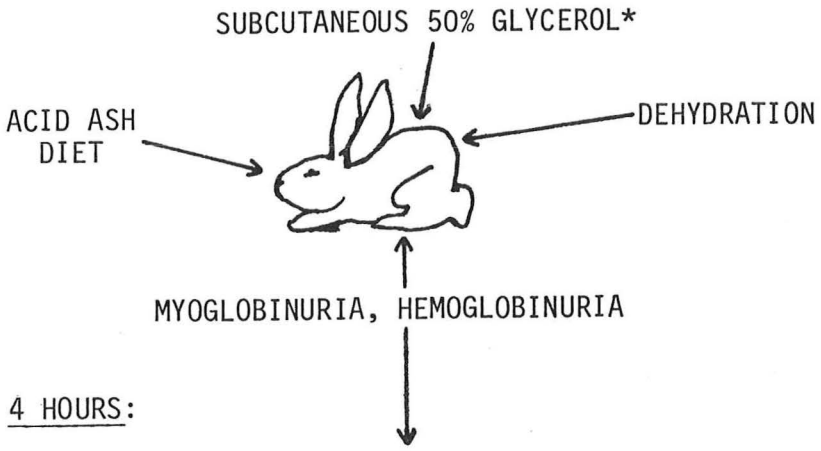

FIG. 2

has been fed an acid-ash diet and deprived of water for 16 hours will consistently result in myoglobinuria and/or hemoglobinuria. If the kidneys are removed four hours later, they show evidence of proximal tubular injury. At 12 hours, similar to patients with the crush syndrome (8) they often show frank tubular necrosis. The lesion at 4 hours consists of swelling and pallor of the epithelial cells and the presence of intracellular pigment granules. If studies are conducted on cortical slices from these kidneys, some very interesting abnormalities are detectable that suggest a derangement of tubular function. These abnormalities are shown in Table IV. Braun and his associates (24) compared accumulation of the organic base, tetraethylammonium, (TEA) and the organic acid, para-amino hippurate (PAH) in cortical slices from animals injected

TABLE IV.

GLYCEROL-INDUCED RENAL INJURY
(BRAUN ET AL 1970)

RENAL CORTICAL SLICES 4 HOURS:

1. DECREASED TEA ACCUMULATION
2. DECREASED PAH ACCUMULATION
3. OXYGEN CONSUMPTION NORMAL

with subcutaneous 50% glycerol and controls. Uptake in the control animals and those receiving 50% glycerol intravenously was not different. However, uptake of TEA and PAH was significantly less in the group receiving subcutaneous glycerol. (This maneuver causes an appreciable loss of circulatory volume). Possibly of great importance, oxygen utilization by the tissue in this group remained normal. This means that net transport of organic ions in terms of metabolic expenditure was subnormal. It might also mean that something, an ion or another organic compound, was possibly leaking into the cell at an abnormally rapid rate, and the transport system in the cell was successfully extruding this substance at cost of increased energy. Certainly other explanations are possible. Nevertheless, as occurs in other tissues, subtle cellular injury is associated with decreased net transport and a wasteful state of energy metabolism.

Braun and his associates also attempted to determine why an acid urine appears to be so critical to the development of acute renal failure in the

wake of myoglobinuria (24). Table V summarizes this portion of their study. Using renal cortical slices from untreated, normal animals, they again examined accumulation of TEA and PAH under several conditions. First, myoglobin

TABLE V.

NORMAL RENAL CORTICAL SLICES
(BRAUN ET AL 1970)

UPTAKE OF TEA AND PAH:

- DEPRESSED BY MYOGLOBIN BUT NOT HEMOGLOBIN
- DEPRESSED BY HEMOGLOBIN AT pH 5.4
- NOT AFFECTED BY GLOBIN
- DEPRESSED BY FERRIHEMATE IRRESPECTIVE OF pH
- FERRIHEMATE DEPRESSION REVERSED BY ALBUMIN

depressed uptake of both substances. Hemoglobin did not so long as the incubation mixture had a pH of 7.4. However, when the pH was lowered to 5.4 by addition of either HCl or NH_4Cl, hemoglobin depressed uptake of TEA and PAH similar to that of myoglobin. Irrespective of pH, globin, whether derived from hemoglobin or myoglobin, had no effect. Since a pH of 5.4 dissociates either hemoglobin or myoglobin into their respective components, (23), viz., globin plus ferrihemate, they next examined the effects of ferrihemate. Ferrihemate alone, irrespective of whether pH was 7.4 or 5.4 equally depressed accumulation of TEA and PAH. This depression was promptly restored to normal by addition of albumin in sufficient quantity to bind the ferrihemate. Presumably, ferrihemate is small enough to readily enter those cells in which transport occurs, interfere with that process and thereby depress net accumulation of organic ions. Since ferrihemate readily binds to albumin, that complex is too large to enter cells. Consequently, tissue accumulation of the organic ions returns to normal. Of importance, this also indicates that the depressive effect is reversible. Obviously, the foregoing mechanisms are excessively simplistic and probably cannot account for the gamut of experimental and clinical observations on renal failure with pigmenturia. Nevertheless, it is particularly impressive that there seems to be an early stage of injury in the experimental model, which is pivotal, implying that at this particular stage, there are two courses, viz., either recovery by removal of the toxin or progression to acute tubular necrosis.

The observation that oxygen utilization remains normal despite reduced net accumulation actively transported ions has especially enticing implications. Thus, in a variety of tissues, excessive utilization of energy can

apparently exhaust stores of energy and irreversibly damage the cell. Such a hypothetical scheme is shown in Figure 3. Consider for example, that myoglobin or its product ferrihemate injure the cell by simply increasing permeability to sodium ions. In response, the cell would attempt to remove these ions from its interior. This would be accomplished at a cost of energy, which would be reflected by increased oxygen utilization. For a time, compensation without anatomical injury would prevail. However, if energy supplies become inadequate to meet the demands of increased transport, for example by anoxia, cellular content of Na will rise, the cell will swell osmotically and eventually, it will reach a decompensated state and suffer irreversible damage.

MECHANISM OF RENAL INJURY IN MYOGLOBINURIA

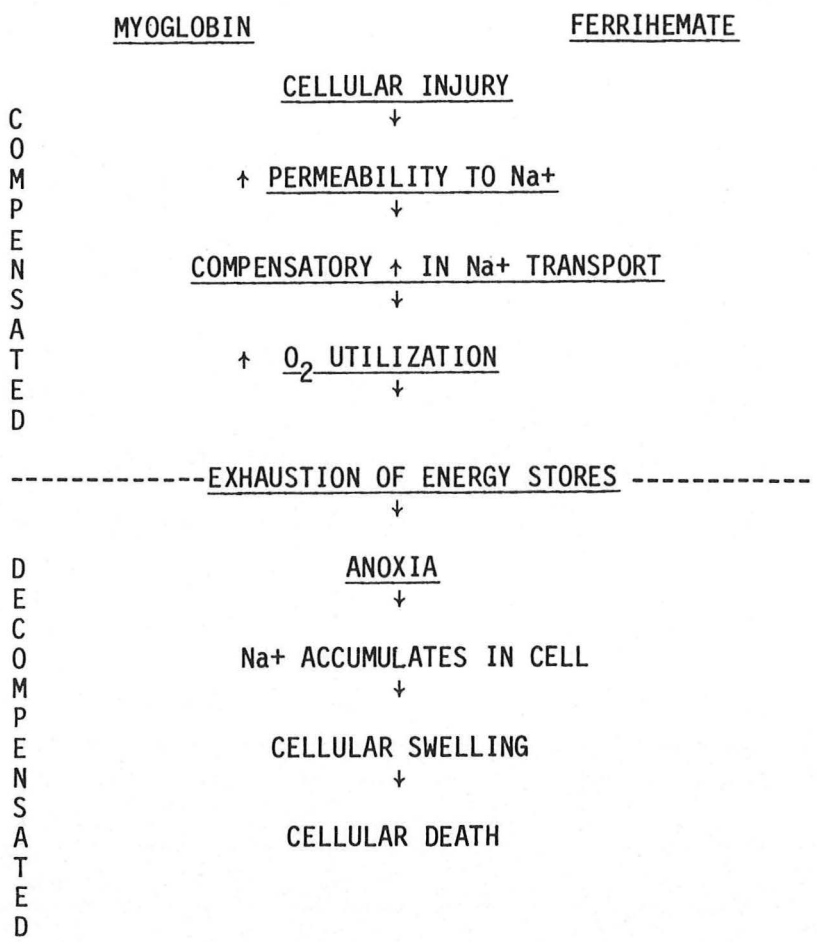

FIG. 3

Evidence from the studies by Braun and his co-workers (24) has already been presented showing that in the experimental setting of pigment nephropathy, oxygen utilization is normal in the face of apparent decreased net transport. From other studies, there is a remarkably consistent relationship between utilization of oxygen by the kidney and tubular reabsorption of sodium (25). Indeed, molecular oxygen is directly utilized as energy for Na transport. For example (26), if sodium is being avidly reabsorbed, urine oxygen tension will be extremely low, as indicated in Table VI.

TABLE VI.

	REVERSIBLE ARF	IRREVERSIBLE ARF
1.	URINE VOLUME LOW	LOW
2.	URINE [Na] LOW	HIGH
3.	URINE pO_2 LOW	HIGH??

Consider a clinical situation in which there is subtle but reversible tubular injury as a result of myoglobinuria. Urine volume could be low, urine sodium concentration relatively low and urine pO_2/low. In this situation, two drugs, furosemide or mannitol, are very likely effective as means not only to avert further tubular injury but also to help restore renal function to normal. Both agents increase urine flow, decrease Na reabsorption and decrease oxygen utilization. Urine pO_2 rises sharply. If either agent somehow decreases sodium entry into cells (furosemide) or accelerates its rate of passage through the tubule, (mannitol), the cell no longer needs to actively transport sodium out of its interior. Thereby oxygen would be conserved along with other substrates and perhaps improve its overall functional and structural integrity. Alternatively both furosemide and mannitol sharply reduce medullary ~~toxicity~~ tonicity and thereby would decrease concentration of myoglobin or ferrihemate in the tubular fluid. This effect alone should diminish the risk of ~~toxicity~~. In this regard, it is notable that acute tubular necrosis is extremely rare in a person who has chronic renal failure with impaired concentrating capacity.

Those who work in the field of experimental acute renal failure generally list three factors in the pathogenesis of pigment nephropathy. They include (1) decreased renal blood flow, (2) tubular obstruction due to precipitation of high molecular weight heme proteins and (3) direct nephrotoxicity. The foregoing evidence suggests that a fourth factor should be considered, viz., tubular anoxia, created by a demand for increased energy to mediate transport.

Thus far, only the possible mechanisms underlying renal injury resulting from the effects of myoglobin or its products have been considered. More recent evidence suggests that uric acid may play a contributory role in cases of exertional rhabdomyolysis followed by myoglobinuria and acute renal failure, it has been shown that normal men undergoing intensive training become frankly hyperuricemic (27,28). Intense exercise is associated with a marked decrease of glomerular filtration rate (29) which could impair uric acid excretion. In addition, lactic-acidemia during exercise can impair uric acid excretion by impairing its tubular secretion (30). However, in such individuals, total uric acid excretion is abnormally increased. Since it occurs simultaneously with creatinuria and elevated CPK activity in serum, it has been assumed that uric acid is overproduced as a result of muscle injury. Damage to skeletal muscle, release of purines into the circulation and their subsequent conversion to urate in the liver would appear to be an adequate explanation (28). Therefore, a high concentration of urate in serum or uric acid in an acid tubular fluid could well be a contributing factor in the pathogenesis of acute renal failure in such instances. A diagram illustrating these relationships is shown in Figure 4.

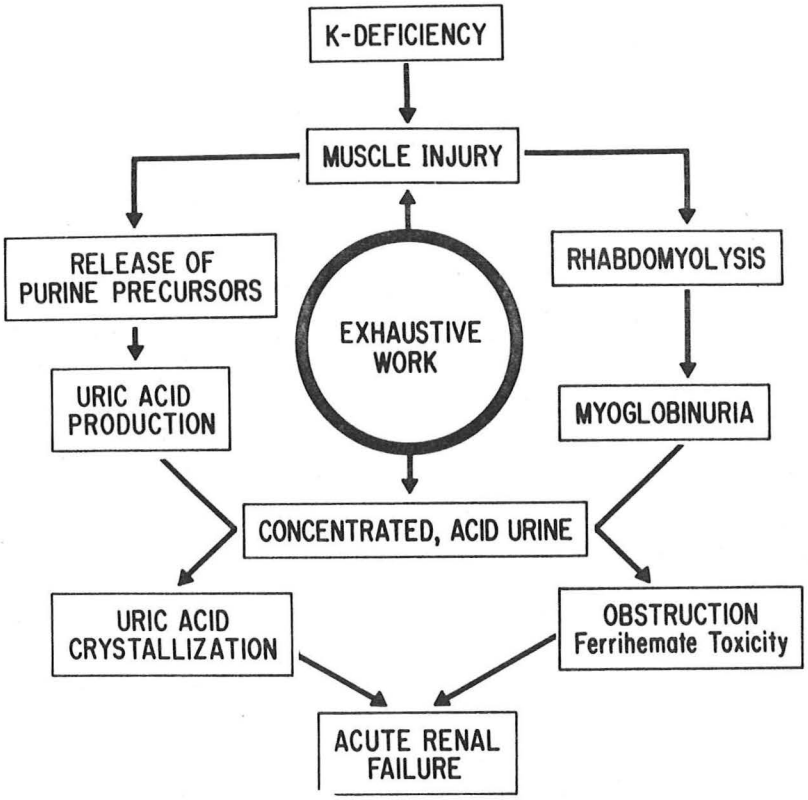

FIG. 4

The following case appears to represent a good example of acute renal failure that tends to occur in the setting of exertional rhabdomyolysis with myoglobinuria and hyperuricemia.

EXERTIONAL RHABDOMYOLYSIS IN A LONG DISTANCE RUNNER

A 32 year old physician who had no past history of significant illness was accustomed to running approximately 30 miles per week. As part of a physical fitness promotion, he took part in a marathon run (26 miles) with the recent olympic champion. The outside temperature was approximately 85°F and the relative humidity about 35%. He was able to keep pace for approximately 9 miles. At that distance he developed severe pain in his calves and thighs, attempted to continue, but collapsed.

Physical examination on arrival at the hospital showed a rectal temperature of 103.8°. His skin was flushed, moderately cyanotic and moist. His blood pressure was 86/50 mmHg. His pulse rate was 140 beats per minute. He responded to pain but was disoriented and severely confused. Examination of the eyes, heart, lungs, abdomen and central nervous system were otherwise unremarkable. His extremities appeared normal. Knee jerks and achilles reflexes were decreased. Laboratory examination showed a white blood cell count of 19,400 per mm^3 of which 70% were neutrophils. Hematocrit and hemoglobin were 49 volumes percent and 16.5 gm per 100 dL, respectively. His platelets numbered 60,000/mm^3. Serum electrolyte concentrations showed a sodium of 152 mEq/L, potassium 3.9 mEq/L, chloride 108 mEq/L and total CO_2, 18 mmoles/L. Serum glucose was 125 mg/dL. Creatinine phosphokinase (CPK) activity on the same blood sample was 36,000 International units/L. Serum uric acid concentration was 34 mg/dL, calcium 8.2 mg/dL; phosphorus 6.8 mg/dL and urea nitrogen 36 mg/dL. Serum albumin concentration was 5.1 gm/dL.

A urine sample obtained by catheter was dark brown in color and was benzidine positive. The specific gravity was 1.018 and the pH 4.6. Glucose was 2+ and protein 300 mg% by dipstick. The spun sediment showed a few red cells, numerous granular and pigmented casts.

Following hydration with appropriate intravenous fluids, his mental function became normal. The following morning he complained of intense pain in the legs and thighs. He had received 8 liters of fluids during the first 18 hours in the hospital. Examination showed tense, tender swelling of both legs. Pulses and sensations remained normal. Laboratory examination on that morning showed a further decline in platelets to 25,000/mm^3, CPK activity greater than 100,000 IU/L, serum calcium 4.1 mg/dL, phosphorus 8 mg/dL uric acid 39 mg/dL, and urea nitrogen 86 mg/dL.

The patient was transferred to another hospital with hemodialysis facilities because of persistent, severe oliguria. He required dialysis therapy for a total of ten days at which point diuresis appeared. He had apparent complete recovery of all abnormalities over a period of six months.

The foregoing case displays several important features which deserve comment. First, it shows clearly that normal, trained men can develop massive rhabdomyolysis if they exceed their capacity for exercise endurance. The fact that the environmental heat stress factor was marginally high may not have

had much bearing on this individual's illness since other cases almost identical to this one have occurred under much milder climatic conditions. There were other important factors to consider (Table VII):

TABLE VII.

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

Disseminated intravascular coagulation. Every patient with this illness will demonstrate evidence of disseminated intravascular coagulation. It is equivocal whether this is the result of muscle necrosis and liberation of activating substances from injured cells which in turn induce clotting, or whether exercise itself, as has been reported (31), might induce DIC.

Hyperkalemia. Many fatalities in rhabdomyolysis, especially during the first few days, are the result of arrhythmias due to hyperkalemia. The potassium content of skeletal muscle is about 110 mEq/Kg. In a patient who may be both acidotic and oliguria, release of K from injured muscle can cause fulminating hyperkalemia.

Hypocalcemia. This patient displayed hypocalcemia very early which might seem paradoxic in view of the fact that his serum albumin concentration was 5.1 g/dL. However, it has become clearly established that hypocalcemia in these patients is the result of deposition of calcium phosphate and calcium carbonate in injured skeletal muscle (32). After showing an initial value of 8.2 mg/dL, the patient's serum calcium on the following day had fallen further to 4.1 mg/dL. Although his blood urea nitrogen at that time was 86 mg percent, a

serum calcium value of 4.1 mg/dL is inappropriately low for this degree of azotemia. The record hypocalcemia recorded to date in patients with acute exertional rhabdomyolysis is 3.5 mg/dL (33).

Hyperphosphatemia. The total phosphorus content of whole skeletal muscle is 75 mmoles (2.25 gm) per kg. Its leakage from injured muscle can cause hyperphosphatemia and in turn, precipitation of $CaPO_4$ in soft tissue, blood vessels and eyes.

Hyperuricemia. Another problem deserving mention is the extreme hyperuricemia often seen in this particular type of skeletal muscle injury. Several years ago, it was reported (27,28) that normal men undergoing intensive physical conditioning display frank hyperuricemia, with values up to 15 mg/dL in serum. As discussed earlier, this appears to be the result of overproduction as well as impaired excretion (28).

Figure 5 compares CPK activity vs. serum urate concentration in a group of patients with alcoholic rhabdomyolysis and another group with exertional rhabdomyolysis. The patients with alcoholic rhabdomyolysis were selected for comparison since these are by far the most common cause of alcoholic rhabdomyolysis existing in this community. It seems apparent from this figure that serum urate tends to be much higher in patients with exertional rhabdomyolysis. It has been assumed that the source of this uric

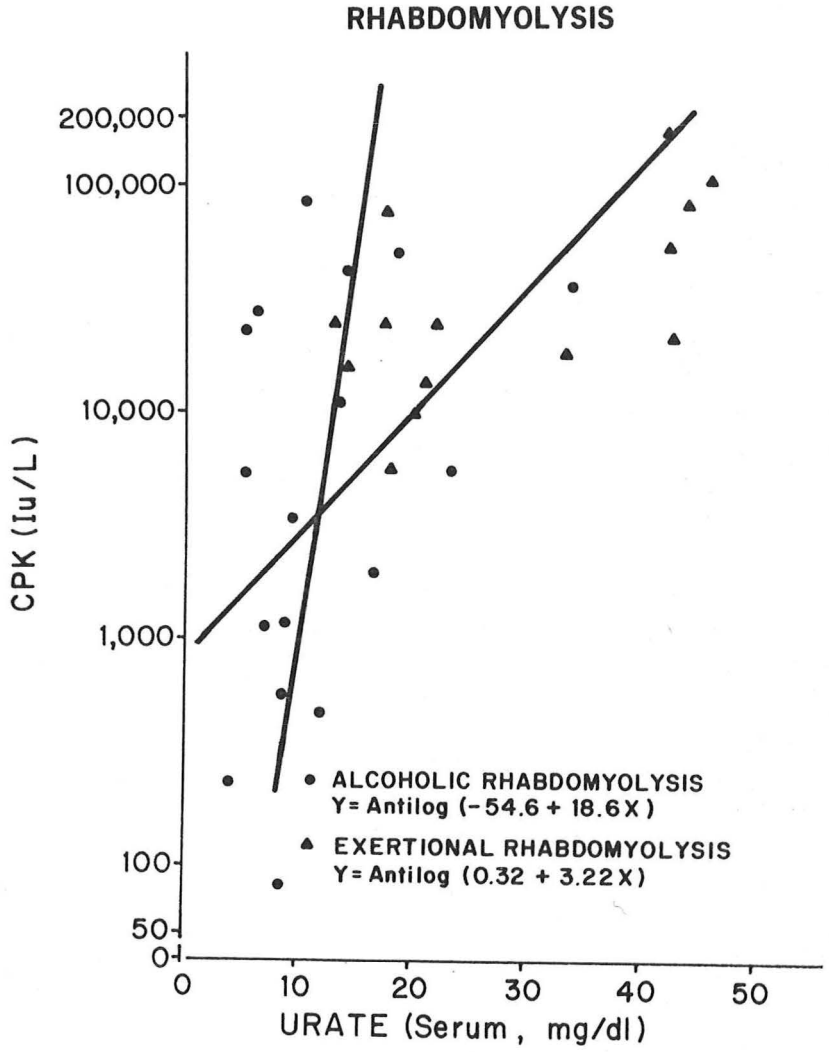

FIG. 5

acid is purines released from injured muscle cells which are promptly converted to uric acid in the liver. Indeed, this was shown to be the case by Cathcart in 1902 (34). There is little question that patients with exertional rhabdomyolysis are usually overtly healthy, well-muscled individuals. Therefore one would estimate that larger total muscle mass would in turn yield more precursors for conversion to uric acid by the liver. On the other hand, one might speculate that even if an equal amount of muscle were destroyed in the patient with alcoholism, that he might have sufficient liver disease so that the purine precursors would not be converted to uric acid. A recent study on patients with stable alcoholic cirrhosis suggested that their capacity to produce uric acid from yeast RNA was normal (35). Nevertheless, the normal subject must have a greater capacity to produce uric acid than a patient with alcoholic cirrhosis.

Although it may seem possible that the apparently disproportionate hyperuricemia in exertional rhabdomyolysis is a function of azotemia, such is not the case. Figure 6 compares urea nitrogen concentration to urate concentration in a variety of conditions. These include patients with rhabdomyolysis due to alcohol, drug overdosage, and amphetamine poisoning. The closed squares indicate those with exertional rhabdomyolysis. It seems apparent that patients with exertional rhabdomyolysis have a disproportionate elevation of uric acid to urea nitrogen.

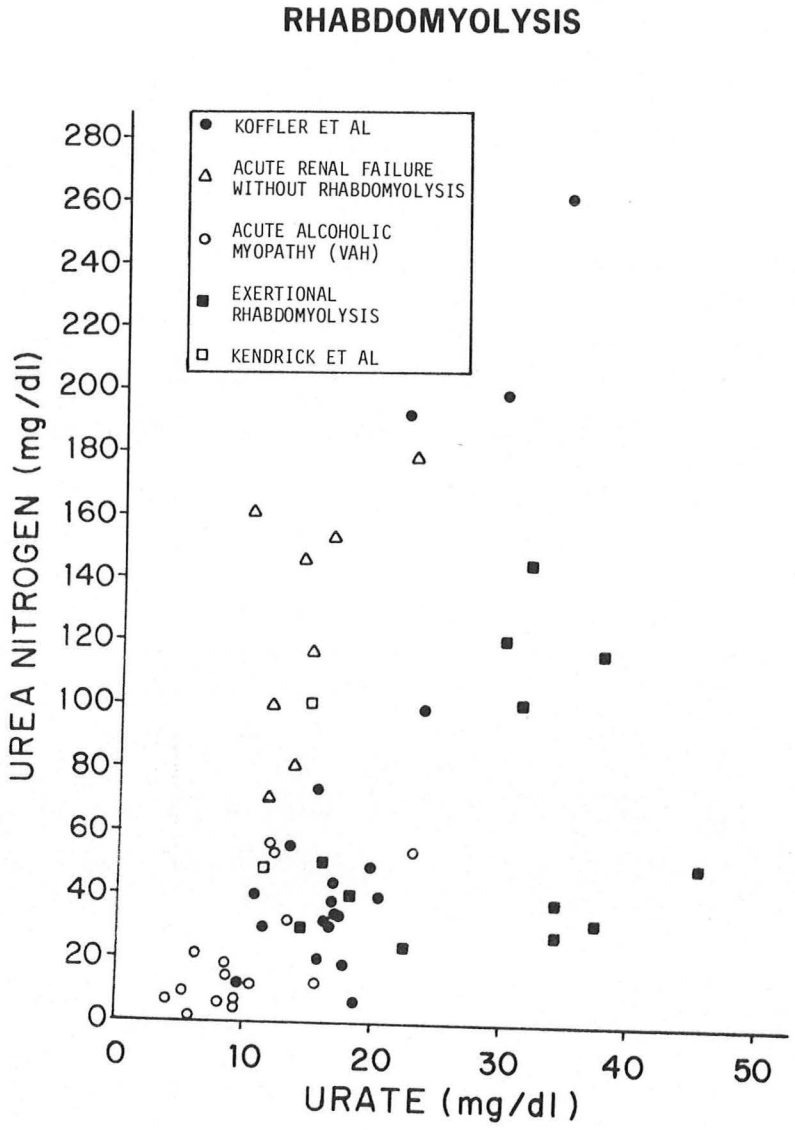

FIG. 6

Disproportionate elevation of serum creatinine. Although information was not available on this patient, in many such instances there is a disproportionate elevation of serum creatinine concentration in comparison to urea nitrogen. In some instances, one will observe a serum creatinine value 12 hours after rhabdomyolysis in the vicinity of 6-7 mg/dL at which time the serum urea nitrogen concentration may be 35 mg/dL. It seems that creatinine is released in massive quantities from injured muscle cells and transiently accumulates in serum. If one follows urinary excretion of creatinine, it will be seen that unduly large amounts are rapidly excreted into the urine within the first 24-36 hours if acute renal failure is absent.

This patient showed glycosuria without hyperglycemia. This is a common finding in patients with exertional rhabdomyolysis. It is generally transient. It has been proposed that this may reflect proximal tubular injury (Kagen). Low molecular weight proteinuria has also been observed in exertional rhabdomyolysis. This may also reflect proximal tubular injury (36).

SECOND WAVE PHENOMENON

In those patients who have massive skeletal muscle necrosis involving the legs, there is an imminent danger that the extremities may become gangrenous. Such an event should be anticipated in patients who have been crushed, those who have sustained rhabdomyolysis by exhaustive exercise such as the marathon runner, patients with rhabdomyolysis due to exertional heat stroke and in some cases following administration of drugs.

Beginning on the second day, their extremities begin to swell and become tense and painful. There may follow increased pain, parathesias, decreased sensation and decreased peripheral pulses. In some of these patients, tenderness and swelling may have been minimal at the time of admission to the hospital. Patients destined to show this course are those who display hypotension which required large amounts of saline to correct. If fasciotomy is not performed immediately, vascular compression will result in gangrene. Figure 7 illustrates a typical pattern of CPK activity in such a case. As is generally the case, this patient's initial CPK activity peaked at 24 hours after injury. Without further muscle injury, CPK should decline by 50% each 48 hours thereafter. However, this patient displayed a secondary rise which occurred shortly after notation of pain and parathesias. These were followed by decreased sensation and decreased pulses. This "second hump" or "second wave phenomenon" heralds either a recurrence or extension of muscle necrosis and renewed release of enzymes from the swollen extremities. This, along with the clinical findings demands a fasciotomy to relieve vascular compression. The tibialis anterior is especially liable to this complication. Since it is in a small fascial compartment, rigidity and tenderness overlying this muscle might well indicate impending necrosis. This would not necessarily be associated with circumferential swelling and tenderness of the leg and consequently, the severity of this complication might not be appreciated. If there is a question, a two

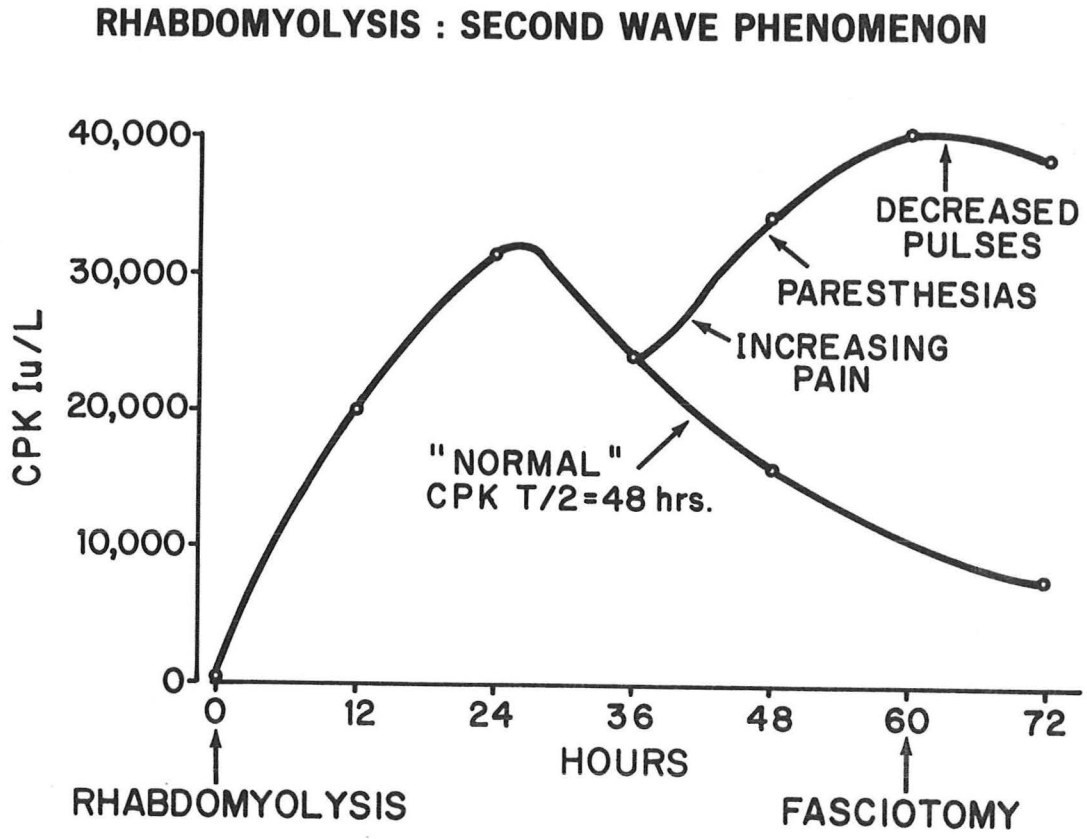

FIG. 7

inch incision can be made to expose the muscle surface. If there is no contractile response to pinching the muscle, the fascia should be incised more extensively. Obviously, timely consultation with an experienced surgeon in such cases may prevent permanent foot drop.

To explain the 2nd wave phenomenon, one can postulate that there is a massive quantity of injured muscle tissue in extremities which in turn takes up a large quantity of the salt and water given during resuscitation. Alternatively, one could speculate that necrotic muscle decomposes into small protein fragments. Having osmotic activity, they would promote movement of water and salt from the circulation in sufficient volume to induce a pronounced elevation of hydrostatic pressure. Quantitively, the elevated osmotic activity in a semi-rigid fascial compartment required to produce such an effect would by very small, that is, less than 10 mOsm/Kg, since the hydrostatic pressure generated by each mOsm is 17mm Hg. By this means, the intrafascial pressure could easily supersede the arterial blood pressure

and thereby induce vascular compression. In some patients with this phenomenon, the erroneous diagnosis of thrombophlebitis is made. Homan's test will be positive and many other features of phlebitis can occur.

POTASSIUM DEFICIENCY AND RHABDOMYOLYSIS

An ever-increasing number of clinical reports have firmly established the relationship between potassium deficiency and rhabdomyolysis. The following case from the Dallas VA Hospital is quite typical.

A 78 year old black man had been treated in the eye clinic at the VA Hospital for chronic open angle glaucoma. He had taken acetazolamide (diamox) 250 mg four times a day for seven years. In December 1975, one year before this admission, his blood pressure was 168/102 mm Hg. His physician prescribed a mixture of reserpine and hydrochlorothiazide. The hydrochlorothiazide dosage was 100 mg per day. Diamox was continued.

Three weeks before hospitalization in December 1976, the patient complained of increasing muscle weakness, and for one week severe muscle pain in the shoulders, back and legs. He had not been able to eat normally for a period of four weeks and experienced dysphagia for solid foods. He continued to take his medications. On the day of admission, the patient became so weak he could not lift his head.

Physical exam on admission showed an extremely ill and profoundly weak man whose blood pressure was 130/70 mm Hg, pulse 66/min with numerous premature contractions. Upon sitting him up in bed his blood pressure fell to 60/20 mm Hg. His rectal temperature was 97.6^{o}F. The cardiac rhythm was grossly irregular with occasional runs of trigeminy. His heart was slightly enlarged. He had inspiratory rales at the right lung base. The abdomen was tender and distended. Bowel sounds were hypoactive. No organs were palpable.

Examination of the skeletal muscles showed generalized tenderness which was especially prominent in the shoulders, back, arms and lower extremities. The patient was unable to walk. He was areflexic.

Laboratory examination showed: serum Na+ 142 mEq/L, Cl 82 mEq/L and K 1.1 mEq/L. These values were confirmed. Arterial blood showed a pH of 7.50, pCO_2 of 38.4 mm Hg and pO_2 73 mm Hg. The calculated bicarbonate was 29 mEq/L. His BUN was 36 mg/dL. Glucose concentration was 169 mg/dL. CPK was 36,040 International Units/L, LDH 1,780 and SGOT 540. An electrocardiogram showed a rate of 56 beats per minute, first degree heart block, increased QU interval, absence of T waves and multifocal premature ventricular contractions. His urine was benzidine positive, showed a 2+ reaction for protein and had a pH 5.5. The urine specific gravity was 1.020 and was amber in color.

The patient was treated with potassium chloride intravenously. On the first day he received 360 mEq which elevated his serum potassium concentration to 2.8 mEq/L. His muscular strength improved. However, his cardiac arrhythmias did not clear until the third day and after he had received a total of 788 mEq of potassium.

A sample of skeletal muscle was obtained from the lateral thigh by needle biopsy to determine electrolyte composition. The values obtained were as follows: (all are expressed as mmoles/100 g fat free dry solids)

	K	Na	Cl	P	Mg	Ca
patient	23.8	38.3	13.9	29.6	7.9	2.3
normal	43.8±2.0	9.4±2.0	5.0±1.2	28.9±0.9	6.9±0.4	1.3±0.1

Based upon history and chemical composition of serum and skeletal muscle, this case is felt to represent a typical example of rhabdomyolysis resulting from otherwise uncomplicated potassium deficiency. When potassium deficiency becomes sufficiently severe to induce frank rhabdomyolysis, many of the patients become paralyzed. Indeed, their illness is often mistaken for the Guillain-Barre syndrome (37). Usually, when paralysis occurs under such conditions, serum potassium concentration has nearly always been less than 2 mEq/L and is often less than 1 mEq/L. Late in the course and after rhabdomyolysis has occurred, severe muscle necrosis may liberate sufficient potassium into the serum to correct the hypokalemia and thereby obscure the diagnosis.

Many patients who develop kaliopenic myopathy do so rather slowly. Their first complaints are weakness, fatigability, loss of energy and a feeling of malaise. With progression, anorexia and poor food intake develop, which by further limiting K intake, accelerate the course so that paralysis occurs in one to 4 weeks. This succession of events was seen in the patient presented. Although myalgias may occur, they are not common in uncomplicated K-deficiency. On the other hand, muscle pain has been a prominent complaint in patients with carbenoxolone-induced K-deficiency. Muscular cramps appear to be distinctly uncommon in kaliopenic myopathy in contrast to their common occurrence in other myopathies such as McArdles' Syndrome (38).

As in any chronic myopathy, fatigue, excessive muscular exertion, convulsions, fasting or fever may precipitate acute rhabdomyolysis in K-deficiency.

In the case presented herein, potassium deficiency was most likely the result of diuretic therapy. The patient had received Diamox for a period of seven years. However, if potassium deficiency had been the result of Diamox therapy and if it were uncomplicated by other factors, one would have expected to find hyperchloremic metabolic acidosis. The primary action of this drug is to block carbonic anhydrase activity in the proximal tubule and thereby decrease bicarbonate reabsorption. Once a steady state is reached, volume contraction is apparently sufficient so that bicarbonate reabsorption becomes complete in the proximal tubule. Under these conditions, distal hydrogen secretion may be adequate to acidify the urine.

These findings, namely, hyperchloremic metabolic acidosis and a urine pH of about 5 are classical of the steady state in patients receiving chronic Diamox therapy. Such patients usually display plasma bicarbonate concentrations in the vicinity of 16 mEq/L. Most often, serum potassium concentration is normal or only slightly depressed. The patient presented today, in addition to Diamox therapy, had taken chlorothiazide for one year before onset of rhabdomyolysis. In fact, his laboratory values were more consistent with potassium deficiency induced by a thiazide diuretic. Thus his findings were those of metabolic hypokalemic alkalosis.

In the majority of reports of "Kaliopenic myopathy", potassium deficiency has occured as a result of mineralocorticoid excess. Most patients had ingested licorice or carbenoxolone. Licorice contains glycirrhizic acid which has mineralocorticoid activity. Carbenoxolone, a related compound, also possesses mineralocorticoid activity. It is used in Europe for treatment of gastric ulcer.

Chronic diuretic therapy for conditions such an essential hypertension usually cause only a mild potassium deficit. In most cases this reaches a steady state with a serum potassium concentration in the vicinity of 3.5 mEq/L and slight elevation of total CO_2 content. In terms of total body potassium, measured by exchangeable isotopic ^{42}K, the total losses are usually in the vicinity of 250 mEq (39). Overt abnormalities of muscular function or structure do not apparently occur with such levels of potassium deficiency. For this reason, overt rhabdomyolysis is exceptionally rare as the result of diuretic therapy alone. The thirteen cases of potassium deficiency associated with frank rhabdomyolysis reported in patients receiving diuretic therapy are shown in Table VIII (40-50). They have been separated into two categories: (A) patients using only diuretics, and (B) patients using diuretics who also ingested kaliuretic agents or had an associated disease favoring potassium loss.

Of the first category it can be seen that chlorthalidone was the diuretic agent in three of the four cases. The fourth, as was described in the patient from the VA, took hydrochlorothiazide and Diamox. In the second group, chlorthalidone was again the diuretic agent in cases 1,2,3,4 and 6. Furosemide and thiazides were implicated in the remainder.

From the foregoing information it would seem that chlorthalidone has an unusual propensity to produce potassium deficiency sufficiently intense to cause frank muscle necrosis. Chlorthalidone is a long acting, potent diuretic which acts at the same tubular site as the thiazides. The reason why agents possessing mineralocorticoid activity aggravate potassium deficiency in the presence of diuretics, and especially chlorthalidone, is reasonably clear. In patients who take only thiazide diuretics, there occurs a steady state characterized by mild or modest potassium deficiency in association with a contraction of extracellular fluid volume. Although aldosterone production may be elevated in such patients, the associated volume contraction would serve to increase fractional reabsorption of sodium in the proximal nephron so that lesser quantities of sodium reach the distal tubular site where potassium exchange for sodium could occur. In contrast, patients

TABLE VIII.

DIURETIC RELATED K-DEFICIENCY WITH MYOPATHY

A.	DIURETICS ALONE			
	1. CHLORTHALIDONE	CRAWHALL	1976	(40)*
	2. CHLORTHALIDONE	OH	1971	(41)
	3. CHLORTHALIDONE	COHEN	1959	(42)
	4. HYDROCHLOROTHIAZIDE, ACETAZOLAMIDE	DALLAS, VAH	1977	
B.	DIURETICS AND OTHER FACTORS			
	1. CHLORTHALIDONE, TRICHLORMETHIAZIDE, METAMPHETAMINE, THYROID	JELLIFFE	1969	(43)
	2. CHLORTHALIDONE, PRIMARY ALDOSTERONISM	CRAWHALL	1969	(40)
	3. CHLORTHALIDONE, LICORICE	TOURTELOTTE	1970	(44)
	4. CHLORTHALIDONE, LICORICE	CONN	1968	(45)
	5. FUROSEMIDE, CARBENOXOLONE	DAVIES	1974	(46)
	6. CHLORTHALIDONE, CARBENOXOLONE	DESCAMPS	1977	(47)
	7. CHLORTHIAZIDE, LICORICE	GROSS	1966	(48)
	8. BENDROFLUAZIDE, CARBENOXOLONE	FYFE	1976	(49)
	9. HYDROCHLOROTHIAZIDE, DEXTROAMPHETAMINE, THYROID	VAN HORN	1970	(50)

*Reference number in bibliography

who ingest agents with mineralocorticoid activity or have primary aldosteronism, circulatory volume would probably be higher, their filtered sodium load would in turn be higher and that quantity of sodium reaching the distal tubule for exchange with potassium would be substantially greater than that in patients taking thiazide diuretics alone. Thereby potassium deficiency would be much more severe.

Figure 8 shows an interesting inverse relationship between serum CPK activity and serum potassium concentration. The points were collected from all reports in the literature regardless of the cause of K-deficiency, whenever simultaneous values for serum K and CPK were made available.

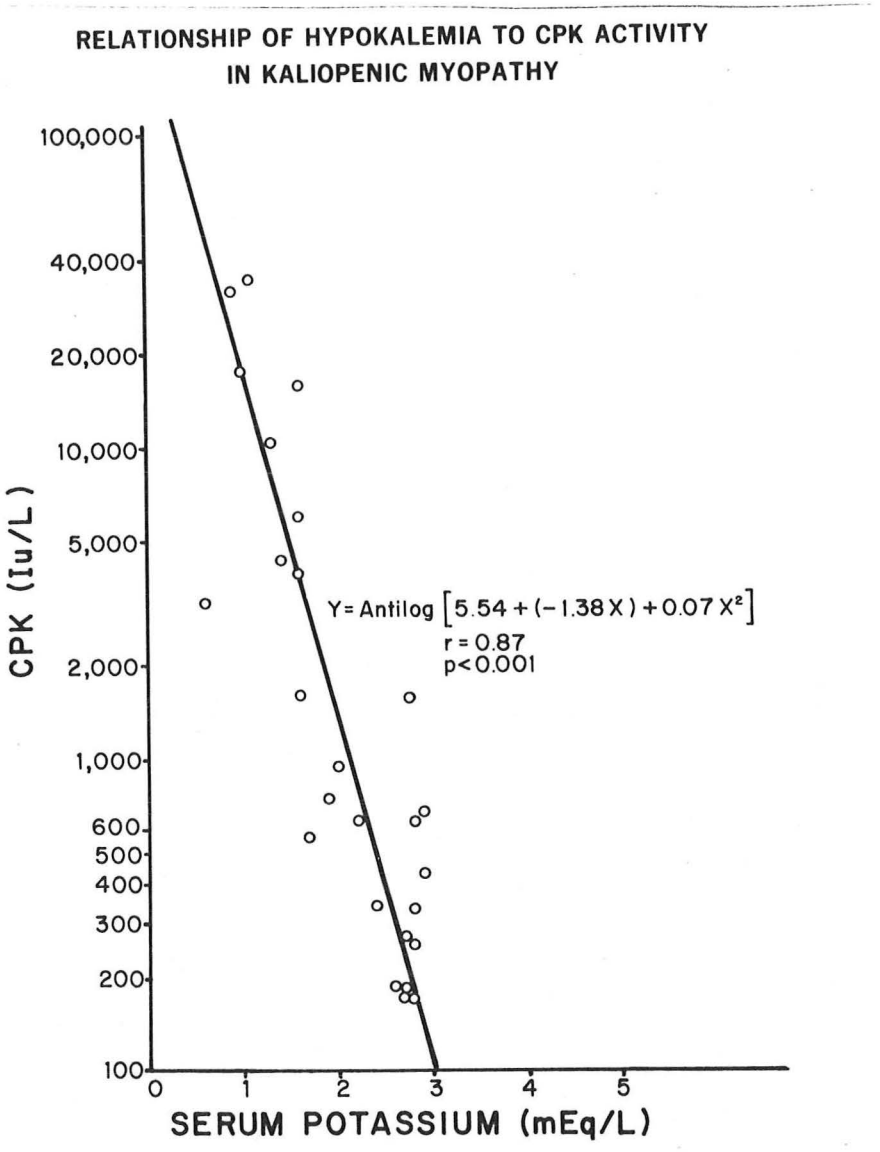

FIG. 8

PATHOPHYSIOLOGY OF MUSCLE CELL INJURY IN POTASSIUM DEFICIENCY

Studies conducted in our own laboratory show four abnormalities that could contribute to injury of the muscle cell in potassium deficiency. These are shown in Table IX.

TABLE IX.

MECHANISMS OF CELLULAR INJURY IN K-DEFICIENCY

1. ABNORMALLY LOW BLOOD FLOW DURING EXERCISE.
2. DECREASED CARDIAC OUTPUT DURING EXERCISE.
3. IMPAIRED GLYCOGEN SYNTHESIS.
4. ABNORMAL Na-K TRANSPORT

During hard work, muscle blood flow normally increases up to 40 times above its resting rate. This so-called "exercise hyperemia" is probably initiated by potassium ions. As muscle contracts, potassium ions are released from the muscle cells into the interstitial space where they act upon adjacent anterioles to induce vasodilation. In Figure 9, it is shown that

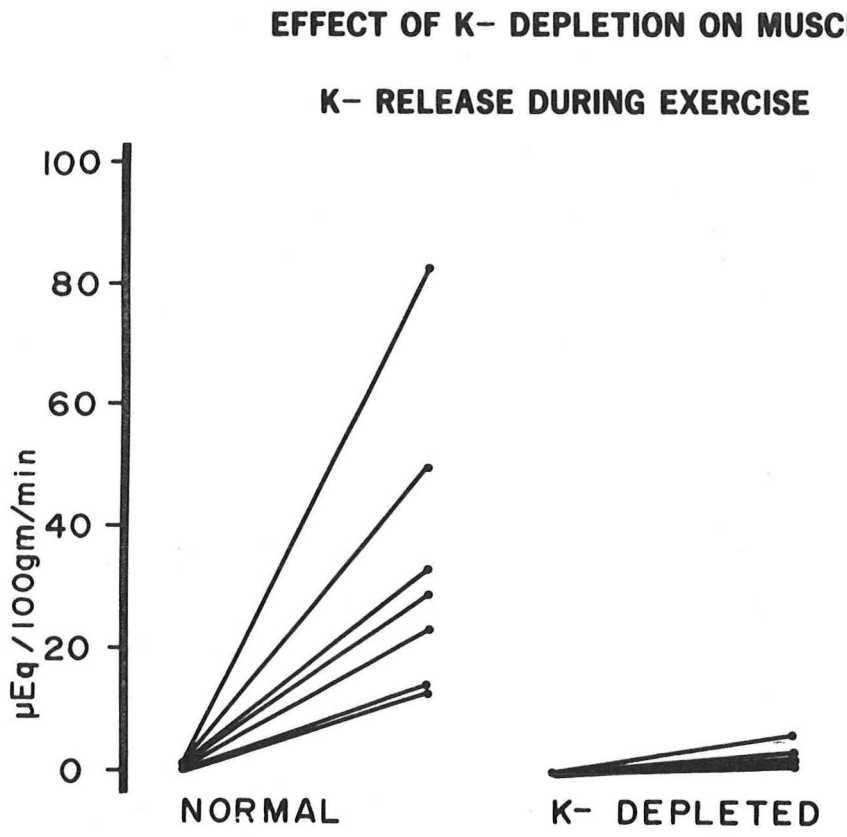

FIG. 9

potassium release does not occur normally from potassium deficient muscle during work. The result of this abnormality is shown in Figure 10. Muslce blood flow does not rise appropriately during exercise. Those observations suggest that relative ischemia occurs during exercise and causes muscle necrosis in the potassium deficient animal. In the K-deficient dog, muscle blood flow during exercise could be restored toward normal by simultaneous infusion of KCl (51).

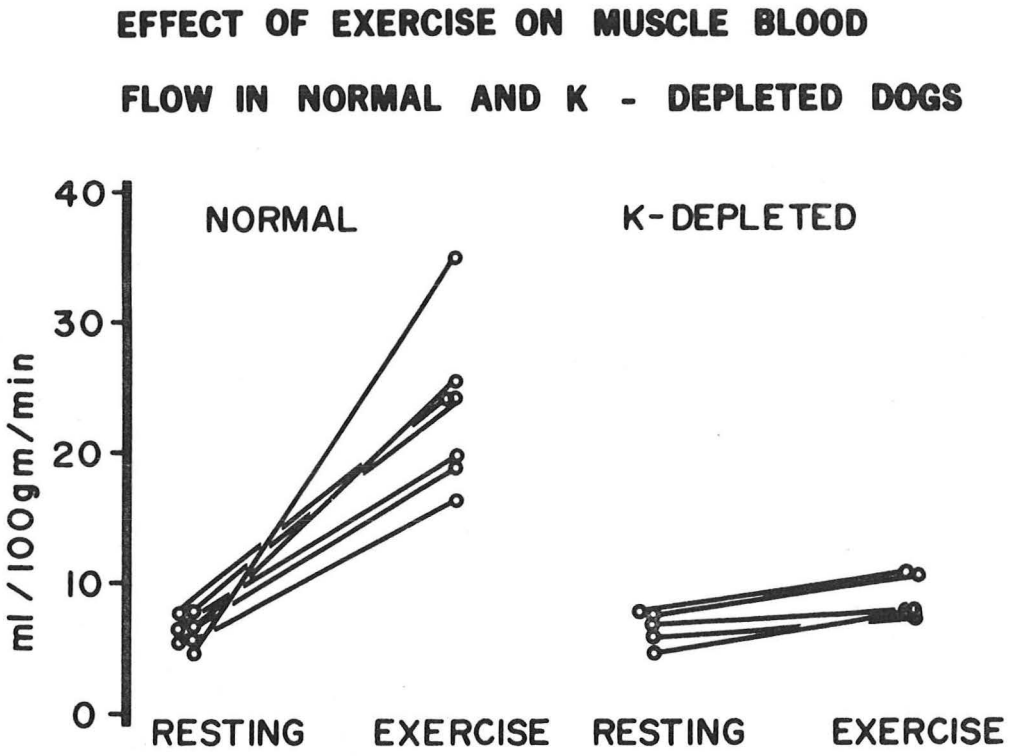

FIG. 10

A second and perhaps equally important effect of potassium deficiency, at least in the dog, is an abnormal response of the heart to exercise. This is illustrated in Figure 11. In this study, cardiac output was measured in dogs before and after induction of potassium deficiency. In each case the response to exercise was quantitated. The figures show that running on a treadmill increased cardiac output in normal dogs. After potassium deficiency was induced, the resting cardiac output was substantially elevated. However, during exercise it fell. To underscore the potential importance of this observation, it was noted that some of these dogs developed overt pulmonary edema.

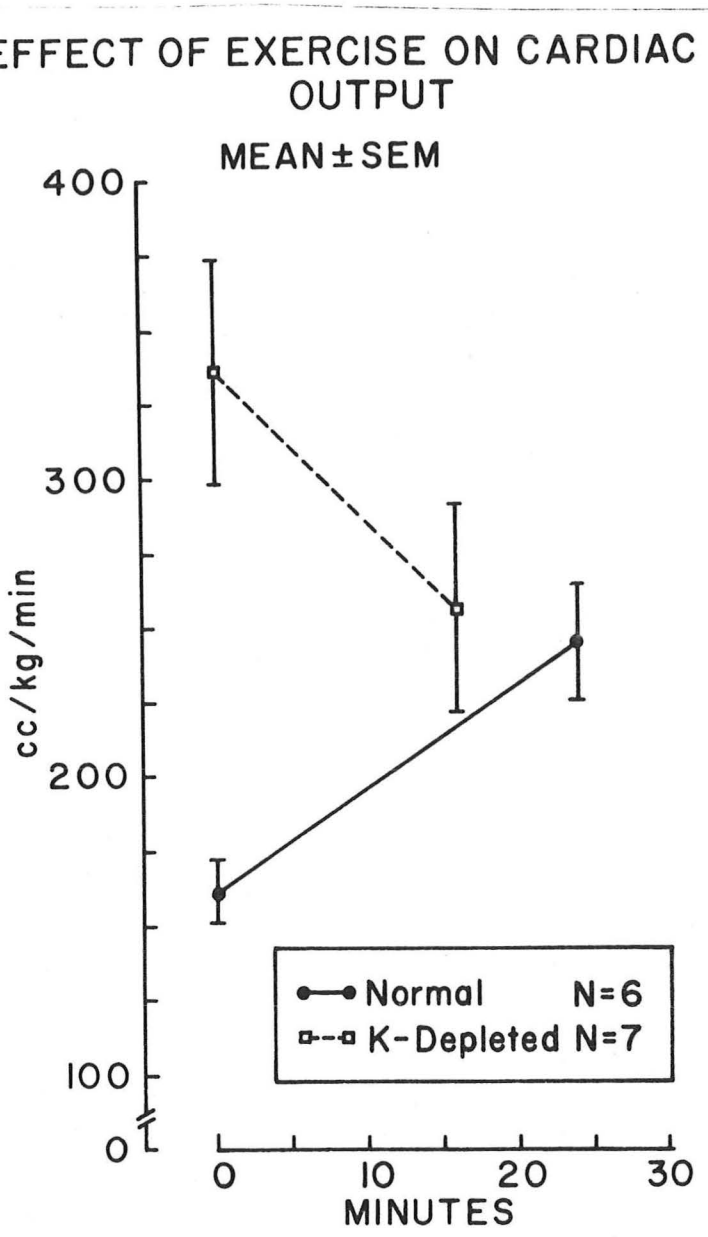

FIG. 11

This suggested that the decline of cardiac output was mediated by left ventricular failure. A decrease in cardiac output during exercise would also serve to limit delivery of blood to working skeletal muscle.

We also examined the effect of potassium deficiency on glycogen metabolism in dogs and rats. Earlier studies by others on intact rats and tissues from other species *in vitro* (52,53) suggested that potassium deficiency impairs glycogen synthesis in muscle. If muscle glycogen could not be synthesized normally, the single major fuel for intense work would be lacking. Thus, one would anticipate not only a limitation of endurance for hard work, but also, failure to provide adequate fuel for energy could lead to cellular injury. This response would be quite similar to the muscle injury that occurs when energy

cannot be provided adequately during exhaustive exercise. Studies by Niedermeier and Carmichael (54) showed that when potassium deficiency was induced in rats by administration of DOCA, glycogen disappeared from skeletal muscle. However, if DOCA was administered in conjunction with potassium supplementation, muscle glycogen content remained normal. That study eliminated the possibility that DOCA itself might be the toxic influence suppressing synthesis of glycogen. A major difficulty in older *in vivo* studies was the possible role of malnutrition or starvation in the K-deficient animals. The K-deficient animal becomes anorectic and loses weight. Thus, independently of K-deficiency, malnutrition and starvation could lead to a fall of muscle glycogen content. In our studies, animals were gavage - fed to ensure maintenance of adequate nutritional intake. We measured muscle glycogen content as shown in Figure 12. First,

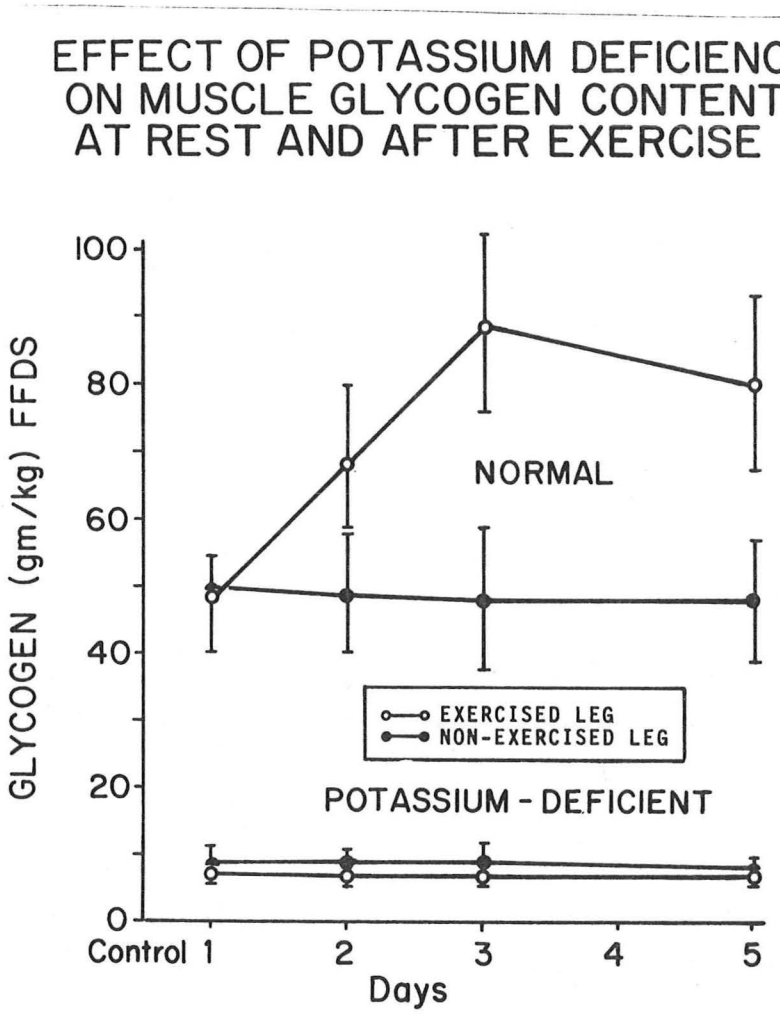

FIG. 12

glycogen content in skeletal muscle was determined before and after inducing a total body potassium deficit of approximately 20%.

In the second study, control measurements of muscle glycogen were obtained from the left leg of a normal dog. Immediately after the biopsy, muscular work in the right leg was stimulated by external electrodes until the muscle was exhausted. Samples of muscle for glycogen analysis were than obtained on the third and fifth days following this single episode of exhaustive exercise. The study was repeated in the same dog after establishment of potassium deficiency.

Resting muscle glycogen content in the normal dog averaged 59 gm/Kg FFDS. After a single bout of exhaustive exercise, resting muscle glycogen content in the exercised muscle rose to an average value of 90 g/Kg FFDS on the third day after exercise. Glycogen content in the non-exercised muscle, sampled simultaneously, did not change. In contrast, resting muscle glycogen content fell to almost unmeasurably low values in the potassium deficient dog. Furthermore, after exhaustive exercise, there was no apparent rise in glycogen content of the muscle.

In summary, there are two important effects of potassium deficiency on skeletal muscle glycogen metabolism. First, muscle glycogen content virtually disappears thus eliminating the major fuel for intense muscular work. Second, failure to synthesize muscle glycogen and increase muscle glycogen storage after a single bout of exhaustive exercise nullifies one of the most important biochemical adaptations of skeletal muscle to training; namely, an increased glycogen reserve. Hard work by a glycogen depleted muscle provides an excellent opportunity for rhabdomyolysis.

A fourth goal of our studies was to examine the capacity for work in the potassium deficient animal. Miller and Darrow (55) suggested that the strength of contractile work was normal or even increased in the potassium deficient rat. However, endurance was shortened. During our studies using the gracilis muscle preparation from the potassium deficient dog, it seemed that the contractile response to electrical stimulation was just as brisk as normal. To measure work the dogs pelvis was fixed to a wooden table, the distal tendon of the gracilis muscle was tied to an umbilical tape which then passed over a wheel of a potentiometer to a suspended weight of 1 Kg. The potentionmeter leads were connected directly to a Sanborn recorder. Electrical stimulae of 30 seconds alternating with 30 seconds of rest were continued until the muscle became unresponsive. Muscle work was quantitated by two methods. First, maximum strength could be ascertained by determining the distance the muscle could lift the weight from a resting position. Second, as an index of endurance, the time was recorded when strength had declined to one-half of its initial value. These values are shown in Table X.

TABLE X

WORK CAPACITY IN K-DEFICIENCY

	Normal	P	K-Deficient
Maximum strength g/min/g muscle	1022 ±261	NS	811 ±749
Endurance (T/2;mins)	6±4	<0.05	3±2

These studies show that initial or maximum strength may be normal in the potassium deficient dog. However, endurance is shortened. Of importance, this means that hard work is possible even though energy reserves, i.e., glycogen in muscle, is virtually absent. For this reason we measured glucose uptake and lactate output from the isolated gracilis muscle. The results of these studies are shown in Table XI.

TABLE XI

CARBOHYDRATE METABOLISM IN K-DEFICIENT MUSCLE

		Normal		K-Deficient
Glucose Uptake (μmoles/Kg/min)	Resting	88±7		91±9
	Working	118±14		116±9
Lactate Output (μmoles/Kg/min)	Resting	26±5		32±7
	Working	610±80	←p<0.01→	240±60

That lactate production was greater during work and glucose uptake was the same in normal compared to K-deficient muscle carries several implications. First, since muscle glycogen is virtually absent in K-deficient muscle, the lactate produced should have been derived almost exclusively from glucose delivered by the arterial circulation. If this is the case, the molar equivalent of lactate produced should be twice that of simultaneous glucose uptake. The average lactate production during exercise in the K-deficient dogs was 240 μmoles/Kg/min. The average glucose uptake was 116 μmoles/Kg/min. This ratio of lactate output: glucose uptake 2:1, suggests not only that all lactate was produced from arterial glucose, but also conforms with the finding that glycogen had been virtually absent in the K-deficient muscle. Secondly, since lactate production was approximately three times higher in the normal dogs although glucose utilization was identical, suggests that most lactate in normal animals

was derived from glycogen.*

The final parameter we examined in the potassium deficient animal was a more subtle effect on cellular function, namely, resting muscle membrane potential (56-58). We were interested as to how this might relate to the appearance of a "leaky" muscle cell membrane, as reflected by the abnormal elevation of CPK activity in serum. Those results are summarized graphically in Figure 13. In this figure resting muscle membrane potential (in mV) is indicated by the upper solid line, CPK activity is indicated by the line with circles and cumulative potassium deficiency by the bars. Skeletal muscle cells normally have a resting transmembrane potential difference of about -90mv.

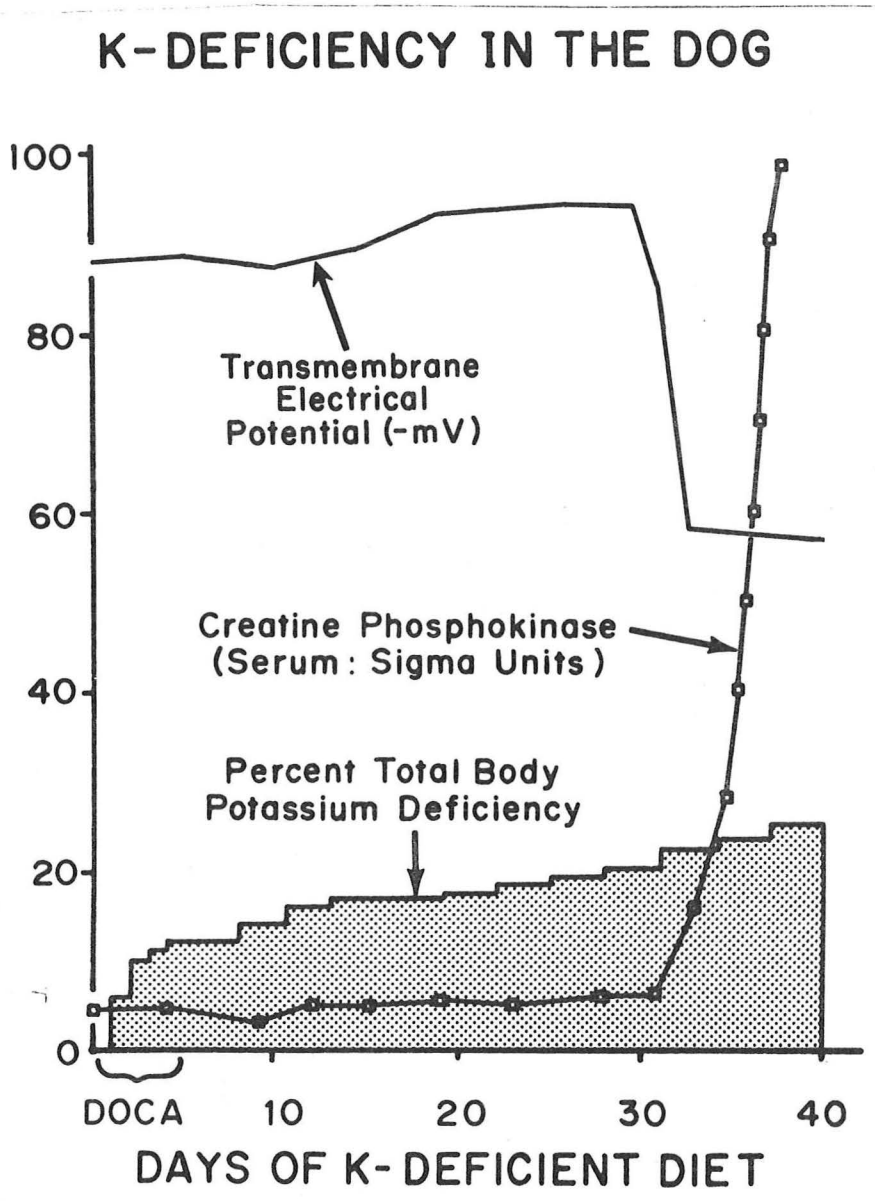

FIG. 13

*work was not measured in this portion of the study.

As one induces potassium deficiency in an animal, there is initially a major fall in serum potassium concentration and a more gradual fall in intracellular potassium concentration. Since the membrane potential in a large way is determined by the ratio of the intracellular to the extracellular potassium ion concentrations, the disproportionate fall of serum potassium concentration in the early stages of potassium deficiency would result in cellular hyperpolarization. This is indicated in the top line. Thus when total body potassium deficiency is in the vicinity of 10-15%, the muscle resting membrane potential is abnormally elevated. At this time, as indicated by the line below, serum CPK activity remains normal. However, as potassium deficiency exceeds 25% of total body stores, the resting membrane potential difference abruptly falls, suggesting an abnormality of transport or a loss of cellular membrane integrity. This is followed by an abrupt rise of CPK activity. Once this occurs, two possible events are observed: first if the potassium deficient diet is continued, the animal may become profoundly weak, become unable to breathe normally and die of paralysis. Second, some animals display transient, mild, but nevertheless definite, improvement. In these animals serum potassium concentration may rise presumably as a consequence of cellular necrosis which serves to partially correct their hypokalemia. Apparently, this permits a short period of partial recovery of cells that have not died. When the potassium deficient diet is continued, as first demonstrated by Smith and associates many years ago (59), the animals eventually die of heart failure. At autopsy, they show pulmonary edema, myocardial necrosis and rhabdomyolysis.

An unsettled issue is the role of sodium in the pathogenesis of kaliopenic myopathy. Potassium deficient rats die of myocardial necrosis rather than rhabdomyolysis (60). In the sodium-deprived, potassium-deficient rat, myocardial necrosis does not occur. Whether such a relationship prevails in skeletal muscle has not been examined conclusively. Evidence that sodium may be important is based upon the clinical observation that most cases of kaliopenic myopathy in man have occurred in the presence of diseases that are themselves associated with sodium retention. These diseases are primary aldosteronism, prolonged administration of desoxycorticosterone, licorice ingestion, malabsorption syndrome with edema or when "insulin edema" occurred during recovery from diabetic ketoacidosis. Even in those instances where the foregoing cannot be implicated, such as in the case presented today, intracellular sodium has been consistently elevated in muscle. Since the mass of muscle is so large, one can say that total body sodium is elevated in potassium deficiency. In the liver, a sodium concentration inside the hepatocyte which exceeds 25 mEq/L is sufficient to impair the activity of glycogenolysis (61). Whether this prevails in skeletal muscle is unknown. Consequently, no definite statement can be made at the present concerning the possible role of sodium in the pathogenesis of kaliopenic myopathy.

In summary, the kaliopenic myopathy model in the dog appears to be quite comparable to a variety of myopathies resulting from nutritional disorders or by hereitary defects. Its derangements include anoxia via ischemia during exercise, abnormal carbohydrate metabolism, and deranged ion transport.

MEDICAL MANAGEMENT OF ACUTE RHABDOMYOLYSIS

1. Hypovolemia and shock. Massive rhabdomyolysis is often associated with typical findings of hypovolemic shock; hypotension, tachycardia and a cold, clammy skin. Such patients usually respond following adequate volume replacement with normal saline. Large quantities, that is, up to 10 liters or so during the first 24 hours, may be required to adequately maintain the circulation.

Some patients with extensive rhabdomyolysis behave in a similar fashion to that of a patient with a severe third degree burn. Thus, fluid may be slowly sequestered and circulatory collapse may appear on the second or third day after the injury occurred. Such an event should be looked for carefully.

2. Renal function. Oliguria will always be present in persons in shock. If it persists after restoration of the blood pressure, one should suspect the presence of acute renal failure. Before any drugs are administered, a urine sample should be obtained. This should be carefully examined for evidence of pigment, red blood cells, casts and perhaps of most importance, a simultaneous determination of the concentration ratio of urea in urine and plasma. Urine sodium concentration may also be of value. In the patient who has not received diuretics, a low concentration of sodium in the urine suggests intact tubular function. Perhaps more reliable evidence of intact tubular function would be the finding of a high urine to plasma ratio for urea nitrogen. Unlike urine sodium concentration, this index is not disturbed by administration of a diuretic. Normally, the ratio of urine: plasma urea nitrogen should be 10 to 1 or higher. In patients with acute tubular necrosis or severe tubular injury, the value will be usually less than 5 to 1. When oliguria persists despite repair of fluid and circulatory deficits, it is my personal feeling that lasix and mannitol should both be administered with a goal of preventing oliguric renal failure. Both of these agents tend to decrease oxygen utilization by the kidney and thereby perhaps prevent further tubular injury. Lasix should be given in a dose of 40 to 120 mg intravenously. It should be given in conjunction with mannitol, 100 cc of a 25% solution intravenously over a period of 15 minutes. If there is no diuretic response, lasix may be repeated in a dosage of 200 mg intravenously after two hours. Mannitol should not be administered more than once.

The detection of pigment in the urine by either dip stick or benzidine reaction indicates the presence of either hemoglobin or myoglobin. If the urine is deeply stained with pigment and the serum is clear, this, in conjunction with the clinical findings, is adequate for the presumptive diagnosis of rhabdomyolysis and myoglobinuria.

It has been widely recommended that urinary alkalinization should be induced in order to decrease the potential nephrotoxicity of myoglobin. The evidence that an acid urine potentiates myoglobin nephrotoxicity has been reviewed previously.

There are two means by which the urine could be alkalinized in a patient with acute myoglobinuria. The first is by infusion of sodium bicarbonate or sodium lactate; the second, by administration of acetazolamide. There are potentially serious problems associated with either type of treatment. First, in order to alkalinize the urine in a patient with extensive rhabdomyolysis, it is generally necessary to administer huge quantities of sodium bicarbonate or sodium lactate. The urine pH usually does not become alkaline until substantial elevations of plasma bicarbonate have occurred. Although in some respects this might be useful, induction of metabolic alkalosis will invariably result in more extensive precipitation of calcium salts in injured tissues. Thus, one will aggravate hypocalcemia and possibly induce tetany. Administration of acetazolamide (DIAMOX) to these patients is also generally ineffective. In most instances, plasma bicarbonate concentration in the untreated case is depressed to the vicinity of 18 to 20 mmoles/L. Therefore, even with suppression of proximal tubular carbonic anhydrase activity, very little of the filtered bicarbonate will appear in the urine.

Theoretically the pH at which myoglobin dissociates and thereby becomes more toxic is 5.6 or less. In patients whose urine flow is substantially increased as result of furosemide or mannitol therapy, or indeed simple volume expansion, the urine pH almost always rises above 6 simply by dilution. The degree of acidosis these patients usually display is not a threat to life and in fact may forestall metastatic calcification. For the foregoing reasons the use of alkalinizing solutions or acetazolamide therapy is not recommended.

3. Hyperkalemia. Hyperkalemia is a constant threat in any patient with tissue destruction. Its occurrence is much more likely if acute renal failure and severe acidosis prevail. If rhabdomyolysis has been so severe that the muscles of respiration are involved and hypoventilation occurs, hyperkalemia may occur both by acute respiratory acidosis as well as by anoxia. In that event, assisted ventilation is mandatory. Hyperkalemia usually becomes most prominent between 12 and 36 hours after the original injury. For this reason, electrocardiograms and measurements of potassium in serum should be obtained at regular intervals. If injury is extensive and especially if acute renal failure is present, kayexalate, the potassium exchange resin, should be started immediately either orally or rectally even though frank hyperkalemia does not exist.

If hyperkalemia occurs, one should be extremely careful about which form of therapy is chosen. It is entirely safe and effective to use glucose and insulin to promote movement of potassium into cells. However, this may not be as effective in a patient with extensive muscle necrosis as it would be in another patient with acute renal failure who has no muscle injury. On the other hand, one should be extremely careful about administration of calcium salts since elevation of serum calcium will only be transient and the bulk of the calcium administered will be precipitated in injured tissues as calcium salts.

It is apparent that one is faced with a dilemma in selecting a treatment for hyperkalemia should this become necessary. There is no question that hyperkalemia of modest degree may become extremely cardiotoxic in the presence of severe hypocalcemia. Therefore, the best treatment for hyperkalemia is its prevention. To avoid the necessity of calcium salt therapy, one should make intense efforts to avoid hyperkalemia by early administration of kayexalate in conjunction with 30% sorbitol to promote its rapid movement through the intestine.

4. Hypocalcemia. Hypocalcemia of a profound degree is common in massive rhabdomyolysis. It usually becomes most prominent after the first 24 hours. Levels as low as 3.5 mg percent have been observed. Despite such extremely low levels calcium, I know of no case in which tetany has occurred unless large amounts of alkali have been administered. Treatment of hypocalcemia therefore produces little observable benefit. In fact, deposition of calcium salts in tissues tends to mobilize later and may create a problem of severe and sometimes fatal hypercalcemia. Ordinarily the hypocalcemia observed in early rhabdomyolysis will correct itself spontaneously.

Whether or not the severe hypocalcemia has anything to do with impairment of blood clotting has not been examined or reported. This would seem a potential problem worthy of examination.

5. Hyperphosphatemia. Hyperphosphatemia usually does not exceed 8 mg percent even in the presence of severe muscle necrosis. This is probably because of deposition as calcium phosphate in injured tissues as fast as phosphate is released from inside the injured cells. If a patient can tolerate oral medication, phosphate binding antacids might be useful for this problem. Ordinarily maintenance of adequate urine volume is sufficient to prevent severe hyperphosphatemia.

6. Disseminated intravascular coagulation. Evidence of DIC is generally present at the time these patients are first admitted to the hospital. The chemical findings will usually become more pronounced on the second or third day and consist of hypofibrinogenemia, thrombocytopenia and abnormal elevations of fibrin split products in blood or urine. There has never been strong evidence that treatment with heparin improves the outlook of these patients. The natural course is that of spontaneous recovery which usually begins on the third or fourth day. In the event of fibrinolysis, some would recommend therapy with epsilon amino caproic acid (EACA). This would seen an unwise move since this compound itself can induce rhabdomyolysis and myoglobinuria (62).

7. Rhabdomyolysis involving the extremities. These patients should be observed carefully during the first week for evidence of increasing edema and vascular compression. In such instances it is wise to seek surgical consultation early so that fasciotomy may be performed before extensive tissue necrosis occurs. As indicated previously in this discussion, CPK activity usually peaks on the 2nd or 3rd day and thereafter should decline at a rate equal to 1/2 of any given value each 48 hours. If this does not occur, it suggests that ongoing tissue necrosis exists which could be related to vascular compression.

8. Hypercalcemia. Severe hypercalcemia may supplant the early hypocalcemia in patients who survive the first week or two of massive rhabdomyolysis. Most but not all of these instances occur in patients who have had acute tubular necrosis and who are undergoing a brisk diuresis. Thus the question of dehydration always arises. When measured, parathormone concentration in serum has generally been normal or even elevated despite the presence of hypercalcemia (1,15,33,63,64). This suggests that not only the early hypocalcemia but also uremia per se increased parathyroid gland activity to such an extent that the gland behaves autonomously during late hypercalcemia. There seems to be little question that those patients who had received calcium therapy for hypocalcemia during the first few days after rhabdomyolysis tend to develop much more severe hypercalcemia later in the course.

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