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The Spectrum of Rhabdomyolysis

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Introduction

Rhabdomyolysis may be defined as a clinical and laboratory syndrome resulting from skeletal muscle injury with release of muscle cell contents into the plasma. The increased plasma concentrations of these released substances such as creatine kinase (CK) permit the clinician to diagnose this syndrome. Rhabdomyolysis may or may not result in visible myoglobinuria, that is, red or brown urine, depending on the amount of myoglobin released into plasma, the glomerular filtration rate, and the urine concentration. Thus the term "rhabdomyolysis" is preferable to "myoglobinuria" as a general description of the syndrome. Rhabdomyolysis is not an uncommon disorder (137) as judged by recent reviews (74) and reports (2, 22).

Although the first reference to this syndrome probably is found in the Book of Numbers, the earliest modern reports in man appear in the German literature (44, 101 and 104). During the blitz of London, Bywaters described the major clinical sequelae of rhabdomyolysis, including the first causative association with acute renal failure (20). In the subsequent 40 years, numerous case reports of patients with rhabdomyolysis-related acute renal failure have identified a host of etiologies and a number of important clinical and laboratory manifestations. The purpose of this study is to present the spectrum of findings in a large group of patients with rhabdomyolysis both with and without renal failure, and to review the literature, largely from the past decade, to provide practical diagnostic and predictive guidelines for the clinician.

We studied 77 patients during 87 episodes of rhabdomyolysis to address four questions: 1) What are the most common etiologies of rhabdomyolysis in a civilian population in peacetime; 2) What clinical or laboratory variables alert the clinician to the presence of rhabdomyolysis; 3) What factors predict the development of renal failure; and 4) Does the clinical course of acute renal failure associated with rhabdomyolysis differ substantially from the course of acute renal failure due to other causes?

Materials and Methods

Seventy-seven patients hospitalized at Denver General Hospital (DGH) (n=66) or University of Colorado Health Sciences Center (UCHSC) (n=11) were observed during 87 hospital admissions. The study population was drawn from two sources: first, the records of all patients with a recorded discharge diagnosis of rhabdomyolysis hospitalized from January 1976 to January 1979 at DGH and from July 1978 to March 1980 at UCHSC; second, other patients assigned the diagnosis of rhabdomyolysis by the Renal Service at DGH between August 1974 and March 1980. The last 16 patients entered were studied prospectively. The patients were seen personally by one of the authors during 46 of the 87 hospitalizations.

The two criteria for inclusion in the study population were a serum creatine kinase (CK) concentration greater than 500 IU/L during the hospitalization (normal, $\leq$ 85 IU/L) and determination of serum creatinine on admission. Patients were excluded from analysis if evidence existed for a myocardial infarction or cerebral vascular accident unless the laboratory documented the presence of only MM isoenzymes of CK.

All patients had serum obtained within 24 hours of entry for measurement of sodium, potassium, chloride and CO_2 content (electrolytes), urea nitrogen (BUN) and creatinine. A majority of patients had contemporaneous analyses of arterial blood for pH, P_{CO_2} and P_{O_2} and serum for phosphorus, calcium, albumin, uric acid, CK, lactate dehydrogenase (LDH), glutamic oxaloacetic transaminase (SGOT), bilirubin and alkaline phosphatase. Patients had repeated laboratory determinations of many of these variables during 79 of 87 hospitalizations. A urinalysis was performed at the time of admission or at the time of the episode of rhabdomyolysis in 81 of the 87 episodes. Four patients had rhabdomyolysis due to an intercurrent event during hospitalization. The day of onset of the event was considered to be "hospital day" 1 for the purpose of data analysis. All laboratory analyses were performed by the clinical laboratory of the respective hospital.

The etiology of the rhabdomyolysis for each event was determined by patient interview, chart review or both. Assigned etiological factors included alcoholism, seizures, drug ingestion, compression from immobilization, direct trauma, cold exposure, influenza-like illness, and the metabolic derangements of diabetic ketoacidosis or hyperosmolar nonketotic coma, hypokalemia and/or hypophosphatemia. Alcohol was implicated if the patient's problem list included chronic alcoholism or if the patient had alcohol detected in the blood on admission. The diagnosis of

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a seizure required a witness to the event. Drug abuse was diagnosed if a serum screen for toxins was positive or if the patient admitted to drug use. Immobilization with compression implied that the patient was found lying on a floor or street either unconscious or incapable of ambulating. The diagnosis of cold exposure required an initial body temperature of ≤ 35°C. Hypokalemia was considered of etiological importance if the admission serum potassium was less than 2.0 mmol/L; hypophosphatemia was implicated if the serum phosphorus concentration was less than 2.0 mg/dl.

Only patients with serial laboratory data were included in those analyses involving the natural evolution of the biochemical changes. Peak values were the highest values for a given variable that occurred during hospitalization. Trough values were the lowest values recorded during hospitalization.

Sixteen patients with acute renal failure due to causes other than rhabdomyolysis were compared with the patients with rhabdomyolysis-related acute renal failure. These patients were hospitalized during the same time periods as the patients with rhabdomyolysis. They met all of the following requirements: age over 18 years; previous normal renal function; a renal failure index greater than 1.0 (103); absence of evidence for glomerulonephritis, urinary tract obstruction, hepatorenal syndrome; no sign of rhabdomyolysis such as elevated serum CK level, positive urine orthotolidine testing without hematuria, history of crush or ischemic injury; and survival for longer than 24 hours after the appearance of azotemia.

Mean values are presented throughout with standard deviations. Student's *t*-test was used to compare group means. Descriptive data were compared by chi-square testing. Correlations and linear regressions were performed using a programmed method of least squares. Multiple regression and discriminant analyses were carried out by Dr. Philip Archer and Ms. Kay Ryschon of the Biometrics Department of the University of Colorado School of Medicine using the Biomedical Computer Programs packaged programs (Department of Biomathematics, UCLA School of Medicine, Los Angeles). P values less than 0.05 are considered significant.

Results

General: The study population consisted of 66 males and 11 females with a mean age of 48 ± 17 years and range of 21 to 85 years. Three of the 77 patients were observed during multiple admissions, 3, 4 and 6 respectively.

Etiologic factors: Alcohol abuse, compression, and seizures were the etiologic factors most commonly implicated (Table 1). Metabolic derangements were considered of etiologic importance in one episode of diabetic ketoacidosis, three of severe hypophosphatemia, two of hypokalemia, and one of combined hypophosphatemia and hypokalemia. In three patients no precipitating factor was apparent. In the 33 patients with a single identified factor, alcohol abuse and compression were again the most common events. The three patients with recurrent rhabdomyolysis had chronic alcoholism. Two had aggressive courses of rhabdomyolysis with progressive muscle loss. No genetic cause for rhabdomyolysis was apparent. Both had normal lactate responses to intense exercise and one had normal ketone production during fasting. Muscle biopsies were similar: all stages of degenerating and regenerating muscle fibers, no cellular infiltration, and no abnormal storage of glycogen or lipid.

TABLE 1. Etiological Factors in 87 Episodes of Rhabdomyolysis

	N	%
Alcohol	58	67
Compression	34	39
Seizures	21	24
Direct trauma		
major	6	6
minor	10	11
Drug abuse	13	15
Metabolic derangement	7	8
Hypothermia	4	4
Influenza-like illness	3	3
Sepsis	2	2
Gangrene	1	1
Summary		
No factor identified	3	3
Single factor identified	33	38
Multiple factors	51	59

Symptoms and signs: Patients presented with muscle pain in 25 of the 50 episodes with reliable histories. However, objective findings such as firm swelling of muscles were detected at the time of admission in only 4 of the 87 episodes. In nine patients observed daily for this finding, muscle swelling became apparent in four only after administration of intravenous fluids.

Urinalysis: The urine contained red blood cells in 25 of 79 urinalyses (32%). In the 54 other episodes without hematuria, urine testing with orthotolidine was positive for heme in 40 episodes (50% and negative in 14 instances (18%). Proteinuria was found in 54 of 81 (67%) urinalyses. Seventeen specimens contained 1+ proteinuria by dipstick determination, 25 had 2+ proteinuria, and 12 had 3+ proteinuria. Four of 12 patients with 3+ proteinuria had repeat urinalyses at time of discharge: 2 had 1+ protein, 2 had negative testing.

Admission blood chemistries: In the remainder of the Results section the patients will be partitioned into a variety of groups for comparison: 1) the entire population is divided into those with initial serum creatinine concentrations less than 3.0 mg/dl (non-azotemic) and those with initial serum creatinines greater than 3.0 mg/dl (azotemic); 2) the initially non-azotemic group is subdivided into patients who developed acute renal failure (RFD) and those who did not (NRF); and 3) all patients with rhabdomyolysis-related acute renal failure (R-ARF) are compared to a control group of patients who had renal failure from other causes (NR-ARF).

The mean admission values for three groups, "NRF," "RFD" and "azotemic," are displayed in Table 2. The admission serum creatinine concen-

TABLE 2. Initial Serum Chemical Values in Patients with Rhabdomyolysis

	Non-azotemic		Azotemic
	NRF	RFD	
	$n = 52$	$n = 13$	$n = 22$
Creatinine mg/dl	1.3 ± 0.6	1.8 ± 0.6⁺	5.5 ± 3.5*
BUN mg/dl	19.1 ± 18.4	16.0 ± 5.6	6.4 ± 3.9*
Potassium mmol/L	3.8 ± 0.9*	4.8 ± 1.1	4.8 ± 1.2
Anion gap mEq/L	20.7 ± 8.3	24.7 ± 9.2	28.5 ± 12.5⁺
Calcium mg/dl	9.1 ± 1.0	9.0 ± 1.4	8.0 ± 2.2⁺
Phosphorus mg/dl	3.7 ± 2.0	5.0 ± 2.0	7.3 ± 3.9*
Uric acid mg/dl	9.1 ± 3.3	11.3 ± 1.7⁺	14.0 ± 3.9*
CK IU/L	10109 ± 18408	13314 ± 14392	7665 ± 6769
LDH IU/L	780 ± 1032	1218 ± 1898	1577 ± 2425
SGOT IU/L	474 ± 851	1443 ± 3084	888 ± 1066

NRF = no renal failure; RFD = renal failure developed after admission.

* significantly different from the other two groups. ⁺significantly different from the NRF group.

trations for the entire study population ranged from 0.4 to 19.6 mg/dl. The mean serum potassium concentration was significantly lower in the patients without renal failure (NRF). The admission serum potassium concentration was greater than 5.5 mmol/L in only 5 of 22 initially azotemic and 2 of 65 non-azotemic patients ($P<0.005$).

Acid base derangements manifested by abnormal blood pH occurred in 47 of the 66 patients with arterial blood gas determinations. Acidemia (pH less than 7.36) (21 patients) and alkalemia (pH greater than 7.44) (26 patients) occurred with similar frequency in the initially azotemic and non-azotemic groups.

Eighteen patients had hypocalcemia (less than 8.0 mg/dl) on admission. Two had albumin concentrations less than 3.0 g/dl and eight had phosphorus levels above 6.0 mg/dl. Three patients were transiently hypercalcemic on admission (12.4, 12.3 and 12.5 mg/dl) with serum phosphorus levels above 6.0 mg/dl and Ca x P products greater than 75.

Multiple regression analysis was used to define the relationships of potassium (K), phosphorus (P), calcium (Ca), and uric acid (UA) to a number of biochemical variables. The best fit formulas demonstrated that potassium related best to creatinine and pH, phosphorus to anion gap and bicarbonate; calcium to albumin only, and uric acid to anion gap and creatinine. None related well to the log CK.

Hospital Course

Renal function: The patterns of renal function in the 87 episodes of rhabdomyolysis are pictured in Figure 1. In the six patients with prerenal azotemia, the creatinine concentrations decreased to less than 1.5 mg/dl within 48 hours of admission following volume repletion. Overall, 29 patients had acute renal failure (ARF) during the 87 episodes of rhabdomyolysis (33%).

We attempted to identify clinical and biochemical factors which are associated with a high risk of ARF. Patients with major trauma appeared more likely to develop ARF. Four of 13 patients who developed renal failure (RFD) had major trauma in contrast to 2 of 52 patients without renal failure (NRF) ($P<0.005$).

Urinalysis had little predictive value. Myoglobinuria at the time of admission did not predict increased risk for ARF.

The initial serum laboratory values in the RFD and NRF groups are shown in Table 2. No single laboratory value could accurately predict an individual at high risk for ARF. Therefore, multiple serum variables were tested by discriminant analysis to derive a predictive index (R) for such individuals. Fifty-seven patients with initial serum creatinine concentrations less than 3.0 mg/dl had all of the utilized variables measured. The best discriminant function included only potassium (K), creatinine (creat) and albumin (alb) in an equation which divided the patients into two groups, a "high-risk" group containing all the patients who developed ARF and a "low-risk" group containing no patients with ARF as displayed in Table 3.

Biochemical abnormalities: In order to further

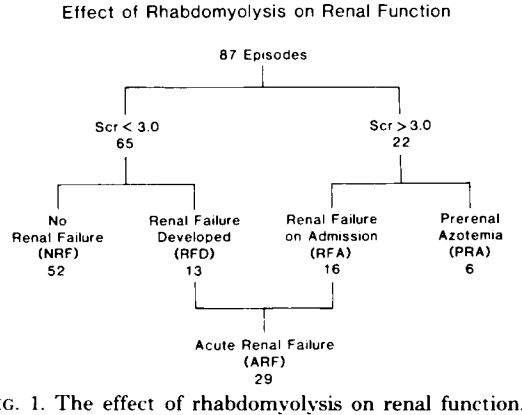

FIG. 1. The effect of rhabdomyolysis on renal function. On admission, 65 patients had a serum creatinine (Scr) less than 3 mg/dl and 22 patients had a Scr greater than 3 mg/dl. Of the former group 52 had no renal failure (NRF) during the hospital course, whereas 13 developed renal failure (RFD). Of the 22 patients with admission Scr greater than 3 mg/dl, 6 had a course compatible with prerenal azotemia (PRA) and 16 had renal failure from the time of admission (RFA). Overall 29 had a course compatible with acute renal failure (ARF).

TABLE 3. Results of Discriminant Analysis for Predicting Patients with Rhabdomyolysis at High Risk for Developing ARF*

R value†	NRF	RFD	% RFD	Group
≥0.1	16	11	41	high risk
<0.1	30	0	0	low risk

* Applies to patients with admission serum creatinine values less than 3.0 mg/dl. ARF = acute renal failure; NRF = patients who never had renal failure; RFD = patients who developed renal failure after admission.

† R = 0.7 [K] + 1.1 [creat] + 0.6 [alb] − 6.6 where [K] is serum potassium concentration in mmole/liter, creat is serum creatinine concentration in mg/dl and alb is serum albumin concentration in g/dl.

characterize the hospital course, all patients who had or developed ARF were compared to those who never had renal failure (NRF in Figure 1). Laboratory values are listed in Table 4.

Although mean peak serum calcium was within the normal range for the ARF and NRF groups, five patients had serum calcium levels greater than 11.0 mg/dl. Serum calcium levels of 12.4, 12.5 and 12.3 mg/dl occurred in three patients on the day of admission in association with serum albumin concentrations of 6.1, 5.0 and 4.1 g/dl respectively. Two other patients from the RFD group developed hypercalcemia with peak serum calcium values of 11.2 and 11.4 mg/dl on hospital days 10 and 8 about 16 hours after a hemodialysis treatment. Hypercalcemia persisted for 3 and 5 days. Trough calcium concentrations preceding institution of dialysis were 5.0 and 4.2 mg/dl on hospital days 3 and 4. Sixty percent of the NRF group and 90% of the ARF patients had trough serum calcium values during their hospital stay of less than 8.5 mg/dl occurring on hospital day 3.5 ± 3.1 in the NRF group and hospital day 4.4 ± 4.0 in the ARF group.

Seven patients had hypophosphatemia (less than 2.5 mg/dl) on admission. Twenty-one of 53 patients developed hypophosphatemia after admission. Thus hypophosphatemia occurred in 42% of patients with rhabdomyolysis. Patients with phosphorus concentrations greater than 5.5 mg/dl on admission tended to develop hypophosphatemia more frequently than those with admission values of 2.5 to 4.5 mg/dl: 14 of 23 patients vs. 7 of 30 ($P<0.01$).

Comparison of rhabdomyolysis-related acute renal failure (R-ARF) and non-rhabdomyolysis-related acute renal failure (NR-ARF): Overall 33% or 29 of the 87 episodes of rhabdomyolysis resulted in ARF (Fig. 1). The 29 patients with R-ARF were younger and more frequently males, but the frequency of oliguria, dialysis and death was similar to that of the patients with NR-ARF. Eighteen of the 29 episodes of R-ARF were nonoliguric (62%); 11 were oliguric (less than 400 ml of urine per 24 hours). Seven nonoliguric and six oliguric patients in the R-ARF group required hemodialysis. Comparison of admission, peak and trough laboratory values for patients with R-ARF and NR-ARF patients revealed significant differences only for admission anion gap (28 ± 14 vs. 17 ± 6 mEq/liter) and phosphorus (7.3 ± 3.5 vs 4.5 ± 1.5 mg/dl).

The rate of rise of creatinine was similar during the first 24 hours in both groups, 1.3 ± 0.7 mg/dl in R-ARF vs. 1.4 ± 0.8 mg/dl in NR-ARF (P=NS). Eight of nine patients without renal failure excreted less than 25 mg/kg of creatinine in 24 hours (14 to 24 mg/kg).

Creatine kinase (CK) changes: In the present study, 3 or more CK determinations were obtained in 64 of the 87 episodes (74%). The peak CK occurred on day one in 69% of the patients. Eleven patients had peak CK levels of greater than 20,000 units/L (24,000 to 238,000). Three of these patients had ARF. However, in the whole population, the peak level of CK did not correlate with the development of ARF or the level of other chemical variables. The serum CK declined at a relatively constant rate, falling by 39% of the previous day's value per day.

Morbidity and mortality: Two patients required fasciotomy owing to the development of acute compartment syndromes. The patient with the highest CK, 238,000 IU/L, appeared clinically to have cardiac as well as skeletal muscle involvement. This 35-year-old man had recurrent rhabdomyolysis and congestive heart failure with no evidence of other causes of heart disease.

Eight patients in the present study died. Three of these patients had undergone hemodialysis. Four patients had major trauma, burns, or gangrene. The

TABLE 4. Peak and Trough Serum Chemical Concentrations in Patients with Rhabdomyolysis with (ARF) and without (NRF) Acute Renal Failure

Serum Variable	ARF	NRF
Peak creatinine (mg/dl)	7.6 ± 3.7 (29)	1.5 ± 0.6 (45)*
Peak BUN:creatinine ratio	11 ± 6 (27)	13 ± 9 (42)
Peak potassium (mmol/liter)	5.6 ± 0.9 (29)	4.7 ± 0.6 (46)*
Peak phosphorus (mg/dl)	7.0 ± 2.7 (29)	4.5 ± 1.8 (44)*
Peak uric acid (mg/dl)	14.1 ± 4.4 (24)	9.3 ± 3.7 (38)*
Peak calcium (mg/dl)	9.4 ± 1.1 (29)	9.5 ± 0.8 (45)
Trough calcium (mg/dl)	7.0 ± 1.1 (29)	7.9 ± 1.0 (45)*
Trough phosphorus (mg/dl)	3.0 ± 1.2 (23)	2.8 ± 0.9 (34)

* indicates that the two groups differ significantly, $P < 0.05$. The parentheses contain the number of patients tested for the given variable.

peak CK values in the patients who died ranged from 803 to 238,880.

Discussion

Rhabdomyolysis literally means "striped muscle dissolution." However, a more useful definition is "skeletal muscle injury, reversible or irreversible, that alters the integrity of the cell membrane sufficiently to allow the escape of cell contents into the extracellular fluid." These cell contents include enzymes such as creatine kinase, glutamic oxaloacetic transaminase, lactate dehydrogenase, aldolase; the heme pigment, myoglobin; electrolytes such as potassium and phosphate; and purines. Creatine kinase is the most sensitive enzyme marker of muscle injury (59) and is readily determined in most hospital laboratories. In the present study, we used a fivefold or greater increase in serum CK in patients without apparent cardiac or brain injury as the single diagnostic criterion for rhabdomyolysis.

Elevation of serum myoglobin concentration and/or the presence of myoglobinuria also indicate skeletal or cardiac muscle injury. However, detection of these phenomena is neither a practical nor sensitive way to diagnose rhabdomyolysis for a variety of reasons. Serum levels may fall to normal by the time a patient is hospitalized owing to the rapid clearance of myoglobin from plasma within 1 to 6 hours by both renal excretion and metabolism to bilirubin (81). In addition, myoglobinuria correlates poorly with myoglobinemia (161). Myoglobin enters the urine when plasma concentrations exceed 1.5 mg/dl, in contrast to free hemoglobin which reaches the urine at plasma levels above 30 mg/dl (66). Myoglobinuria is visible when urine myoglobin exceeds 100 mg/dl. Achievement of this concentration depends on the amount of myoglobin released from muscle, the plasma concentration of myoglobin, the amount of plasma protein binding of myoglobin, the glomerular filtration rate and the urine flow rate (74). Thus serum and urine concentrations may be minimal by the time of hospitalization in some patients. In contrast, serum CK levels would be likely to remain elevated at the time of initial laboratory testing because of the slower plasma clearance of CK than of myoglobin (34). This relatively slow clearance of CK is illustrated by the rate of decline of about 39% per day with an apparent serum half-life of about 1.5 days. Although the orthotolidine dipstick has been found to be as sensitive as immunodiffusion in detecting myoglobinuria (51), the absence of myoglobin in the urine does not eliminate the diagnosis of rhabdomyolysis as discussed above. In fact, 26% of our patients with rhabdomyolysis documented by a CK elevation had a negative dipstick test for myoglobin within 24 to 48 hours of admission.

Utilizing the historical, clinical and laboratory data derived from 87 episodes of rhabdomyolysis, we attempted to answer the four questions raised in the introduction about the etiologies, clinicopathological markers, prognostic indices, and effects on renal function of rhabdomyolysis. These 87 patient-episodes represent a broad spectrum of clinical and laboratory manifestations of rhabdomyolysis which allows some separation of the manifestations of rhabdomyolysis from those of acute renal failure.

Etiological Factors

The three most common presumed pathogenic disorders in our patients were alcohol, muscle compression and generalized seizures (Table 1). In four series compiled in the United States, drug abuse and compression are the most common etiologies (39, 51, 78, 138). In a study compiled in India there were no patients with drug abuse but four with complications of pregnancy (26). Two very recent large studies describe 30 patients with drug abuse and rhabdomyolysis (22) and 25 patients with phencyclidine-related rhabdomyolysis (2). Compression is probably the critical factor in producing rhabdomyolysis in most patients with drug-related coma. Thus, two common social diseases, alcoholism and drug abuse, appear responsible for the majority of cases of rhabdomyolysis.

The most striking difference in the discussion of etiology between this study and previous studies is the reported prevalence of multiple factors. In this study, multiple factors capable of injuring muscle were present in 51 of 87 episodes. This difference from other series reflects patient population selection and methods of accounting. Most large series in the literature focus on acute renal failure (26, 39, 78, 138) or a specific etiology for rhabdomyolysis (2, 22), whereas the present study was designed to investigate rhabdomyolysis with initial disregard for renal function or cause. In addition we included alcohol as a causative factor in any patient with a history of alcoholism or a measurable blood ethanol level on admission. This liberal definition of alcohol-related rhabdomyolysis may have exaggerated the epidemiologic role of alcohol in rhabdomyolysis. However, it has probably excluded those patients with chronic alcoholic myopathy. Although Perkoff et al have described a chronic myopathy in alcoholics (121), the 18 patients in our series who had alcohol abuse as a sole etiologic factor had evidence such as myoglobinuria, acute renal failure or CK levels greater than 1500 IU/L indicating a more acute form of rhabdomyolysis.

Many mechanisms for alcohol-related myopathies have been suggested. Ethanol itself appears to be a direct toxin (158). In addition, other abnormalities such as starvation (54), refeeding (54, 75),

TABLE 5. Reported Causes for Rhabdomyolysis

I. Excessive Muscular Activity
- Contact sports (46, 125)
- Noncontact sports (3, 7, 10, 34, 51, 56, 87, 91, 111, 143)
- Seizures (26, 39, 98, 153, 160, 164)
- Delirium tremens
- Status asthmaticus (25)
- Psychosis (30)

II. Direct Muscle Injury
- Trauma (20, 33, 39, 49, 102, 178)
- Burns (43)

III. Ischemia
- Compression (24, 39, 48, 113, 117, 119, 131, 147)
- Vascular occlusion (53, 64, 112)
- Sickle cell trait (79)
- Air embolism (43)

IV. Immunological Diseases
- Dermatomyositis (65, 71, 93)
- Polymyositis (65, 82, 92, 123, 156)

V. Metabolic Disorders
- Diabetes mellitus
  - hyperosmolar nonketotic coma (51)
  - ketoacidosis (127)
- Hypokalemia
  - diuretics (110)
  - carbenoxolone (9, 35)
  - amphotericin (38)
  - parenteral nutrition (107)
  - licorice (166)
  - primary hyperaldosteronism (37)
  - cortisone therapy (57)
  - renal tubular acidosis (23)
- Hyponatremia (18)
- Hypernatremia (169)
- Hypophosphatemia (107, 174)
- Myxedema (55)

VI. Drugs
- Heroin (32, 39, 50, 73, 78, 128, 135, 137, 147, 148, 150, 167, 177)
- Methadone (45)
- Phencyclidine (2, 11, 28, 116)
- Amphetamines (51, 70)
- L.S.D.
- Glutethimide (58)
- Salicylate overdose (14, 155)
- Succinylcholine (140)
- Clofibrate (157)
- Epsilon aminocaproic acid (15, 17, 136)

VII. Toxins
- Ethanol (4, 39, 42, 78, 84, 94, 121, 122, 129, 139, 146, 150, 158, 176)
- Isopropyl alcohol
- Carbon monoxide (89)
- Mercuric chloride (27)
- Ethylene glycol (114)
- Toluene, paint sniffing (162)
- Quail ingestion, ? hemlock (13)
- Snake bite (61, 130)
- Hornet or wasp sting (154)
- Brown spider bite
- Haff's disease

VIII. Infections
- Bacterial
  - tetanus
  - Legionnaire's disease (124)
  - pyomyositis (6)
  - other (134, 159)
- Viral
  - influenza (31, 60, 72, 105, 106, 133, 152, 181)
  - infectious mononucleosis (67)
  - other (12, 31, 63, 67, 72, 133, 144, 175)

IX. Genetic Disorders
- Abnormal carbohydrate metabolism
  - myophosphorylase deficiency (51, 52, 99, 115, 145)
  - alpha-glucosidase deficiency
  - amylo-1-6-glucosidase deficiency
  - phosphohexomerase deficiency (141)
  - phosphofructokinase deficiency (83)
- Abnormal lipid metabolism
  - carnitine deficiency (172)
  - carnitine palmityl transferase deficiency (8, 62, 118, 132)
- Muscular dystrophies (120)

X. Miscellaneous
- Idiopathic, recurrent (16, 29, 41, 80, 86, 90, 165)
- Temperature extremes
  - hyperthermia (26, 76, 85, 95, 155, 170)
  - hypothermia (126)
- Electric shock, lightning (179)

hypokalemia (77), hypophosphatemia (75) and induced enzymatic defects (122) have been shown to be operative factors in acute alcoholic rhabdomyolysis.

Drug overdose frequently causes rhabdomyolysis owing to limb compression rather than a direct effect of the drug. The weight of the body on a limb raises the pressure in the muscle compartment to a sufficiently high level to obstruct blood flow (113). The muscle becomes ischemic and edematous, further raising compartment pressure. Thus a vicious cycle of increased compartment pressure, ischemia, and increasing compartment pressure is established (113).

It has been said that "rhabdomyolysis is an uncommon consequence of an uncommon group of diseases" (137). Perhaps this saying stemmed from the early descriptions of rhabdomyolysis in the fleeing Israelites induced by eating quail which had fed on hemlock seeds (13) or in the Londoners crushed during the German blitz (20). Certainly the list of causes of rhabdomyolysis is long and diverse, as recorded in Table 5. In this country in a nonindustrial, urban population, rhabdomyolysis is a common manifestation of a common group of disorders (Table 1).

Clinical Features of Rhabdomyolysis

The usual description of a patient with rhabdomyolysis emphasizes muscle pain and swelling. However, fifty percent of our patients voiced no complaints of muscle pain and only four had objective muscle swelling on admission. Thus, muscular symptoms and signs are not discriminatory for rhabdomyolysis on initial evaluation. However, the accumulation of fluid by injured muscle may cause readily detectable muscle swelling following intravenous fluid therapy. Thus limb swelling after ad-

mission to the hospital may be a valuable clue to a recent episode of rhabdomyolysis.

Laboratory Features of Rhabdomyolysis

Urinalysis: The orthotolidine dipstick for heme is reputedly as sensitive in detecting myoglobin as is immunodiffusion (51). Thus, levels of 0.5 to 1.0 mg/dl may be detected (78). Orthotolidine does not distinguish between myoglobin and hemoglobin; therefore substantial hematuria prohibits a diagnosis of myoglobinuria by dipstick. In half of the episodes of rhabdomyolysis in the present study hematuria was present (32%) or the dipstick was negative (18%). Thus, the presence of a negative test for urinary heme pigments by dipstick or hematuria should not exclude a diagnosis of rhabdomyolysis.

Proteinuria was detected by dipstick in a surprising 45% of the episodes of rhabdomyolysis in the present study. A review of 56 patients reported in the medical literature yields an even higher frequency (90%) (6, 10, 18, 23, 28–30, 36, 41, 55–57, 65, 67, 69, 71, 73, 82, 95, 98, 105, 114, 116, 117, 123, 126, 128, 129, 138, 142, 146, 148, 151, 152, 160, 164, 165, 170, 171, 173, 175–177, 180, 181). Quantitative 24-hour protein excretion ranged from 0.7 to 8.2 g in four patients (10, 71, 105, 123). The nature of the proteinuria is not clear. We performed studies that indicate that horse myoglobin reacts with the dipstick for protein to the same degree as does human albumin. Myoglobin or other substances released from muscle may alter glomerular permeability or tubular handling of low molecular weight proteins (129) and thus some of the proteinuria may be due to the presence of proteins other than myoglobin or albumin (129).

Serum Chemistry Findings

Potassium: Muscle cell potassium content is about 100 mmol/kg (74); therefore, rapid total necrosis of only about 150 g of muscle will release more than the 15 mmoles needed to elevate acutely plasma and extracellular fluid potassium concentration by 1.0 mmol/L. We were surprised to find that mean admission serum potassium concentration was normal in our patients and that only seven patients had levels over 5.5 mmol/L. Six of these seven patients had or developed ARF. Review of 71 reports in the literature revealed hyperkalemia (greater than 5.5 mmol/L) on admission in 47 of 109 patients or 43% (9–11, 17, 18, 23–24, 27–30, 32, 35–40, 42, 43, 50, 55–57, 60–63, 67–69, 71–73, 78, 80, 82, 84, 90, 93–95, 98, 105, 110, 114, 116, 117, 119, 123, 124, 128, 131, 137, 138, 142, 146, 148, 149, 151, 154, 156, 160, 164, 166, 169–171, 176, 177, 180). Thirteen of these 47 patients had admission serum creatinine levels less than 3.0 mg/dl (range, 2.0–2.9) or BUN levels less than 50 mg/dl (range, 13–44). However, all but two of this group developed clinical acute renal failure. Renal function is the most important determinant of serum potassium in rhabdomyolysis (Table 2). This is supported by the average serum potassium concentration of 4.4, 4.5 and 6.3 mmol/L reported in patients with rhabdomyolysis without renal failure, with nonoliguric ARF, and with oliguric ARF, respectively (22). In addition, in our series potassium was significantly related inversely to blood pH as expected. The absence of hyperkalemia should not deter consideration of the diagnosis of rhabdomyolysis, particularly in patients with normal renal function.

Anion gap: The serum anion gap in patients with R-ARF was significantly higher than the anion gap in patients with NR-ARF. In addition, the mean serum anion gap was significantly higher in the NRF group than in 37 patients randomly selected on a single day from the wards of Denver General Hospital (21.5 ± 8.6 vs 13.4 ± 5.8 mEq/L, $P < 0.001$). McCarron et al described a patient with rhabdomyolysis with serum creatinine 2.7 mg/dl, bicarbonate 4 mmole/L, lactate 0.9 mmole/L and an anion gap of 39 mEq/L (98). This suggests that an unidentified organic acid(s) may be released or produced in rhabdomyolysis.

Phosphorus: An elevated serum phosphorus concentration was not a sensitive marker of rhabdomyolysis in our study. Serum phosphorus concentration correlated best with serum anion gap and inversely with bicarbonate concentration. This suggests that hyperphosphatemia in part may be due to leakage of phosphorus released from hydrolyzed non-regenerated adenosine triphosphate in injured muscle along with some organic acid(s) which is responsible for the increased anion gap and hypobicarbonatemia. A similar mechanism has been proposed for the hyperphosphatemia of lactic acidosis (108, 109).

Uric acid: Marked elevations of serum uric acid have been noted frequently in rhabdomyolysis. While serum uric acid has been correlated with CK values in exertional rhabdomyolysis, this relationship is weak in alcoholic rhabdomyolysis (74, 76). Many of our patients were alcoholics which may explain the poor correlation between serum uric acid and CK in our study.

BUN and creatinine: Another biochemical manifestation of rhabdomyolysis suggested by Hamilton et al is markedly decreased BUN to creatinine ratios of 6:1 in patients with rhabdomyolysis-related ARF (56). This low ratio has not been found in most patients reported in the literature nor in the present study. The mean BUN-to-creatinine ratio was similar in the NRF, the R-ARF and the NR-ARF groups (Tables 2, 4). Similarly the allegedly

increased rate of rise of the serum creatinine in rhabdomyolysis-related renal failure (51) was not demonstrated in the present study. Preliminary experimental data also suggest that creatinine production is not enhanced in rhabdomyolysis (163).

Calcium: Hypocalcemia occurs frequently and early in the course of rhabdomyolysis-related ARF (74). We found hypocalcemia in 55 of 87 patient episodes of rhabdomyolysis (63%). Hypocalcemia in rhabdomyolysis has been attributed to deposition of calcium salts in injured or necrotic muscle (1, 100). Surprisingly, patients with non-rhabdomyolysis-related ARF were also hypocalcemic with the same frequency and to the same degree as the rhabdomyolysis-related ARF patients. A recent study demonstrated decreased serum 1,25-dihydroxycholecalciferol (1,25-$(OH)_2$-D_3) levels during hypocalcemia in six patients with rhabdomyolysis and advanced acute renal failure (88). The authors suggest that hyperphosphatemia is responsible for the decreased 1,25-$(OH)_2$-D_3 levels. Therefore, the frequency of hypocalcemia should be influenced by the degree of hyperphosphatemia. In the present study, however the level of serum phosphorus did not appear to determine the presence of hypocalcemia; 56% of hypocalcemic patients had simultaneous normal serum phosphorus concentrations. Thus, hypocalcemia is a frequent accompaniment of rhabdomyolysis with and without renal failure even in the absence of hyperphosphatemia.

Hypercalcemia (11.0 mg/dl) has been reported in 56 patients with rhabdomyolysis without immediately proximate intravenous calcium therapy. The clinical and laboratory features of these patients and two patients from the present series who developed hypercalcemia after admission are listed in Table 6. All patients had acute renal failure and only one was reported not to require dialysis. Ninety percent were known to be hypocalcemic during the early stages of their illnesses. The mechanism of the hypercalcemia is suggested to involve the release of calcium from damaged muscle (1, 36) and inappropriately normal or high PTH and 1,25-$(OH)_2$-D_3 levels during the recovery period (88). However, the literature contains reports of patients with pronounced tissue calcium deposition who did not develop hypercalcemia (1) and patients with undetectable PTH levels who did (36).

TABLE 6. Clinical and Laboratory Features of Patients with Rhabdomyolysis Who Developed Hypercalcemia*

Day of Onset†	N	Duration	N	Peak Serum Calcium‡	N
before diuresis	5	1–5 days	8	11.0–11.9	10
diuresis days 1–5	6	6–10 days	10	12.0–12.9	12
diuresis days 6–10	11	11–15 days	11	13.0–13.9	9
diuresis days 11–15	4	>15 days	6	14.0–14.9	9
diuresis day 16 +	2	not reported	23	>15.0	9
not reported	30			not reported	9

* Data from two patients in this study and 56 patients reported in references 2, 14, 19, 22, 26, 30, 33, 36, 42, 43, 47, 49, 51, 52, 78, 85, 86, 91, 96, 97, 102, 116, 117, 137, 149, 165, 168, 171, 173, 176, 178, and 180.

† Diuresis day 1 is first 24 hour period of urine output of 1000 ml or greater.

‡ Serum calcium in mg/dl.

Acute Renal Failure

The frequency of ARF in the setting of rhabdomyolysis is not known. In the present study the frequency was 33%, but this probably is an exaggeration of true frequency due to the nature of the patient selection. Thirteen of our 29 patients with renal failure developed the picture of ARF after admission. It may be important to the clinician to identify these patients in order to permit the use of prophylactic treatment such as mannitol, furosemide or dopamine aimed at altering the subsequent course. Therefore, we attempted to find clues which marked these patients. Using discriminant analysis, we developed a predictive formula using admission laboratory date (Table 3). The formula separated our patients into those with no episodes of renal failure and those with a 41% prevalence of acute renal failure. Therefore, when this formula is applied it would be expected to yield a low incidence of false negatives and a high incidence of false positives for developing acute renal failure. In those patients studied by Eneas et al, the hematocrit was higher in the patients who developed ARF despite volume replacement and mannitol and sodium bicarbonate therapy (39). The relationship of hypovolemia to renal failure with rhabdomyolysis has also been demonstrated experimentally (21).

Patients with rhabdomyolysis-related ARF in this study differed little from patients with other types of ARF. The morbidity (dialysis) and mortality of the R-ARF and NR-ARF groups were similar. The frequency of oliguria was 38% in both groups. This low frequency of oliguria may relate to the vigorous therapeutic approach during the early phase of ARF utilizing volume repletion and furosemide employed at our institution (5). Eneas et al have reported that 9 of 20 patients with myoglobinuria and oliguric ARF responded to the infusion of mannitol and sodium bicarbonate solutions with a significant increase in urine output (39).

Certainly rhabdomyolysis-related ARF may cause spectacular elevations of uric acid and phosphorus and even fatal hyperkalemia (36, 39, 98, 112). These findings probably require more massive muscle injury or greater content of these substances

or their precursors in muscle than we observed in these victims of largely "medical" rhabdomyolysis in a predominantly alcoholic population.

We did not observe evidence of chronic renal failure due to rhabdomyolysis in this study. Kagen has identified myoglobin in renal tubules (64) and McCarron et al have attributed chronic interstitial nephritis to recurrent myoglobinuria (99).

Summary

We studied 87 episodes of rhabdomyolysis in 77 patients and found the following.

1). Alcoholism was the most common etiologic factor (67%). This may reflect in part our liberal definition of alcoholic rhabdomyolysis. Multiple factors existed in 59% of the episodes.

2). Myoglobinuria was detected by orthotolidine dipstick in the absence of hematuria in only 50% of patients. Thus, urine testing is not a sensitive clue to the presence of rhabdomyolysis.

3). Twenty-two patients were azotemic (creatinine > 3.0 mg/dl) on admission. These patients had higher average values for serum potassium, anion gap, phosphorus, and uric acid and a lower average serum calcium concentration than did non-azotemic patients.

4). Discriminant analysis of the 65 patients without admission azotemia separated them into two groups: a group at high risk for renal failure, 11/27 or 41%, a group at low risk, 0/30 or 0%. The low risk group had an R value less than 0.1 where R = 0.7 [serum K] + 1.1 [serum creatinine] + 0.6 [serum albumin] − 6.6.

5). Twenty-nine patients had ARF (33%). Six of these patients died.

6). Hypocalcemia developed in 63% of the patients. It was similar in frequency and degree in 16 patients with ARF not due to rhabdomyolysis.

7). Two patients had hypercalcemia during the course of ARF. These 2 and 56 patients with hypercalcemia described in the literature are reviewed.

8). Hyperkalemia and hyperphosphatemia were similar in degree and frequency in patients with rhabdomyolysis-related ARF and other types of ARF.

9). The anion gap on admission was markedly increased in rhabdomyolysis-related ARF (28 mEq/L) in contrast to the other types of ARF (17 mEq/L).

10). The frequency of oliguria, need for dialysis and mortality were not different in rhabdomyolysis- and non-rhabdomyolysis-related ARF.

In conclusion, the answers to the four questions posed in the introduction are given: 1). Alcohol and compression with or without drug abuse are common pathogenic factors for rhabdomyolysis. 2). A dark brown, orthotolidine-positive urine without red cells remains an important clue to rhabdomyolysis, but this finding is absent in more than half of patients and is an insensitive marker. Elevations of CK and myoglobin levels are diagnostic of muscle injury. Other routine blood chemistry tests are not sensitive indicators of rhabdomyolysis. 3). A formula may be used to predict high and low risk for developing acute renal failure after rhabdomyolysis. This formula utilizes admission serum potassium, creatinine, and albumin concentrations. 4). Patients with rhabdomyolysis-related ARF do not differ from patients with non-rhabdomyolysis ARF with regard to serum potassium, phosphorus, and calcium concentrations, rate of rise of serum creatinine, BUN-to-creatinine ratio, oliguria, dialysis and mortality. Patients with rhabdomyolysis with ARF do have higher serum uric acid and anion gap levels.

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