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Myoglobinuria, 1984

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The year is included in the title of this review because the subject is the diversity of conditions that result in myoglobinuria, and new causes keep appearing as conditions in society change or new drugs are introduced. The syndrome is often linked to seamier aspects of society or medicine: war; sadistic drill sergeants; drug abuse; attempted suicide; self-medication or inadequate supervision of drug therapy. On the other hand, study of myoglobinuric syndromes has informed us about new hereditable biochemical causes and we have learned more about the action of viruses on muscle.

The numerous causes of myoglobinuria and the renal effects capture the attention of physicians in many different medical specialties. The condition was once thought to be rare; 20 years ago, there were only 150 recorded cases (Rowland et al., 1964). Now myoglobinuria is recognized as a major cause of renal failure, accounting for 5-25% of all cases of acute renal failure (Anderson et al., 1977; Grossman et al., 1974; Koffler et al., 1976). My own interest has been sustained by the research of three illustrious members of our department, Salvatore DiMauro (1979), Audrey S. Penn (1980) and Joseph Willner (1981); each is concerned with a different group of diseases, but all are linked to myoglobinuria.

Definition of a Clinical Syndrome:

Here is an irony. Nephrologists focus not on the kidney but on muscle; they use the term "rhabdomyolysis". Students of muscle disease turn the other way, look at the urine, and call the same syndrome "myoglobinuria". Why the difference?

We can only surmise possible answers. Myologists understand that the major threat of the disorder is renal failure but they may be more interested in understanding how the muscle injury arises, and that can be done best by splitting one muscle disorder from the others, looking for common or distinguishing features. To nephrologists, however, muscle injury is muscle injury; the nature of the injury may be less important to them than the end result, acute renal failure.

There are other reasons, of course. Nephrologists point out that myoglobin need not be demonstrated in the urine to make the diagnosis and they note that many constituents of muscle other than myoglobin are also released in the process and may also be important in the pathogenesis of the renal disorder (Bowden et al., 1956). However, there is reason to believe that myoglobin (like hemoglobin) is the major nephrotoxin released from muscle (Braun et al., 1976). Also, clinical myoglobinuria does not occur without muscle necrosis; "rhabdomyolysis" has been nothing more than a synonym for myoglobinuria for decades.

Rarely, rhabdomyolysis has been used in another sense, as a histologic diagnosis, but the old-fashioned term "muscle necrosis" suffices for that purpose and without ambiguity. No pathologist could look at an unidentified muscle section and proclaim a histologic diagnosis of rhabdomyolysis. No new term was ever needed to supplant "muscle necrosis".

"Rhabdomyolysis" is presumably analogous to "hemolysis" by lysis of red blood cells is a general process while muscle necrosis is often focal (Schmitt et al., 1983). Besides, hemolysis has been studied thoroughly and there is no strictly analogous disorder in muscle. "Rhabdomyolysis" conveys an unwarranted aura of precision and implies a uniform process in different cases, but muscle necrosis, with or without myoglobinuria, can result from any of numerous diverse causes (Stringer et al., 1972).

For years, there has been a kind of lexical standoff; authors have been free to use either term and the problem of terminology has never been discussed. Redundancies such as "rhabdomyolysis with myoglobinuria" have somehow become popular, and "nontraumatic rhabdomyolysis" (Akmal and Massry, 1983; Chaikan, 1980; Chugh et al., 1979; Grossman et al., 1974; Koffler et al., 1976) has been used incomprehensibly to include the modern version of the crush syndrome in comatose patients (which is as traumatic as it could possibly be) and exercise-induced syndromes (in which trauma is probably important).

"Rhabdomyolysis" was never formally defined until Gabow et al. (1982) used it to designate any condition in which serum creatine kinase (CK) activity was more than five times normal (in the absence of brain or heart disease). In our hospital, that would mean anyone with a serum CK of 250 units. In contrast, patients with Duchenne muscular dystrophy or polymyositis often have values between 5,000 and 10,000; even higher values, up to 50,000 or more, are characteristic of attacks of myoglobinuria. Patients with Duchenne dystrophy do not have overt

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myoglobinuria except as a reaction to succinylcholine or halothane; whether and why Duchenne patients might be especially susceptible to these drugs are important questions that should not be buried by using the same term (rhabdomyolysis) for both the general state of Duchenne patients and their acute reactions to anesthesia (Rowland, 1983; Willner and Nakagawa, in press).

On the other hand, CK values about 500 are commonly encountered in asymptomatic individuals for unknown reasons and of no practical consequence, a situation we have called "idiopathic hyperCKemia"; similar values occur often in athletes after conventional exertion. Gabow et al., (1982) must have encountered similar patients; 26% of their cases had negative tests for heme pigment in urine. To lump the mild exertional rise of CK with frank attacks of myoglobinuria by calling both "rhabdomyolysis" would be analogous to making no distinction between angina and myocardial infarction, or between transient ischemic attacks and cerebral infarction or hemorrhage. All cases of increased serum CK activity do not have the same disorder in muscle (Rowland, 1980; Jones et al., 1983).

"Myoglobinuria" therefore seems to be the much more preferable term but it, too, must be defined. Within the past decade, the widespread use of radioimmunoassay has identified normal myoglobin levels of up to 100 ng/ml in serum, and other immunologic technics can detect similarly small amounts in urine of asympotmatic individuals after exercise or myocardial infarction (Table 1). The syndrome of concern, however, is a *clinical disorder*, not just a biochemical state; it is not recognized by "abnormal levels" of myoglobin that may be detected by these sensitive tests. Rather, it is identified by the following conditions:

1. In the least controversial situation, the patient is alert, notes myalgia or limb weakness, and the urine is unequivocally darker than normal. The urine give positive chemical tests for both albumin and heme (a concentration at least 4 u/ml) but there are few or no red blood cells; casts are often present and may include the pigment. The urinary pigment is identified as myoglobin an an immunochemical method or by electrophoresis. Serum content of CK and other sarcoplasmic enzymes is high, usually more than 100 times the upper limit of normal (but it is difficult to set an arbitrary limit). Hyperuricemia, hyperphosphatemia and hypo- or hypercalcemia are inconstant features; if there is renal failure, serum potassium and calcium levels may rise.

2. If the patient is comatose, or if the presenting disorder is one of acute renal failure, there may be no muscle symptoms or signs. In these cases, the diagnosis can be made without even examining urine if two conditions are met: 1) The serum content of sarcoplasmic enzymes is about 100 times normal. 2) There is renal failure. (In the absence of renal failure, it is not likely that serum enzymes values of this magnitude would even occur without heme-positive reactions in urine). Usually, the cause of the syndrome can also be discerned; extreme muscular exertion and prolonged coma are probably the most common causes but there are many others, as indicated in the following paragraphs.

Table 1: Sensitivity of Tests for Myoglobinuria

	ng/ml
Visible Pigmenturia	250,000
Dipstick (Orthotolidine Reagent)	4,000
Immunodiffusion	4,000
Hemagglutination Microcomplement Fixation	300
Radioimmune Assay	5

Data from Adams et al. (1978); Donald (1978); Kagen (1978); Karlsson et al. (1978); Knochel (1982); Malvano et al. (1978); Markowitz and Wobig (1977); Sarachak and Bernstein (1974); Stone et al. (1975).

Table 2: The Diverse Causes of Myoglobinuria: Hereditable Diseases

Enzyme Abnormality Known	Phosphorylase (McArdle)
	Phosphofructokinase (Tarui-Layzer)
	Phosphoglycerate kinase (DiMauro)
	Phosphoglycerate mutase (DiMauro)
	Lactate dehydrogenase (Kanno)
	Palmityl carnitine transferase (DiMauro)
Incompletely Characterized	Excess lactate production (Larsson)
	Impaired fatty acid oxidation(?) (Engel)
	Impaired function of sarcoplasmic reticulum (?) (Familial malignant hyperthermia)
Uncharacterized	Familial, biochemical abnormality unknown
	Repeated attacks in an individual

A Classification of Myoglobinuria Based on Pathogenesis

A functional classification of myoglobinuria best begins with a division into hereditary and sporadic forms because recognition of the hereditable enzyme abnormalities suggests modes of pathogenesis (Tables 2, 3). However, there is often more than one cause in each attack. For instance, hereditable myoglobinuria is usually induced by exercise but sometimes infection and fever are responsible. Sporadic myoglobinuria may also be induced by exertion, with no recognized genetic disorder.

The complex nature of individual attacks is illustrated by drug-induced coma; crushing injury is not the only disorder because the sedative drug may also depress cellular metabolism in muscle, brain and other organs. Cerebral depression is followed by inadequate ventilation, leading to hypoxia and respiratory acidosis. Concomitantly, shock and metabolic acidosis follow tissue injury and lead to heme-induced renal failure, which further aggravates the already complex metabolic disorder. (It is believed that myoglobin does not injure the kidney unless there is also shock, impaired renal perfusion, and acidosis.) Myoglobinuria due to drug-induced coma is therefore related to the drug, trauma and several other factors as well.

Multiple causes may be involved in other cases, too. For instance, some drug-induced syndromes involve agitation and fever, as well as possible drug effects directly on muscle. In some exertional cases, it may not be possible to determine whether fever resulted from myoglobinuria or whether heat

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stroke caused the muscle damage. That is why the same "cause" may appear in more than one category of the accompanying tables. Despite these complexities, it is possible to separate the numerous causes of myoglobinuria for purposes of discussion.

Hereditable Myoglobinuria

A decade ago, there were only two identified hereditable causes: lack of phosphorylase or lack of phosphofructokinase (Rowland and Penn, 1972). Now, six enzyme disorders have been recognized; five affect glycogenolysis or glycolysis and one involves lipid metabolism (DiMauro, 1979; DiMauro et al., 1973, 1982, 1983; Kanno et al., 1980). In all six, there is a disorder of muscle energy metabolism and it can be suspected that maintenance of muscle surface membranes fails when ATP levels fall below some critical level. However, this has not been proven. In rats, iodoacetate can impair the replenishment of ATP in working muscle and this can lead to two symptoms, muscle contracture and myoglobinuria (Brumback et al., 1983). In humans, however, phosphorylase-deficient muscle was exercised during contracture and there was no change in total intracellular ATP content (Rowland et al., 1965). Failure to demonstrate the expected drop in ATP was unexplained but could have been due to regeneration of the nucleotide during the process of freezing the tissue, which required a few seconds. However, more rapid freezing in later studies gave similar results (Edwards et al., 1980) and so did an NMR study that avoided freezing altogether (Ross et al., 1981). These methods would not detect a change in ATP that was restricted to one intracellular compartment (such as sarcoplasmic reticulum) but there is no evidence of such focal intracellular change of ATP in any other condition. It is therefore not proven that a drop in ATP causes contracture or, by extension, an attack of myoglobinuria but it is still the most logical explanation.

The biochemical abnormality in these genetic disorders is permanent but attacks of myoglobinuria are intermittent. The provoking factor is almost always exercise and, except for the hemolytic anemia that accompanies lack of phosphofructokinase or phosphoglycerate kinase, it is difficult to predict a patient's specific biochemical abnormality on clinical grounds. Patients lacking carnitine palmityl transferase activity may be more likely to have attacks if they miss a meal before commencing vigorous exercise; in the original pair of brothers, one attack was provoked by overoptimism on a fishing trip and they went without eating before taking a long hike back from the water, carrying an empty basket. Taking a meal before anticipated exercise and other measures designed to raise blood glucose levels have also been recommended to patients with the other genetic myoglobinurias; the results have been inconsistent, almost never dramatic. Literally, patients learn to live with these diseases by limiting physical activity. Exercise-induced attacks may be linked to the energy crisis in muscle, but even in familial cases, attacks are sometimes induced by fever or infection and that mechanism is obscure.

DiMauro (1979) has pointed to other unexplained features of these diseases. Although all are congenital as well as inherited, symptoms never start before adolescence despite the considerable running and jumping of childhood. Also, the number of men affected seems excessive, even considering the greater likelihood of men to indulge in vigorous muscular activity, but there is no suggestion of an X-linked disorder except for phosphoglycerate kinase.

Table 3: The Diverse Causes of Myoglobinuria: Sporadic (Aquired) Disorders

A. Exertion
1. Military training, wrestling, squat jump or situp exercises, long distance running, skiing.
2. Anterior tibial syndrome.
3. Convulsions (status epilepticus).
4. Agitated delerium, restraints.
5. High voltage electric shock, lightning stroke.
6. Status asthmaticus.
7. Prolonged myoclonus or acute dystonia.

B. Crush
1. Compression by fallen weights.
2. Compression by body in prolonged coma.

C. Ischemic
1. Occlusion of major artery.
2. Ischemia in compression or anterior tibial syndromes.
3. Coagulopathy in sickle cell disease or syndromes with disseminated intravascular coagulation.
4. Ligation of vena cava.

D. Metabolic Depression or Distortion
1. Carbon monoxide, barbiturates, narcotics.
2. Diabetic ketoacidosis.
3. Nonketotic hyperglycemia hyperosmolar states.
4. Renal tubular acidosis.
5. Hypernatremia.
6. Hyponatremia.
7. Hypokalemia (see table 3).
8. Hypophosphatemia
   a. Intravenous fluid therapy for acute and chronic alcohol abuse.
   b. Diabetic ketoacidosis.
   c. Parathyroidectomy.

E. Drugs and toxins (See table 4)

F. Abnormalities of Body Temperature
1. Hypothermia.
   a. Exposure to cold.
   b. Hypothyroidism.
2. Fever.
   a. Tetanus toxin.
   b. Thyroid vaccine.
   c. Heat injury: heat cramps, heat exhaustion, heat stroke.
   d. Malignant hyperthermia.
   e. Malignant neuroleptic syndrome.

G. Infections
1. Viral: Influenza A, influenza B, herpes simplex; infectious mononucleosis; coxsackie.
2. Bacterial: typhoid fever; E. coli sepsis.
3. Other Organisms: Legionnaire's disease; mycoplasma.
4. Toxic shock syndrome.

H. Progressive Muscle Disease
1. Polymyositis.
2. Dermatomyositis.

I. Cause Unknown

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Another conundrum is exemplified by carnitine palmityl transferase deficiency. The enzyme is necessary for the transport of long-chain fatty acids into mitochondria and subsequent oxidation. Transport is possible only after the fatty acid has been esterified with carnitine. Deficiency of either substrate or enzyme should have similar consequences. In fact, however, loss of the enzyme results in a syndrome of recurrent myoglobinuria while loss of carnitine results in a lipid storage myopathy that is manifest by limb weakness, with no myoglobinuria. Why the syndromes should differ remains a mystery.

The glycogen diseases have also raised similar conundrums; some are manifest by recurrent myoglobinuria, others by limb weakness, and some by both (Rowland and DiMauro, 1983). These differences are also unexplained.

Although progress has been made in identifying the biochemical causes of hereditable myoglobinuria, there are still unidentified cases. In some families, more than one person has had attacks of myoglobinuria but all tests for known enzyme abnormalities give normal values; similarly, even if no other family member is affected, heredity causes may be suspected when a patient has repeated attacks (Christensen et al., 1982; McNaught et al., 1974). Among the cases of unidentified causes were a pair of twins with recurrent myoglobinuria; although Engel et al. (1970) predicted lack of carnitine palmityl transferase activity, that enzyme activity was normal when it was assayed by DiMauro (1979). Another pair of brothers had single episodes of myoglobinuria with influenza (Zamkoff and Rosen, 1979); the familial incidence seemed tied to exposure to the same viral agent but the patients were not tested for known enzyme disorders.

Malignant Hyperthermia: A Special Problem

Malignant hyperthermia is another condition that is held to be hereditary (Denborough and Lovell, 1960), but there is serious question about this. It is stated that 50% of cases are inherited as an autosomal dominant trait (Britt et al., 1969; McPherson and Taylor, 1982). However, there have been few families in which fully affected individuals presented the evidence of transmission; in these families there was more than one person who actually had an attack, but the number of family members so affected was never sufficient to suggest any mode of transmission. In most families some other "market" was used to identify "affected" individuals. Often this marker was merely a serum CK level above an arbitrarily established upper limit (Kelstrup et al., 1973; Plotz, 1980); less often, a physiologic test was used to identify "susceptible" individuals.

The validity of these markers has not been established. Normal serum CK values are found in at least 20% of those who survive MH attacks; there are false negatives. There are undoubtedly false positives, too, because control populations were not usually studied simultaneously with the family at risk and there is no way of validating the implications of an "abnormal" test result except by putting the individual to the risk of general anesthesia. Understandably, this has not been done deliberately but many operations have been done on patients with abnormal serum CK (Owen and Kerry, 1977).

Similarly, the numerous physiologic tests have not been standardized. The most popular tests are tension responses of excised strips of muscle to halothane, caffeine, or both; survivors of MH attacks seem abnormally sensitive to these agents. It is implied that at least one of these three tests will give an abnormal result in any survivor of MH and that there are no false negatives (Nelson and Flewellen, 1983). This conclusion seems dubious because the most accurate test or combination of tests has not been the same in all reports. That there are false positives also seems likely; in one study 15% of the local population was deemed to be "MH-susceptible" (Nelson et al., 1983). Biochemical tests have also been used; the activity of adenylate cyclase, the content of cAMP, and the proportion of phosphorylase a are all increased in muscle of MH survivors (Willner et al., 1979, 1980, 1981).

For many reasons, MH seems to be a syndrome of diverse etiology, only rarely genetic. The evidence includes the following:

1. It is difficult to define the syndrome. Fully expressed, it includes rapid rise in body temperature; "rigidity" of masseter and limb muscles; metabolic acidosis; tachycardia and arrhythmias; and myoglobinuria (Britt et al., 1969; Gronert, 1980; Rutberg et al., 1983). Problems arise when one or more of the major characteristics is missing (Flewellen and Nelson, 1983; Kripke et al., 1982). It is stated that rigidity is not seen in 20% of acceptable cases (Britt and Kalow, 1970) and even fever may be lacking (Bernardt and Horder, 1978). If a child develops masseter rigidity at the start of general anesthesia and then there is no fever because cooling measures are promptly instituted (Carballo, 1975; Caseby, 1975; Davis, 1977, Donlon et al., 1978; Dodd et al., 1981; Inoue et al., 1977; Jago and Payne, 1977; Schmitt et al., 1975), was this an aborted attack of MH or some other kind of reaction to succinylocholine? It is clear that fullblown attacks of MH may start with masseter spasm and there have been cases of masseter spasm alone or with myoglobinuria but no other manifestations of MH; not all of these patients have "positive" tests for MH-susceptibility (Flewellen and Nelson, 1982). Similarly, Willner and Nakagawa (in press) believe that the anesthesia-induced myoglobinuric syndrome of boys with Duchenne dystrophy is not MH because fever and tachycardia are often lacking. However, there are many similarities of the Duchenne syndrome to MH (Rowland, 1983; McKishnie et al., 1983).

Even if a broad view were taken, that any one of the major criteria were sufficient to identify MH, there would still be problems. Serum enzyme and myoglobin levels commonly rise after administration of succinylcholine (Lewandowski, 1981); what level would define MH? How much tachycardia or arrhythmia would suffice? Is cardiac arrest a permissible manifestation if there is no preceding tachycardia? How much rise in temperature is necessary to qualify? Is any degree of masseter spasm sufficient? Are all cases of anesthesia-induced myoglobinuria (Bernhardt and Horder, 1978; Chaboche et al., 1982) manifestations of some form of MH? It is possible to state that any person is not MH-susceptible? One patient had an attack after 12 uneventful operations under general anesthesia (Puschel et al., 1978).

2. As stated above, the clinical genetic evidence is weak. When more than one case of such a rare condition appears in a family a genetic basis may be suspected. But when so many cases are sporadic, multifactorial inheritance seems likely (Ellis et al., 1978) or the condition may be heterogeneous, comprising different disorders. Willner and Nakagawa found that only 2 of 50 survivors of MH attacks had a relative who had also experienced an attack. Halsall et al. (1979) encountered no MH attacks when general anesthesia was given to 321 relatives of MH patients. Moreover, there has been no clear evidence what the biochemical disorder might be. The generally accepted

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theory (Gronert, 1980; Nelson and Flewellen, 1983) is that the abnormal gene product affects the function of sarcoplasmic reticulum, which then becomes susceptible to activities of the anesthetics that inhibit binding of calcium; the resulting increased cytoplasmic level of calcium would then be responsible for the muscle stiffness and hypermetabolic state of muscle.

However, there is evidence that sarcolemma is also abnormal in some if not all cases (Gronert, 1980; Halsall and Ellis, 1983). An abnormality of adenylate cyclase was first taken to be an indication of sarcolemmal abnormality (Willner et al., 1979, 1981) but there is evidence that this enzyme may also be found in sarcoplasmic reticulum (Willner, personal communication). Abnormality of function in "skinned" single fibers also implies that the sarcolemma cannot be the primary abnormality in those cases (Takagi et al., 1976; Wood et al., 1979).

3. Among the genetic causes of MH are identifiable disorders such as myotonia congenita, myotonic muscular dystrophy, Duchenne muscular dystrophy, Schwartz-Jampel syndrome (chondrodystrophic myotonia), the King syndrome (a combination of skeletal abnormalities and static myopathy) (King and Denborough, 1973; Kaplan et al., 1977; McPherson and Taylor, 1981), and central core disease (Frank et al., 1980). The diversity of hereditable conditions implies that there is no single cause; the disproportionately large number of cases of Duchenne dystrophy and central core disease suggests that these conditions actually predispose to MH and, that these two associations are not merely fortuitous.

4. The clinical manifestations of MH are almost identical to those of the "neuroleptic malignant syndrome (NMS) (Eiser et al., 1982; Smego and Duralk, 1982), including fever, acidosis, rigidity, myoglobinuria and relief by dantrolene (Kolb et al., 1982; Day et al., 1983; Gouldon et al., 1983). The only difference is that MH is a more acute disorder, with a more easily defined onset and a usually brief course that is measured in hours whereas MNS starts gradually and lasts days or weeks (Table 4).

Despite the similarities, NMS and MH have been considered different because no individual has yet had both disorders (as might be expected if the same genetic biochemical disorder made a person susceptible), and at least one survivor of MNS later had general anesthesia without incident (Lostra et al., 1983). Similarly, the two conditions have not appeared in the same family and the physiologic or biochemical tests for MH-susceptibility have been negative in some survivors of MNS (Tollefson, 1982; Burke et al., 1981). Moreover, there is evidence of cerebral disorder in MNS (Henderson and Wooten, 1981) and bromocriptine therapy has had apparent benefit (Dhib-Jahlbut et al., 1983; Mueller et al., 1983; Granato et al., 1983). However, Caroff et al., (1983) found that excised muscle from one MNS-survivor was sensitive to both halothane and fluphenazine. The relationship of MNS and MH is therefore uncertain but the bulk of evidence suggests that they differ.

"*Heat stroke*" is another disorder with similar manifestations (Jardon, 1982); the diagnostic criteria include metabolic encephalopathy, anhydrosis, and hyperpyrexia (Clowes and O'Donnell, 1974; O'Donnell, 1975) but myoglobinuria is probably a regular feature and dantrolene has therefore been used to treat heat stroke, too (Lydiatt and Hill, 1981). *Toxic shock syndrome* is still another disorder that incorporates fever and myoglobinuria, with additional essential components of fall in blood pressure, desquamating rash, thrombocytopenia, encephalopathy, liver disease and renal disease (Clayton et al., 1982); little wonder that it is sometimes difficult to classify individual cases (Mason and Thomas, 1976). Disseminated intravenous coagulopathy occurs in MH and all of the other heat-related syndromes. Only in MH has genetics been implicated.

These arguments about the genetics of MH have some practical implications. It seems unlikely that there will be a single cause of "MH myopathy". Therefore, it seems unlikely that reliable methods will be developed to identify all relatives at risk once a proband has been recognized. Alternatively, all first-degree relatives should probably be deemed potentially susceptible and wear a warning bracelet so that anesthesiologists could be forewarned in case of emergency. In this public relations problem, the name of the condition seems a double handicap. "Hyperthermia" is limited because fever is not always present and "malignant" raises questions about cancer to unsophisticated families. An eponym (such as Denborough-Britt-Kalow syndrome) would be appropriately inexact.

Sporadic (acquired) Forms of Myoglobinuria

Exertion: The causes of acquired myoglobinuria are numerous and diverse (Tables 2, 3, 4, 5, 6, 7). They probably overlap with genetic causes because some patients with glycogen storage disease, for instance, are first brought to light by an exercise-induced attack of myoglobinuria. These cases are few but another, possibly genetic, question is raised. If hundreds of military

Table 4: Heat, Fever and Myoglobinuria:

	Exercise-Induced Myoglobinuria	Malignant Hyperthermia	Malignant Neuroleptic Syndrome	Heat Exhaustion or Heat-Stroke
Myoglobinuria	+	+	+	+
Provoking Factor	Exercise	Halothane	Neuroleptics	Exercise or Exposure
Tachycardia	+	+	+	+
Acidosis	+	+	+	+
Disseminated Intravascular Coagulation	+	+	+	+
Muscle Rigidity or Spasm	0	+	+	0
Onset, Duration	Minutes	Minutes	Days	Minutes
Familial Attacks	Rare*	Rare	None	None

*Herditable biochemical abnormality may be identified.

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recruits are put to strenuous exercise, why do only one or two have attacks of myoglobinuria? If thousands of runners complete a marathon race, why do only one or two have attacks of myoglobinuria? Are these people unusually susceptible in some way that has not yet been recognized? Does "metabolic exhaustion" link the sporadic cases to the hereditable conditions?

Genetic susceptibility is not thought to be responsible for most exercise-induced attacks. Rather it is widely believed that any one, stressed sufficiently, might have an attack of myoglobinuria (Gitlin and Demos, 1974). Why this should be is not known, and the term "rhabdomyolysis" merely hides our ignorance. We do not know whether muscle is injured by trauma (running downhill is more traumatic than level running) (Friden et al., 1981; Hikida et al., 1983; Schwane et al., 1983), by ischemia in prolonged isometric contraction, by metabolic exhaustion or other biochemical alterations in prolonged running, by distorted heat regulation or blood flow, by hypokalemia and resulting adverse effects on muscle circulation (Knochel, 1978), or even by unsuspected viral infections in some subjects. By all of the above? Or none of the above? Patients with sickle cell trait may be at special risk (Helzlouer et al., 1983).

The sports medicine literature increases progressively but there seems to be a contradiction in advice to runners and workers who are exposed to high ambient temperatures. Workers are instructed to take salt when they drink water; runners are told to drink water without salt (and, also, to sprinkle water frequently) (American College of Sports Medicine, 1975). Yet this difference cannot be cause of myoglobinuria in runners because so few attacks occur among those who take no salt (Bar-Sela et al.,1979; Brooke et al., 1979; Bunch, 1980; Demos and Gitlen 1974; Maxwell and Bloor, 1981; MacSearraigh et al., 1979; Melamed et al., 19782; Olerud et al., 1976; Ross et al., 1983; Schiff et al., 1978; Wyndham and Strydom 1969).

It seems clear that training protects muscle against exercise-induced injury (Ross et al., 1983) but how this occurs is not clear except that fiber types tend to become more "oxidative" than "glycolytic" and mitochondria proliferate. Cardiovascular changes must also play a role in feats of endurance. Also, in some military cases and many marathon cases, lack of training seemed to be exonerated. Among experienced runners, attacks seemed more likely to occur when the competitors set unrealistic expectations for speed or distance, and when they were exposed to high ambient temperatures (England et al., 1982). Dietary modifications in training did not seem important (Bank, 1977). Many cases of myoglobinuria in runners have also had features of heat stroke (defined by the combination of altered consciousness, hemoconcentration and lack of sweating) (Beard et al., 1979; Knochel, 1974; Sprung et al., 1980). In this respect, the syndrome differs from that of "heat cramps", which is attributed to drinking water without salt while sweating profusely; the result is hemodilution and hyponatremia. "Heat exhaustion" is the intermediate syndrome, with hemoconcentration and malaise but without the alterations of consciousness and disappearance of sweating of heat stroke. In fact, myoglobinuria has occurred in all three heat conditions (and they are not always easy to separate) (Rowland and Penn, 1972, 1974). Fever may therefore play a causal role in runner's myoglobinuria but the widespread muscle injury of an attack might even cause the fever, rather than the reverse. In the elderly, exposure to an environmental heat wave, without undue exercise, may suffice to induce heat stroke and myoglobinuria (Kilbourn et al., 1982; Kim et al., 1980.

Exertion also seems to be a factor in some other forms of myoglobinuria, not only strenuous athletics such as wrestling or skiing, but status epilepticus, status asthmaticus (Chugh et al., 1978), or struggling against restraints (Goode and Meltzer, 1976; Goode et al., 1977; Rowland and Penn, 1972). Exertion may also be a factor after the convulsions of lightning or electric shock (Braasch and Demaso, 1980), or after some drugs (such as amphetamines, phencyclidine, strychnine, water hemlock) (Abreo et al., 1982; Barton et al., 1980; Boyd et al., 1983; Carlton et al., 1979; Kendrick et al., 1977; Skjoto et al., 1979; Swenson et al., 1982; Unger et al., 1982), in drug-induced dystonia (Jankovic and Penn, 1982), or prolonged myoclonus in viral encephalomyelitis (Langston et al., 1977). However, drugs or electricity may have more direct effects on muscle (Undterdorfer and Lederer, 1975).

Crush and Ischemic Injury:

These two forms of muscle injury can be discussed together because they clearly involve common mechanisms. Crush injury may directly compress and injure muscle; it also compresses intramuscular blood vessels and larger vessels to make ischemia part of the process. Swelling of the muscle within a fascial compartment may aggravate the injury (Mubarak and Owen, 1975; Owen et al., 1979). On the other hand, if a major artery is suddenly occluded, the muscle it serves will become necrotic and edematous and the edema, itself, further compresses small arteries. In one remarkable case, edema of the legs followed ligation of the inferior vena cava; the edema was so severe that the already marginal circulation of the patient's legs was further compromised and myoglobinuria resulted (Olivero and Ayus, 1978). We have already seen that the circumstances of crush injury in comatose patients are likely to threaten renal function; the edema and prolonged immobility are also likely to lead to pressure palsies or traction injuries of peripheral nerves; the resulting paralysis may prolong the state of immobility and, therefore, the crust (Cadnapaphornchal et al., 1980; Penn et al., 1972). Similar consequences may result from prolonged immobility during anesthesia and surgery (Larcan et al., 1980). Again, interference with the energy metabolism of muscle seems to be compromised. Epsilon aminocaproic acid (Britt et al., 1980) is thought to cause myoglobinuria by enhancing clotting in small intramuscular vessels but this has not been proven. Fibrin thrombi also occlude these vessels in the hemolytic-uremic syndrome (Andreoli and Bergstein, 1983) and may be important in the disseminated invascular coagulation of the heat syndromes. Ischemia could also have been important in the case of myoglobinuria caused by intravenous infection of peanut oil (Lynn, 1975).

Metabolic Depression:

Cerebral depressants may affect muscle directly, or may affect muscle secondarily when cardiorespiratory responses fail (Table 5). Cellular metabolism may also be distorted by diabetic acidosis (Buckingham et al., 1981), nonketotic hyperglycemia (Rumpf et al., 1981), hypothyroidism (Halverson et al.,), and hypothermia (Raifman et al., 1978; Rosenthal et al., 1981). Hypothyroidism may affect muscle directly or through hypothermia.

For other metabolic anomalies, the effect on cellular energy metabolism is even more unclear. For instance, fever itself may

Table 5: Drugs, Toxins and Myoglobinuria*

Mechanism	Drugs		Toxins or Metabolism Disorders
Metabolic Depression	Barbiturates (and other sedatives) Carbon monoxide Ethanol Fenfluramine Tricyclic antidepressants Gluetethemide		Hypothyroidism Diabetic acidosis Nonketotic hyperglycemia Hyperosmolarity Hypernatremia
Hypokalemia	Amphotericin Carbenoxolone Glycyrrhizate (Licorice) Thiazides, other kaluretics Laxative abuse		Diarrhea Hyperaldosteronism Renal tubular acidosis
Hypophosphatemia			Parenteral fluids for acute alcoholism Diabetic keteoacidosis Parathyroidectomy
Ischemia	Epsilon Aminocaproic Acid Peanut oil (intravenous)		Total parenteral nutrition Air embolism
Direct Membrane Effect (?)	Clofibrate Bezafibrate Toluene		Venoms: hornet mulga snake tiger snake sea snake
Agitation or Convulsions	Amphetamines Amoxapine Lithium Loxapine Paracetamol Phencyclidine Phenylpropanolamine	Salicylates Strychnine Water Hemlock Mercuric-Chloride	Electroconvulsive therapy Tetanus Myoclonus (prolonged) Dystonia
Extremes of Body Temperature Hypothermia Fever			Exposure Hypthyroidism Tetanus toxin Typhoid vaccine Heat cramps Heat exhaustion Heat stroke

* Original citations are given in earlier reviews (Rowland and Penn, 1972; Penn, 1979; Gabow et al., 1982). New drugs and toxins continue to appear (Abreo et al., 1982; Boyd 1983; Swenson et al., 1982; Unger et al., 1982).

be responsible alone (Berg and Frenkel, 1958) or as part of more complicated sepsis (Henrich et al., 1980; Kalish et al., 1982; Nahas et al., 1983); sepsis may be important even in newborns (Gilboa and Swenson, 1976; Haftel et al., 1976). Chronic hypokalemia can cause a chronic myopathy that is manifest by increased serum enzymes alone, prolonged proximal limb weakness, or acute myoglobinuria (Altenwerth, 1982; Dominic et al., 1978; Knochel and Schlein, 1979; Nadel et al., 1979) (Table 6). Similar stages of myopathy are seen in hypothyroidism, with the additional complication of hypothermia; serum enzymes and myoglobin may rise in hypothyroidism with little or no histologic change in muscle. Chronic alcoholism may cause persistent myopathy and attacks of myoglobinuria may be superimposed on this chronic myopathy (Fahlgren et al., 1957); poor nutrition has been blamed on the basis of experimental evidence (Haller and Drachman, 1980). Whatever the mechanism, chronic alcoholism is prominent on the list of causes of myoglobinuria in all large series (Pariente et al., 1983). For reasons not known, alcoholic patients with myoglobinuria only rarely have cardiomyopathy (Rowland and Penn, 1972; Senevirante, 1975).

Membrane Myotoxins

Few agents seem to attack muscle membranes directly. Most dramatic are the toxins of snakes (Furtado and Lester 1968; Rowland et al., 1969) or insects (Owenby and Odell, 1983) but the mechanisms of action are not known. Among the drugs, clofibrate and similar drugs may be most likely to affect the lipid composition of muscle surface membranes, but the mechanism of action is not known (Bock, 1981; Heidemann et al., 1981; Schneider et al., 1980). Myoglobinuria may follow use of heroin, without coma, but it is not clear whether the responsible agent is heroin itself or some adulterant and it is not known how the muscle injury arises (D'Agostino and Arnett, 1979). Similarly, the nature of the toxic effect is sepsis or toxic shock (Clayton et al., 1982) is not known.

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Table 6: Causes of Hypokalemic Myoglobinuria

1. Drug therapy	Diuretics, carbenoxolene, amphotericin B
2. Licorice ingestion	Pseudohypoaldosteronism
3. Alcoholism	Dietary deficiency, diarrhea, rehydration and administration of glucose without salt replacement
4. Gastro-intestinal potassium loss	Regional enteritis with steroid therapy
	Laxative abuse
	Nutritional deficiency syndromes with diarrhea
	Gastric drainage
5. Total parenteral nutrition	
6. Renal tubular acidosis	
7. Exercise in hot weather	

From Dominic (1978); Nadel et al (1979)

Progressive Muscle Disease

Increased serum activity of sarcoplasmic enzymes is one of the major diagnostic signs of myopathy, regardless of cause or classification. It might therefore be expected that patients with chronic myopathy would be more susceptible to attacks of overt myoglobinuria, a new insult adding to the old. Yet this has only rarely been reported. In their classic monograph on polymyositis, Walton and Adams (1954) included cases of acute myoglobinuria; there had been a few earlier cases (Gunther, 1924; Paul, 1924) and there have been several since (Kagen, 1971; Korz and Velz-Boers, 1974; Skrabal et al., 1972; Sloan et al., 1978; Wynne et al., 1977). In these cases, limb weakness was sometimes severe and respiratory muscles were affected in a few cases (Wynne et al., 1977). If the patients recovered in weeks or months and there was no permanent muscle disease. Ostensen et al. (1980) recorded penicillamine-induced myopathy with myoglobinuria at the onset.

It is difficult to know how to classify these cases. Some could have been due to viral-induced myoglobinuria; some were idiopathic in the sense that search for common viruses was negative (Wynne et al., 1977) but negative search does not exclude the possibility of infection. Some were diagnosed as polymyositis because there were inflammatory cells in the muscle, but that histologic change can occur in attacks of myoglobinuria due to any cause, including marathon running (Hkida et al., 1983). The term "polymyositis" seems formally justified, but this acute disorder with myoglobinuria is not the same as the subacute myopathy that usually warrants the designation of polymyositis.

In only a few cases was there evidence of longer-lasting myopathy. For instance, the patient of Gamboa et al. (1979) had gait disorder for several months before an attack of myoglobinuria attributed to influenza virus. Kreitzer et al. (1978) described a man with limb weakness for a year; he was treated with prednisone for four months before an episode of myoglobinuria. Marks et al. (1976) described a patient with drug-induced coma and myoglobinuria. On discharge, two months later, there was still weakness and wasting of leg muscles (with sensory loss, too); one week later the patient returned to the hospital with periorbital edema and erythema, new weakness of arm and cranial muscles, Grotton's patches, subcutaneous edema over the shoulders and a new rise of serum enzymes. The picture seemed to be that of dermatomyositis, but Knochel (1982) has attributed eyelid edema in myoglobinuria to loss of serum albumin, and we have reported lid edema in otherwise uncomplicated myoglobinuria (Rowland and Penn, 1972). Kessler et al. (1972) described a patient with an acute myoglobinuric syndrome of rash and edema thought to be compatible with dermatomyositis; the patient died of respiratory failure within two months.

In another case, Pirovino et al. (1979) described myoglobinuria after a syndrome of fever, arthralgia and limb weakness for one month, with gradual improvement in another month. Carleton et al. (1977) presented a patient with a syndrome of myoglobinuria and histologic changes of glomerulonephritis; they attributed both renal and muscle lesions to a hypothetical virus but the syndrome could have been due to thiazide-induced hypokalemia that was evident in the record.

These cases suggest overlap with the ill-defined syndrome of polymyositis, but there has been no case of progressive muscular dystrophy with myoglobinuria except after the anesthetic catastrophes described above, in relation to malignant hyperthermia.

Infections

Myalgia has long been recognized as a symptom of influenza virus infection. Masson and Keller (1975) found that CK was high in the acute phase serum samples from children with serologically-proven infection, but the CK values returned to normal in convalescent serum. It is therefore not surprising that some cases of myoglobinuria are also associated with serological evidence of influenza virus infection (Canaud et al., 1983; Cunningham et al., 1979; Minow et al., 1974; Morgensen, 1974) and that virus has actually been isolated from muscle (Gamboa et al., 1979). How the virus causes either polymyositis or myoglobinuria is not clear but it is not restricted to influenza virus. Among other viruses incriminated in attacks of myoglobinuria are herpes group (Schlesinger et al., 1978); enterovirus (Jehn et al.), mononucleosis (Kanter et al., 1978), and Legionnaires' disease (Posner et al., 1980). Bacterial infections include typhoid (Rheingold et al., 1976); and E. coli (Henrich et al., 1980), or multiple organisms (Kalish et al., 1982; Nahas et al., 1983) mycoplasma (Rothstein and Kenny, 1979) has also been incriminated. The role of fever in these cases is uncertain.

This toxic shock syndrome, attributed to staphylococcal toxin was defined by Todd et al. (1978). The clinical criteria include: hypotension, fever, erythematous rash, involvement of at least four organ systems, and no other cause. The four organ systems include liver, kidney, brain and muscle. Although myopathy has not been emphasized, the data from every series indicate that it can be a major aspect of the disorder (Shands et al., 1980), and myoglobinuria may play a role in renal failure. Among 11 patients at the Mayo Clinic, all had myalgia; myoglobinuria was documented in two cases and myoglobinemia in another. Serum CK was more than 1000 in those three cases and also in a fourth (McKenna et al., 1980).

Concomitants and Consequences of Myoglobinuria

It has been calculated that clinical myoglobinuria can result from destruction of about 200 grams of skeletal muscle. It is presumed that all constituents of the destroyed muscle are discharged into the blood. The circumstances that cause this

catastrophe are also likely to cause dehydration, shock, or acidosis, the conditions that make heme-induced nephropathy more likely (Braun et al., 1976; Knochel, 1976, 1982; Koffler et al., 1976). Renal failure was seen in 33% of the cases of Gabow et al. (1982) but this figure may be exaggerated because renal failure often calls attention to myoglobinuria.

The combination of increased entry and decreased exit of sarcoplasmic components causes rapidly increasing plasma levels of creatinine, potassium, phosphate and urate; the resulting metabolic aberrations may have additional adverse affects on kidneys and heart (Knochel 1976; Warren et al., 1975). Changes in calcium metabolism may be prominent, with hypocalcemia at first attributed to hyperphosphatemia and, later, hypercalcemia. These changes involve altered secretion of parathormone and Vitamin D, with sequential deposition and resorption of calcium in injured muscle (Akmal et al., 1976; Knochel, 1982).

As complicated as these changes may be, the administration of mannitol or other osmotic diuretics can often prevent renal failure (Eneas et al., 1979). Often, however, renal failure requires dialysis. Myoglobin itself is not dialyzable (Hart et al., 1982) and plasmapheresis has been used (Kuroda et al., 1981). With proper treatment, the prognosis should be good but some fatalities result because of the precarious general condition of many of these patients; 6 of 29 patients with renal failure died in the series of Gabow et al. (1982). Fasciotomy has been used to relieve muscle swelling and pressure in compartmental syndromes (Chaikan, 1980; Owen et al., 1979).

Among survivors, there have been no convincing examples of either permanent renal disease (McCarron et al., 1980) or permanent myopathy, even though both might be anticipated. Nerve injuries, however, are too often seen in survivors of coma-crush myoglobinuria (Akmal and Massry, 1983; Chaiken, 1980; Penn et al., 1972).

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