Idiopathic Myoglobinuria in Man

Report of Case

By THEODORE H. SPAET, MARTIN C. ROSENTHAL AND WILLIAM DAMESHEK

The appearance of free hemoglobin in the urine is a dramatic phenomenon which is most frequently encountered during rapid and severe intravascular hemolysis. This may occur in the course of incompatible transfusion reaction, paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria, March hemoglobinuria, blackwater fever, and favism. Less common is the discovery of free myoglobin as a pathologic urinary pigment. Myoglobinuria may follow an acute breakdown of striated muscle tissue, thus corresponding to the hemoglobinuria which follows the intravascular destruction of erythrocytes.

Myoglobinuria has been found most frequently as a result of crushing injuries to the extremities. Early investigations by Minami and the more recent studies of Bywaters and associates have contributed greatly to the understanding of this disorder. Thrombosis of an artery which supplies a considerable muscle mass may likewise cause myoglobinuria as a result of direct muscle injury. Similarly, muscle breakdown and the liberation of myoglobin has been reported following high-voltage electric shock. Another cause of myoglobinuria is the so-called Haff Disease, an acute intoxication resulting from the ingestion of contaminated fish. Several outbreaks of this disorder have been reported in Europe, the most recent of which was described by Berlin. In addition to the myoglobinurias of demonstrable origin, there remains a small number of cases in which there is no known cause for the excretion of the pigment in the urine. Such a situation is extremely rare, only seventeen cases having been reported to the time of the present writing. Since the clinical picture in these cases is by no means uniform, it is possible that several etiologic factors may have been contributory. Despite this clinical variation, the patients have shown certain striking features in common, namely: the acute onset of severe muscle pain with a resulting "paralysis" of the involved muscles; the subsequent appearance of myoglobin in the urine; and a tendency to recurrence. Although some of the patients had specific associated disorders, most of them were free of other demonstrable disease. The case to be reported falls into the latter group. In this case, there were repeated attacks of myoglobinuria precipitated by exercise and accompanied by muscle pain and spasm. No etiologic factors were demonstrated which could explain the disorder, nor were any associated diseases discovered.
IDIOPATHIC MYOGLOBINURIA IN MAN

CASE REPORT

D. B. (New England Center Hospital #61–637), a 23 year old white male soldier, was admitted to the hospital August 9, 1951 complaining of episodes of pain in the back and legs associated with the passage of dark urine. Ever since he could remember, severe exercise of the legs would produce cramps of the muscles of the thighs and calves to such a degree that walking became almost impossible. The pain reached its peak in the course of two or three hours, and gradually cleared over an additional twenty-four hour period. The patient noted that prolonged inactivity produced an increased tolerance to exercise, and previous exertion caused a reduced threshold to attacks induced by subsequent activity. Attacks occurred only following exercise, and could invariably be reproduced with sufficient exercise. At the age of 16 the patient first noted the passage of “black” urine following an attack of muscle pain induced by exercise. It was reported that the urine became dark about two hours after the onset of pain, and gradually returned to its normal color in the subsequent twenty-four hours concomitantly with the disappearance of pain. Since that time each episode of muscle pain had been accompanied by the passage of dark urine. It was estimated by the patient that he had had about fifty such attacks in the intervening seven year period. He was brought to our attention because of his inability to perform the necessary training procedures incident to military service. Activity such as close order drill regularly produced the attacks described above.

With the onset of urinary symptoms the patient first sought medical aid. He was then told by a physician that his blood pressure was 150/110, and that albumin was present in the urine. The diagnosis of chronic nephritis was made. The past history was not contributory. There was no family history of similar disorder nor of any other neuromuscular disease. The father was thought to have pernicious anemia, but was not receiving any treatment for this condition.

Physical examination revealed a healthy-appearing young man who was well nourished and showed no visible evidence of acute or chronic disease. The pulse, temperature, and respirations were within normal limits, and the blood pressure was 135/90. The remainder of the physical examination revealed no abnormalities. There was no evidence of muscle atrophy or weakness, and the reflexes were all present with undiminished activity.

Laboratory studies showed a urine which was normal except for small deposits of intracellular hemosiderin in the sediment, normal blood counts, and a normal erythrocyte sedimentation rate. The blood sugar, serum proteins, serum cholesterol and esters, alkaline phosphatase, bromsulphthalein excretion test, thymol turbidity, serologic test for syphilis, and excretion of phenolsulfonphthalein were all normal. The cephalins flocculation test was 3 plus, and the serum bilirubin totalled 1.6 mg./100 cc. of blood, of which 0.6 mg. was direct and 1.0 mg. indirect. The fecal urobilinogen output was 35 mg./day. Special hemolytic studies including acid, mechanical, and osmotic fragility of the erythrocytes were all within normal limits. The direct Coombs test and the Donath-Landsteiner reactions were negative, as were tests for complete and incomplete agglutinins and hemolysins. X-ray examination of the chest and electrocardiograms showed no abnormalities, and a previously performed intravenous pyelogram had been reported as showing a normal urinary tract.

Course and Special Procedures

On August 14, 1951 the patient was exercised by walking up and down stairs. As a precaution, the urine was alkalinimized by the administration of sodium bicarbonate in doses of 2 gm. every four hours the previous night and continued during the remainder of the day. Exercise was started at 9:30 a.m. and was continued until 12:30 p.m. when pain in the calf and thigh muscles was first noted. This pain reached its peak at 3:30 p.m. and then gradually became reduced to complete clearing by the next morning (August 15). Coincident with the pain, at 2:30 p.m. on August 14, the urine started to darken. In the subsequent two hour period the color increased in intensity and changed from brown to burgundy red (fig. 1). The intense urinary discoloration persisted until eve-
Fig. 1.—Simultaneous urine (in bottle) and plasma (in tube) specimens obtained during acute attack of myoglobinuria induced by exercise. (No. 1, just before exercise; no. 2, two hours after completion of exercise; no. 3, three hours after exercise; no. 4, four hours; no. 5, five hours; no. 6, eight hours; and no. 7, twenty-two hours after completion of exercise.)

Table Ia.—Laboratory Data During Acute Attack of Idiopathic Myoglobinuria

<table>
<thead>
<tr>
<th>Date</th>
<th>8/14</th>
<th>8/15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>9:30</td>
<td>9:30</td>
</tr>
<tr>
<td>Pre-</td>
<td>12:30</td>
<td>12:30</td>
</tr>
<tr>
<td>Post-</td>
<td>9:30</td>
<td>9:30</td>
</tr>
<tr>
<td>a.m.</td>
<td>2:30</td>
<td>12:00</td>
</tr>
<tr>
<td>a.m.</td>
<td>4:30</td>
<td>10:00</td>
</tr>
<tr>
<td>a.m.</td>
<td>6:30</td>
<td>14:00</td>
</tr>
<tr>
<td>a.m.</td>
<td>7:30</td>
<td>18:00</td>
</tr>
</tbody>
</table>

**Hematologic values**

- **Hgb. (Gm./%):** 14.1 13.3 13.3 12.9 12.5
- **RBC:** 4.60M 4.62M 4.80M 5.20M 4.91M
- **Ret. (%):** 0.4 0.5 0.3 0.2 1.9
- **WBC:** 9900 10000 17000 20000 12000
- **Polys (%):** 55 75 75 75 66
- **Lymphs (%):** 23 9 9 22 29
- **P's (X10^9):** 605 480 551

**Blood chemistry**

- **Bilirubin**: 2.2 2.2 1.1 1.2 1.5
- **Blood urea nitrogen**: 19 19 18 18 21
- **Creatinine**: 0.9 0.9 0.9 1.0 1.0
- **Urea**: 6.0 5.0 5.5 5.5 1.5
- **Potassium**: 4.2 3.6 3.6 4.2 3.6
- **Total protein**: 4.3 7.5 5.0 4.0 3.5
- **Plasma Hgb.:** 95 55 55 55 570
- **Color**
  - **Myoglobin**: 0 Trace 75 275 390

**Urine values**

- **Amount (cc.)**: 95 55 25 25 25 35 30 35 35 570
- **Color**
  - **Yellow**: Brown Wine Wine
  - **Brown**: Dark Brown Medium Brown
  - **Wine**: Pale Brown

* mg./100 cc.
† mEq./liter.
‡ mg./100 cc. (expressed as hemoglobin).

Ning, and then gradually disappeared. The night specimen contained small amounts of abnormal pigment, but the first morning specimen of August 15 was clear. Serial studies of the urine and blood were performed during this attack, and the data derived from these studies are reported in table Ia. The peripheral blood findings showed a slight fall in hemoglobin, with a transient slight reticulocytosis during the recovery phase from the attack. Also noted were leukocytosis, due to a marked increase in polymorphonuclear leukocytes, and an absolute lymphopenia. These findings are indicative of a stress reaction precipitated by the induction of myoglobinuria.

Blood chemical values were constant with the exception of a slight fall in
TABLE 1b.—Quantitative Urinary Data, before, during, and after Exercise
(24 hour excretion from 9:30 a.m. to 9:30 a.m.)

<table>
<thead>
<tr>
<th>Date</th>
<th>Condition</th>
<th>8/10</th>
<th>8/11</th>
<th>8/14</th>
<th>8/15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amount (ml.)</td>
<td>850</td>
<td>950</td>
<td>940</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>Sodium (mEq./liter)</td>
<td>294</td>
<td>135</td>
<td>74</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>Potassium (mEq./liter)</td>
<td>77</td>
<td>81</td>
<td>42</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Creatinine (Gm.%</td>
<td>.275</td>
<td>.170</td>
<td>.115</td>
<td>.130</td>
</tr>
<tr>
<td></td>
<td>Creatine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Albumin (Gm.%)</td>
<td>0</td>
<td>0</td>
<td>&gt; .1%</td>
<td>.01%</td>
</tr>
<tr>
<td></td>
<td>Porphobilinogen</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>*Myoglobin (mg.%)</td>
<td>0</td>
<td>0</td>
<td>97</td>
<td>0</td>
</tr>
</tbody>
</table>

* Expressed as hemoglobin.

Fig. 2.—Spectrophotometric analysis of patient's alkaline urine voided during acute attack of myoglobinuria. Note closer similarity to the curve of oxymyoglobin. Note also the maxima at 500 m, suggestive of metmyoglobin.

potassium and a slight increase in plasma hemoglobin values. Most significant was the finding in the urine of a benzidine positive pigment in large amounts concomitant with a plasma that showed no marked increase in free hemoglobin. In addition, the urine contained large numbers of granular casts and a considerable quantity of albumin. The excretion of creatine and creatinine was not significantly different from that of the control period. An equivocal reduction in the urinary output of sodium and potassium was seen on the day of exercise as well as during the next day.

The urinary pigment was subjected to spectrophotometric analysis. Figures 2, 3, and 4 show the results of these studies. The characteristic maxima and
Fig. 3.—Spectrophotometric analysis of patient's alkaline urine compared with the absorption curve of metmyoglobin and oxymyoglobin. The peaks of the curve in the urinary sample are a composite of the peaks produced by the samples of oxymyoglobin and metmyoglobin.

Fig. 4.—Spectrophotometric analysis of the patient’s urine modified by the addition of sodium cyanide. Note the abolition of the peak at 582 μm and the resemblance now to the curve of cyanometmyoglobin.
minima of myoglobin are evident, as well as additional peaks suggesting the presence of metmyoglobin. For comparison the curves of known solutions of hemoglobin, myoglobin, and metmyoglobin are presented. The addition of sodium cyanide to the patient's urine abolished the peak at 582 and broadened the band at 540, confirming the presence of metmyoglobin. The curve of cyanometmyoglobin prepared artificially is also shown. When a solution of myoglobin was incubated with the patient's urine for several days, no conversion to metmyoglobin occurred.

During and between attacks the urinary porphyrins were normal. A muscle biopsy taken from a painful area in the left calf showed merely a minimal swelling of some muscle fibers. No evidence of inflammatory or degenerative changes was present.

August 20. The patient was subjected to three hours of strenuous exercise involving the upper extremities only. This was accomplished by rapid weight and pulley lifting. Although marked fatigue was produced, there was no unusual muscle pain or urinary excretion of pigment.

August 21. The following procedures were performed: A sphygmomanometer cuff was applied to the left thigh at a pressure of 180 mm. Hg (Blood pressure at the time was 120/80). The cuff pressure was maintained for intervals of 1, 5, and 10 minutes respectively, a rest period of one half hour having been given between trials. Three hours after these procedures had been completed the left calf was packed in ice for 30 minutes. Neither muscle cramps nor myoglobinuria was induced by the procedures.

August 22. The patient was given 500 mg. of ascorbic acid by mouth at 9:30 a.m. and again at noon a second dose. Two hours of rapid walking (1:00 to 3:00 p.m.) resulted in a mild attack of typical muscle pain followed by the passage in the urine of small amounts of myoglobin.

September 18. The patient was given cortisone by mouth on the following dosage schedule: 25 mg. were given the preceding evening. On the test day 25 mg. doses were given at 7:00 a.m. and 9:00 a.m., and 50 mg. were given at 2:30 p.m. He walked actively for three hours in the morning, but only mild muscle pain ensued which was unaccompanied by myoglobinuria and was of thirty minutes duration. An additional hour and a half of walking in the afternoon produced a typical attack of muscle pain and myoglobinuria which lasted twelve hours.

The following day (September 19th) the patient became anuric. His subsequent course was that of a typical lower nephron nephrosis with anuria persisting for fourteen days. For this condition he was treated at another hospital where his recovery was aided by the use of an artificial kidney. Diuresis finally occurred, and studies one month later showed almost complete reversal of the renal lesion.

Because of this untoward episode, further experimental studies were not undertaken, and the patient was finally given a medical discharge from the Army.

DISCUSSION

The previously reported cases of myoglobinuria are summarized in table 2. Of the seventeen cases, three occurred in the same family, and an additional
two patients had familial histories of progressive muscular dystrophy. In this group an hereditary factor appears possible. In one patient a diffuse generalized myositis was suggestive of a specific inflammatory process, and in another case the muscle pathology appeared to be part of some obscure systemic disorder. In the remainder of the patients there was nothing in the background which provided a clue to the etiology of the condition. In the majority of cases, the attacks were elicited by exercise and were recurrent in nature. In about half, only the lower extremities were involved; the remainder had symptoms involving the upper limbs and other muscle groups.

The laboratory findings have been of little help in understanding the pathogenesis of the disease. No consistent alterations were found in the serum potassium, lactic acid, glucose, or other metabolites. Increased urinary excretion of creatinine has not been consistently reported, nor was it seen in the present case. When muscle biopsies were performed, a variety of pathologic pictures were reported, so that no conclusions can be drawn from those studies. The only consistent finding was the presence of a urinary pigment together with localized muscle symptoms. In seven cases the pigment was identified as a myoglobin by spectrophotometric methods. In the remainder it was considered to be myoglobin on the basis of indirect evidence. Whenever it was sought, metmyoglobin was demonstrated to be present, accompanying the myoglobin. Albumin, casts, and red blood cells were also present in the urine and were considered evidence of acute renal damage. Characteristically, in these cases tested, there was no elevation of the plasma hemoglobin level during the passage of urinary myoglobin. Thus, the data obtained from the patients with idiopathic myoglobinuria have yielded no consistent pattern to clarify the means by which the muscle hemoglobin is liberated from its natural locus so that it may find its way into the urine.

Myoglobinuria may follow injury to large muscle groups either from crushing injuries, thrombosis of an artery supplying a limb, or from high voltage electric shock. Experimentally myoglobinuria has been produced in dogs by elastic compression of the hind legs and by the intramuscular injection of distilled water. In this traumatic type of muscle damage severe degenerative changes are seen in the muscle tissue on microscopic examination. The fibers appear pale and swollen, and areas of necrosis are seen. There is little in common with spontaneous myoglobinuria.

Haff disease is a toxic form of myoglobinuria in which a generalized muscle disorder results from the ingestion of contaminated fish. This disease was first reported as an outbreak in East Prussia and occurred among persons eating fish from a certain inlet into which ran a river which was polluted by waste products from cellulose factories. The victims of Haff disease developed acute and generalized muscle cramps several hours after eating eel or burbot caught in the inlet. In a short time they began to pass urine which was found to contain myoglobin and metmyoglobin. The illness lasted several days and appeared to carry no permanent sequelae, although a mortality of about 1 percent from renal damage was reported. Children appeared to be most immune to the disorder, adult males the most susceptible, and exercise was considered to be a predisposing factor. The nature of the offending agent was investigated extensively, but no substance withstood critical analysis. Organic acids from
Table 2.—Previously Reported Cases of Idiopathic Myoglobinuria

<table>
<thead>
<tr>
<th>Authors</th>
<th>Age and sex</th>
<th>Etiology or Other disease</th>
<th>Clinical data</th>
<th>Identification of urine pigment</th>
<th>Muscle pathology</th>
<th>Special studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer-Betz, 1910</td>
<td>13-M</td>
<td>Rheumatic fever</td>
<td>Recurrent, acute episodes of a shock-like syndrome accompanied by widespread muscle spasm and the passage of dark urine. Subsequent muscle atrophy.</td>
<td>Designated hemoglobin and methemoglobin spectroscopically</td>
<td>Not reported</td>
<td>Negative Donath-Landsteiner test. Muscles not affected by immersion in cold water</td>
</tr>
<tr>
<td>Paul, 1923</td>
<td>42-F</td>
<td>None</td>
<td>Single acute episode of fever, generalized muscle pain, passage of dark red urine. Died after two weeks of bronchopneumonia.</td>
<td>Designated hemoglobin and methemoglobin spectroscopically</td>
<td>Widespread Zenker's degeneration</td>
<td>None</td>
</tr>
<tr>
<td>Günther, 1924</td>
<td>54-M</td>
<td>Rheumatoid arthritis and heart disease</td>
<td>Subacute course with febrile onset. Arthritis followed by widespread muscle pain and the passage of dark urine. Developed congestive heart failure, severe muscle weakness. Died of cellulitis initiated by Southey tubes one month after onset.</td>
<td>Spectroscopic demonstration of myoglobin and metmyoglobin</td>
<td>Generalized myositis with degenerative, inflammatory, and necrotic changes in the muscle fibers</td>
<td>None</td>
</tr>
<tr>
<td>Hittmair, 1925</td>
<td>48-F</td>
<td>Rheumatic fever and heart disease</td>
<td>Recurrent episodes of arm and leg muscle pain induced by exercise and accompanied by the passage of dark urine. Subsequent development of rheumatic heart disease with congestive heart failure.</td>
<td>Designated hemoglobin and methemoglobin spectroscopically</td>
<td>Not reported</td>
<td>Normal erythrocyte fragility</td>
</tr>
<tr>
<td>Huber, Florand, Liébre, and Neret, 1938</td>
<td>4-M</td>
<td>None</td>
<td>Single episode of severe muscle pain and spasm confined to the legs which was induced by walking. Associated dark urine. No further attacks even with comparable exercise.</td>
<td>Positive chemical test for hemoglobin</td>
<td>Not reported</td>
<td>Negative Donath-Landsteiner test, normal erythrocyte fragility</td>
</tr>
<tr>
<td>Millikan, 1939</td>
<td>?-M</td>
<td>None</td>
<td>Symptomatology similar to that of equine myoglobinuria.</td>
<td>Designated myoglobin</td>
<td>Not reported</td>
<td>Elevation of serum potassium with exercise</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Age</td>
<td>Gender</td>
<td>Signs/ Symptoms</td>
<td>Laboratory Examination</td>
<td>Other Observations</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>-----</td>
<td>--------</td>
<td>---------------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>Bywaters and Dible</td>
<td>1943</td>
<td>21-M</td>
<td>None</td>
<td>Recurrent episodes of leg muscle pain following exercise and accompanied by dark urine. In terminal episode death followed the development of lower nephron nephrosis.</td>
<td>Positive chemical test for hemoglobin</td>
<td>Patchy depigmentation, fragmentation, degenerative changes, necrosis of muscle fibers</td>
</tr>
<tr>
<td>Louw and Nielsen</td>
<td>1944</td>
<td>10-M</td>
<td>Progressive muscular dystrophy</td>
<td>8 cases of progressive muscular dystrophy in family. Since the age of 4, recurrent episodes of leg muscle pain induced by walking and accompanied by “bloody” urine. Pseudohypertrophic muscles</td>
<td>Designated hemoglobin and met-hemoglobin spectroscopically</td>
<td>Not reported</td>
</tr>
<tr>
<td>de Langen</td>
<td>1946</td>
<td>28-M</td>
<td>None</td>
<td>Single episode of “spastic paralysis” of the legs accompanied by red urine following prolonged genuflexion.</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hed</td>
<td>1947</td>
<td>Three brothers, ages 17, 19, 20</td>
<td>Familial</td>
<td>Recurrent episodes of muscle pain following exercise. Legs mainly involved, but sometimes generalized. Pain followed by dark urine.</td>
<td>Spectrophotometric</td>
<td>Minimal degenerative changes</td>
</tr>
<tr>
<td>Kreutzer, Strait, and Kerr</td>
<td>1948</td>
<td>39-M</td>
<td>Syphilis</td>
<td>Since childhood recurrent episodes of leg cramps induced by exercise and accompanied by the passage of dark urine. Atrophic muscles</td>
<td>Spectrophotometric identification of myoglobin and metmyoglobin</td>
<td>Not reported</td>
</tr>
<tr>
<td>Scherwin</td>
<td>1945</td>
<td>38-M</td>
<td>None</td>
<td>Chronic course with edema over involved muscles. Haff's disease excluded.</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wissler</td>
<td>1948</td>
<td>6-M</td>
<td>3 brothers had a form of muscular dystrophy</td>
<td>Isolated attack of myoglobinuria with paresis of trunk muscles and leukocytosis</td>
<td>Spectrophotometric identification of myoglobin</td>
<td>Biopsy not done</td>
</tr>
</tbody>
</table>
the factory, selenium, and other industrial chemicals were all considered, but an outbreak reported in Sweden by Berlin occurred among residents of a lake region where there was no possible industrial taint. Noting the similarity in symptoms between foxes eating fish from this lake and foxes suffering from Chastek paralysis, Berlin postulated the existence of an antivitamin in the fish. Such an element is perhaps comparable to the substance found in carp which is able to inactivate thiamine and produce an acute avitaminosis B₁. Unfortunately, direct evidence is lacking to support this interesting speculation. The exact pathogenesis of Haff disease is not known, although it has been produced with ease in a number of experimental animals. Both the diseased animals and man show degenerative changes in many muscle groups as well as toxic reactions in numerous parenchymatous organs. The muscle changes described in Haff disease resemble those of some of the idiopathic cases.

Equine myoglobinuria is an interesting condition which has long been known to veterinarians. It affects horses, usually of the draft variety. Following several days of rest and a high carbohydrate diet, severe exercise produces spasm in the leg muscles and myoglobinuria. These attacks are accompanied by elevation in the blood lactic acid, glucose, and potassium; they have been attributed to the rapid or incomplete breakdown of glycogen which has accumulated in the resting muscle. The toxic agent thought to be responsible for the muscle damage was either lactic acid or adenyl phosphoric acid in excessive concentrations. The administration of insulin to afflicted animals reversed the metabolic abnormalities. No such changes in blood glucose or lactic acid have been reported in human idiopathic myoglobinuria, nor is the same relationship between attacks and rest evident. In fact, in the case herein reported, rest appeared to be protective against attacks whereas exercise produced increased sensitivity to the effect of further activity.

Studies on the chemistry of hemoglobin have clarified some of the problems presented by the hemolytic anemias. The relative inaccessibility of myoglobin in pure form has hindered the widespread undertaking of corresponding investigations as to its relation to disease. The compound was first established as an independent component of muscle in 1871 when it was found in the thoracic musculature of mollusca, animals which lack blood hemoglobin. In 1897, Morner established the spectroscopic identity of myoglobin; but its minor differences from hemoglobin were long thought to be artefactual and due to extraction methods. In 1933, Theorell prepared pure myoglobin in crystalline form and established its unique identity beyond further question. He then proceeded to establish its properties, showing that it differed from hemoglobin only in the globin fraction of the molecule, this being a considerably smaller protein in myoglobin. The molecular weight of myoglobin is one-quarter that of hemoglobin, being about 17,000. The smaller molecular size of myoglobin accounts for its low renal threshold, estimated at 15 mg./100 cc. of blood in contrast to that of 100 to 150 mg./100 cc. for hemoglobin. The solubility and diffusability of myoglobin were found to be considerably greater than those qualities in hemoglobin. Myoglobin was found to have 1 atom of iron per mole-
TABLE 3.—Spectroscopic Properties of the Hemoglobins and Derived Pigments*

<table>
<thead>
<tr>
<th>Pigment</th>
<th>Maximum</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxyhemoglobin</td>
<td>577</td>
<td>560</td>
<td>540</td>
<td>500</td>
</tr>
<tr>
<td>Oxymyoglobin</td>
<td>582</td>
<td>564</td>
<td>542</td>
<td>500</td>
</tr>
<tr>
<td>Carboxyhemoglobin</td>
<td>570</td>
<td>560</td>
<td>539</td>
<td>492</td>
</tr>
<tr>
<td>Carboxymyoglobin</td>
<td>579</td>
<td>560</td>
<td>540</td>
<td>500</td>
</tr>
<tr>
<td>Methemoglobin</td>
<td>630</td>
<td>600</td>
<td>500</td>
<td>460</td>
</tr>
<tr>
<td>Metmyoglobin</td>
<td>630</td>
<td>595</td>
<td>500</td>
<td>465</td>
</tr>
</tbody>
</table>

* Wave lengths are given in millimicrons.

rapid than that of hemoglobin; and metmyoglobin was formed more readily than methemoglobin. Theorell worked out the spectroscopic properties of myoglobin and its derived pigments, as summarized in table 3. Hemoglobin may exist in several different forms, both normal and pathologic variations having been described. Likewise it has been suggested that myoglobin may have other variants.

There is little direct evidence concerning the rate of myoglobin turnover in the body. Whipple and Rbshcet-Robbins demonstrated that injected myoglobin is rapidly converted into bilirubin and thence into urobilinogen. They concluded that myoglobin catabolism must be considered in studies of total urobilinogen output. However, in 1948, Hahn asserted that the catabolism of myoglobin played an insignificant role in the formation of urobilinogen. Myoglobin turnover may be extremely slow in normal humans, as indicated by the studies of Vanotti. He found that injected radioactive iron appeared in muscle tissue within fifteen minutes, but it was not found in the myoglobin molecule until thirty days had elapsed.

The myoglobin content of various muscles differs considerably. No definite pattern has been established determining those factors responsible for its deposition, but the muscles most heavily endowed appear to be those which perform sustained and heavy work. Muscles involved in walking, for example, are high in myoglobin. The myoglobin content of muscle increases somewhat from infancy to adulthood, and then tends to decrease with old age. These findings may explain the increased resistance of children to Haff disease. Exercise tends to favor the deposition of myoglobin on a long term basis; and conversely, disuse causes its depletion. There is little correlation between the myoglobin content of muscles and the blood hemoglobin concentration. The anemia of disease and that produced in the experimental animal is not accompanied by corresponding reductions of myoglobin in muscles. However, in the polycythemia produced by high altitudes in dogs, the myoglobin content of cardiac and skeletal muscle is increased. Muscles rendered paralytic by destruction of the peripheral nerve innervation rapidly lose their myoglobin. In contrast, division of sensory nerves or section of the spinal cord is not followed by reduction in the myoglobin content of the corresponding muscle groups.

The physiology and biochemistry of myoglobin are presented in two excellent reviews. The oxygen dissociation curve of the pigment lies between that of hemoglobin and the cytochromes; thus it is well adapted to function as a respira-
IDIOPATHIC MYOGLOBINURIA IN MAN

tory pigment. In his discussion concerning the possible role of myoglobin in muscle physiology, Millikan admits that this is still a matter of conjecture. He considers it unlikely that myoglobin serves to effect oxygen transport in the manner of hemoglobin, or that it functions as a respiratory pigment as do the cytochromes. Instead he favors the view that myoglobin acts as an oxygen reservoir for emergency use. This would appear to be the case in diving mammals, such as seals and dolphins. The high myoglobin content found in the muscles of these species seems to be related to their ability to remain under water for prolonged periods.

Previous studies on the physiology and pathology of myoglobin have not shed much light on the disorder presented by our patient. Little further clarification has been effected by the special studies performed in the case reported here. The metmyoglobin found in the urine is probably not of significance, as intravenous injection of oxymyoglobin in animals has also resulted in the appearance of metmyoglobin in the urine. Oxidation evidently takes place in the blood stream or in the urinary tract. Moreover, the use of large doses of ascorbic acid did not affect the appearance of myoglobinuria following exercise. Since ascorbic acid prevents the oxidation of heme pigments, the muscle damage and liberation of myoglobin must have taken place without the formation of metmyoglobin.

Of unusual interest is the finding of hemosiderinuria as a consequence of myoglobinuria. Apparently the iron component of the myoglobin molecule, upon passage through the glomerulus and presentation to the renal tubules, is handled in a manner analogous to the fate of iron contained in hemoglobin. Hemosiderinuria in the case reported was not a constant finding as in the hemosiderinuria accompanying paroxysmal nocturnal hemoglobinuria.

On the basis of the available evidence, even speculation is unwarranted on the mechanism by which exercise induced attacks. The inability to induce attacks by exercise of the upper limbs suggests that the disease manifests itself as a localized rather than generalized disorder. It should be noted, however, that this peculiar precipitation of attacks by exercise involving certain muscle groups, or more specifically, certain types of activity, is not solely confined to idiopathic myoglobinuria. A similar relationship has been noted in paroxysmal nocturnal hemoglobinuria.

As far as can be determined, ischemia was not a factor, since the application of a tourniquet and the application of cold both failed to produce attacks in the vulnerable muscles.

In general it can be said that either of two factors must have been operative: the muscle fibers themselves may have been defective and more susceptible to injury, a situation comparable to the defective erythrocytes of the hereditary hemolytic anemias; or the environment surrounding the muscle fibers may have become unfavorable and toxic due to the accumulation of normal or pathologic metabolites, a situation reminiscent of the acquired hemolytic anemias. Since there is evidence for some familial basis for the disorder in at least three instances of myoglobinuria, while in the others, the disease seemed to arise spontaneously, the clinical syndrome of idiopathic myoglobinuria may result from several widely differing mechanisms, some congenital, some acquired.

The concept of a defect in muscle fibers is fortified by reports of myoporphyria, a disease characterized by the appearance of abnormal urinary porphyrins and
severe muscle wasting not attributable to neurologic involvement. Obvious toxic damage to the muscles is seen in Haff disease, and a similar mechanism may also be responsible for the symptoms in equine myoglobinuria. There is no basis for assigning either type of pathogenesis to the present syndrome.

The diagnosis of myoglobinuria depends upon its differentiation from the various hemoglobinurias and from the porphyrias. If myoglobinuria is suspected, its identification is not difficult and is based upon the properties of myoglobin. As myoglobin is a heme pigment of small molecular size, it imparts a positive benzidine test to the urine but does not fluoresce under ultra violet illumination. In contrast, porphyrins show strong fluorescence under ultraviolet illumination and do not produce a positive benzidine test. The hemoglobinurias of acute hemolytic anemia are invariably accompanied by elevation of the plasma hemoglobin. The renal threshold of myoglobin in the plasma is about 15 mg./100 cc.; this is insufficient to discolor the plasma visibly. The renal threshold for hemoglobin is about 100 to 150 mg./100 cc. of plasma; such an elevation of plasma hemoglobin is readily apparent upon inspection of the plasma with the naked eye. If the plasma is free from visible discoloration, and the urine contains what appears to be hemoglobin, there is strong presumptive evidence that the urinary pigment is not hemoglobin but myoglobin. The final identification of myoglobin must be made by spectrophotometric means. The characteristic maxima and minima of myoglobin and its derivatives are given in table 3. It can be seen that identification is facilitated by treatment with carbon monoxide, as there is greater divergence between the bands of hemoglobin and myoglobin when these pigments are in the carbon monoxide form than there is in the oxy-state. Precautions must be taken that the urine being tested is neutral or alkaline when passed, as a low pH can cause conversion of the heme pigments into the acid hematin. These denatured proteins do not have characteristic spectroscopic patterns. A guide to the differential diagnosis of myoglobinuria is given in table 4.

### Table 4—Differential Diagnosis of Paroxysmal Pigmenturia

<table>
<thead>
<tr>
<th></th>
<th>Attacks precipitated by</th>
<th>Site of pain</th>
<th>Plasma discoloration</th>
<th>Plasma hemo-chromogen*</th>
<th>Urinary pigment</th>
<th>Specific test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>Cold</td>
<td>Muscles</td>
<td>None</td>
<td>Minimally elevated</td>
<td>Myoglobin</td>
<td>Spectroscopic identification of myoglobin, Provocative exercise test, Donath-Landsteiner test</td>
</tr>
<tr>
<td>March hemoglobinuria</td>
<td>Exercise</td>
<td>Lumbar</td>
<td>Prominent</td>
<td>Elevated</td>
<td>Hemoglobin</td>
<td>Ham and Crosby tests</td>
</tr>
<tr>
<td>Cold hemoglobinuria</td>
<td>Cold</td>
<td>Abdominal, back,</td>
<td>Prominent</td>
<td>Elevated</td>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Sleep</td>
<td>Lumbar, abdominal, legs, shoulder girdle</td>
<td>Prominent</td>
<td>Elevated</td>
<td>Hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Acute porphyria</td>
<td>?</td>
<td>Abdominal cramps, peripheral neuritis</td>
<td>None</td>
<td>Normal</td>
<td>Porphobilinogen, uroporphyrin 1, coproporphyrin</td>
<td>Chemical identification of porphyrins</td>
</tr>
</tbody>
</table>

* Measurement of benzidine positive materials, i.e. hemoglobin, myoglobin, methemalbumin.
IDIOPATHIC MYOGLOBINURIA IN MAN

The prognosis of idiopathic myoglobinuria is uncertain. It appears to depend upon the extent of renal damage which the attacks produce, and upon the associated conditions present. Of the reported cases there were several fatalities; but few were directly related to the myoglobinuria. However, most of the patients were not followed for sufficiently long periods of time to determine the ultimate course. The case reported here was well so long as excessive exercise to the legs was avoided. Persistent renal signs appeared to have been established prior to his entry into the hospital, and an intercurrent episode of lower nephron nephrosis followed an attack while he was under study. This possibility should be kept in mind when a patient with possible myoglobinuria is under investigation.

At present, there is no treatment of established value for idiopathic myoglobinuria. In cases of the type described, the maintenance of a sedentary life appears to be the only measure of prophylactic value.

SUMMARY

A case of myoglobinuria of idiopathic origin is described. A diagnostic triad of (1) muscular pseudoparalysis, (2) a highly colored urine containing a benzidine positive pigment, and (3) plasma free from visible discoloration was present. Identification of the urinary pigment as myoglobin was established by spectrophotometry, and the presence of accompanying metmyoglobinuria was detected. Exercise of the lower extremities was the precipitating factor during each attack of myoglobinuria. Attempts to induce attacks by means other than exercise were unsuccessful, and no amelioration of myoglobinuria could be produced by treatment with ascorbic acid or cortisone. The myoglobinopathies are discussed together with the present concept of the physiology of myoglobin. The differentiation of myoglobinurias from hemoglobinuria and porphyrias is readily accomplished by the laboratory procedures indicated above.

SUMMARY IN INTERLINGUA

Es describe un caso de myoglobinuria de origine idiopathic. Le sequente triade diagnostic esseva manifeste: (1) pseudoparalyse muscular, (2) coloratissime urina continent un pigmento positivo a benzidina, e (3) plasma libere de discoloration visibile. Per medios spectrophotometric le pigmento urinari esseva identificate como myoglobina. Le presentia del correspondente metmyoglobinuria esseva establite. In omne attaccos de myoglobinuria le factor precipitante esseva le exercicio del extremitates inferior. Omne effortios a producir tal attaccos per altere medios remaneva sin successo. Nulle melioration de myoglobinuria resultava de tractamentos a acido ascorbic o a cortisona. Le myoglobinopathias es discutite insimul con le presente conception del physiologia de myoglobina. Le supra-indicate technicas laboratorial servi ben a differentiar myoglobinurias ab hemoglobinurias e porphyrias.

REFERENCES

MORNER, 27
MOMENT, 24
CARLSTRÖM, YTL-MLE, 28
KENNEDY, H. P.
LANKESTER, 26
ASSMANN, KAMSERLING, 22
IDIOPATHIC MYOGLOBINURIA IN MAN

Idiopathic Myoglobinuria in Man: Report of Case
THEODORE H. SPAET, MARTIN C. ROSENTHAL and WILLIAM DAMESHEK

Updated information and services can be found at:
http://www.bloodjournal.org/content/9/9/881.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml