tion quarter-strength iso-osmotic solution (0.28%) is suitable. The solutions are easily sterilized in the autoclave. For subcutaneous use Hawkins *et al.* recommend iso-osmotic solution with hyalase to facilitate absorption. Given subcutaneously, potassium chloride solution is painful, but with the usual clouding of consciousness these patients will not, at least initially, object. Given intravenously, potassium chloride rapidly produces a painful phlebitis. The vein usually remains patent, and such a phlebitis is not an indication for changing to another vein or stopping the infusion.

It is probably safe to give a potassium-depleted patient a pint (570 ml.) of quarter-strength iso-osmotic potassium chloride solution intravenously in two hours. It is also probably safe to give a pint (570 ml.) of iso-osmotic potassium chloride solution subcutaneously to a similar patient in four hours. Rapid estimations of serum potassium are necessary such as may be obtained with a flame photometer, and it is essential to check the serum levels daily or more often. In such a case as is here described potassium therapy should be started early and not when a pre-existing deficiency has been made worse by sodium and water administration. Nevertheless, potassium must not be given till rehydration is under way and a flow of urine has begun; otherwise fatal high levels may be attained in the extracellular fluid. Very great caution is required if there is associated renal disease or adrenal insufficiency. Potassium should not be given in the first 24 hours after operation.

I am indebted to Mr. Ian Fraser, in whose care this patient was, and to Sister Harrison, of the Musgrave Clinic, Belfast, for accurate records of treatment and for the devoted nursing which sustained this patient through a long illness.

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PAROXYSMAL PARALYTIC MYOGLOBINURIA

BY

STEPHEN D. ELEK, M.D., Ph.D., D.P.H.
Bacteriologist

AND

HUGH F. ANDERSON, F.R.C.S.
Surgeon

St. George's Hospital Medical School, London

Paroxysmal paralytic myoglobinuria is a rare disease of unknown aetiology, affecting skeletal muscle and resulting in the liberation of myoglobin, which is excreted in the urine. The patient complains of painful muscle spasms and passes brownish urine.

Case Report

On December 13, 1946, a single woman aged 41 fell down "after a few gins" and sustained minor injuries. These were treated and she was sent home and advised to stay in bed. Three days later she suddenly developed cramps in both legs. At first the cramps were painless, but they soon became very painful and so severe that an hour later she was unable to stand. The pain started in the toes and spread upwards, first to the calves and then to the inner sides of the thighs.

On admission to hospital nothing relevant was found in her past medical or family history, and the temperature and pulse were normal. Physical signs were confined to the lower limbs, which were held extended with the feet in talipes equinus. All movements of the ankle-joints were limited by severe pain in the calf muscles, which were swollen, tender, and hard. Their "woody" consistency was similar to that felt in ischaemic contracture. The muscles on the medial side of the thighs were also tender, but their consistency was normal. All the signs and symptoms were more severe on the right side. The texture and colour of the skin were normal. The knee-jerks were normal, but the ankle-jerks were absent. The plantar reflexes were flexor, and there were no sensory changes. No pulsation could be felt in the popliteal, dorsalis pedis, and posterior tibial arteries on either side. Examination of the blood showed: red cells, 4,800,000; Hb, 96% (Haldane); white cells, 9,100 (polymorphs 80%, lymphocytes 15%, monocytes 4%, eosinophils 1%); platelets, normal; bleeding-time (Duke's) 2½ minutes; clotting-time 2½ minutes; prothrombin time 15 seconds. Wassermann reaction and Kahn tests were negative and the Donath-Landsteiner reaction was also negative.

Diagnosis was difficult. Thrombosis of the deep veins of the calves was considered most likely, and, in view of the absence of arterial pulsation and the possibility of permanent ischaemic changes occurring in the muscles, it was decided to perform a decompressing operation on the worst side. On December 16 a vertical incision 8 in. (20 cm.) long was made through the skin and deep fascia of the right calf. Contrary to expectation, the calf muscles did not bulge, and they looked paler than normal. The wound was left open, dressed with penicillin powder and petroleum jelly gauze, and supported on a back splint. Intravenous heparin treatment was started, and intramuscular penicillin was administered. Next day the legs were less painful, though the calves were still hard and tender. The patient said that the right calf felt a little easier after the operation. On this day it was first noticed that the urine was dark red. Clinically the specimen suggested severe haematuria, but microscopical examination revealed only an occasional leucocyte, a trace of albumin, and a heavy deposit of phosphates. There were no red cells or casts.

It was the investigation of this apparent paradox of haematuria without red cells which led to the diagnosis. The next day the urine was still red, but the following day it was normal in colour. During the ensuing days the symptoms and signs slowly subsided, the calves becoming softer and less tender. On December 24, eight days after the decompressing operation, secondary suture of the wound in the right calf was undertaken, and a piece of the right gastrocnemius muscle was excised for examination. Healing by first intention followed. The serum potassium level while at rest in bed was 15.5 mg. per 100 ml., and a day later after a brisk walk it was 17 mg. She was discharged from hospital free from signs and symptoms three weeks after admission. Unfortunately it has since been impossible to trace the patient.

Spectroscopic examination of the urine on December 17 showed an alpha band at 585 mμ. On substituting oxyhaemoglobin for the urine there was a clear-cut shift of the band. The position of the absorption band suggested myoglobin (Theorell, 1934; Millikan, 1939). A crude preparation of myoglobin obtained from human muscle gave a similar band at 584 mμ. The pigment was tentatively identified as oxymyoglobin, and this finding was confirmed by Dr. J. C. White.

Professor Crawford reported on the muscle biopsy: "The specimen consists of skeletal muscle which shows a scattered lesion involving individual fibres, shrunken and separated from their sheaths; they stain poorly and the appearances suggest that myoglobin has diffused out from the fibres. There is some increase in the nuclei of the sarcolemma and of the interstitial fibrous tissue. Special staining shows patchy loss of striation in the affected fibres.

Serial sections have been examined, but they do not show any lesion of the blood vessels of the part. The appearances suggest a primary lesion of the muscle fibres, resulting in disintegration of the fibre, unassociated with vascular damage" (Figs. 1 and 2).

FIG. 1.—Haematoxylin-eosin ($\times 200$). Biopsy of gastrocnemius muscle showing localized necrosis of fibres surrounded by oedema and lymphocytic infiltration. One fibre is seen shrunken and separated from the sarcolemmal sheath.

FIG. 2.—Mallory's phosphotungstic acid haematoxylin ($\times 330$). Same specimen as Fig. 1 showing strictly localized necrosis of muscle fibre with loss of striation and staining. The unaffected part of the fibre and the surrounding fibres show well-preserved striation.

The Literature

Up to the time of our observation, we could find only six case histories of this disease. Two further cases were ascribed to this syndrome (Millikan, 1939; Bywaters and Dible, 1943), but in one a clinical description was not available, and in the other the diagnosis was retrospective after death. Since 1946 five further cases have been described, three of them in the same family.

We owe the first description of the disease to Meyer-Betz (1910).

A 13-year-old boy was admitted to hospital in a state of collapse and apparently moribund. The disease started suddenly with abdominal pain, bleeding from the nose, and vomiting. He became very weak and a few hours after the onset voided some black urine. The family history revealed nothing. His past medical history showed that at the age of 10 his urine appeared to contain blood for two days, but he was not obviously ill.

From that time he had "haematuria" once or twice a year, lasting for two days and associated with severe muscular weakness. About nine months before admission he had a more severe attack: he could hardly move and his urine was black. Four months before admission he had an attack of abdominal pain associated with severe weakness lasting for about 14 days. His mother noticed at this time that his legs and feet were swollen.

On examination the child could barely move. The lower extremities were more affected and were almost paralysed. The feet were in talipes equinus and the calf muscles contracted and hard. Passive movement of knee and hip caused pain. The elbows could not be straightened and there was limitation of wrist movement. The patellar reflexes were absent. All the muscles involved felt hard and tender to pressure. There was mild anaemia, with moderate leucocytosis.

The urine voided at the time of admission was chocolate-coloured and turbid, and showed a heavy deposit. There was some detritus, believed to be red cells, but no actual red cells were seen. A few granular and hyaline casts were also present. The test for albumin was strongly positive and spectroscopically the pigment resembled both oxyhaemoglobin and methaemoglobin. The output of urine was severely reduced during the first day, but its colour rapidly became paler and by the end of the second day the pigment had disappeared. At this stage hyaline, granular, and red-cell casts were seen in abundance. Gradually the urinary output rose and the child recovered. The contractures disappeared in this order: hands, flexors of left arm, flexors of right arm; last to disappear were the contractures of the most severely affected calf muscles. Within three months of the onset the child appeared to be normal again.

Two minor attacks involving only the calf muscles and leading to discoloration of the urine were also observed.

Meyer-Betz noticed the striking similarity between this condition and "paralytic equine haemoglobinuria," and, although unable to confirm the nature of the pigment, he was aware that myoglobin was involved.

The cases since observed closely resemble the first. The pattern is the same and the variation is only in the severity of the episodes. The Table summarizes the main features.

The onset is sudden. With minor attacks there is bilateral but not necessarily symmetrical involvement of the muscles of the lower limbs. The attacks, which are frequently repeated over a period of months or years, often follow exertion after a period of rest in bed. The calf muscles are most often affected; they are painful and feel wooden as if in tonic contracture. The feet are in the position of a ballet dancer, and the attack is followed within a few hours by transient myoglobinuria. The duration and intensity of myoglobinuria is proportional to the severity of the attack and to the extent to which the musculature is involved. It may well be that minor attacks are more common than hitherto believed, and are missed because the staining of the urine is not noticed. The attacks are not associated with neurological changes, either sensory or motor. There is no oedema or involvement of the overlying skin. The course is generally afebrile, except in severe attacks in small children. Normal red- and white-cell counts appear to be the rule, and the urine shows no red cells or stromata to account for the blood-stained appearance.

Major attacks differ only in extent. The involvement of muscles spreads upwards until all the skeletal muscles are affected; this leads to the apparent paralysis which is included in the name of the syndrome. Myoglobinuria is more intense and prolonged.

Even the most severe cases on record ended favourably; renal failure seems to be unusual. The attacks have a tendency to recur, but in several of the cases they became less frequent and ultimately disappeared. The remote prognosis is more difficult to assess. Case 1 was well—apart from some residual contracture of the calf muscles—a year later, when last seen. Case 2 had three lesser attacks in the next two years. We have been able to follow up Case 3 in France 16 years later, as her father is a medical practitioner. She had one severe and two milder attacks within three years of the onset, and then recovered completely. The other cases could not be traced.

Details of Cases in the Literature

Author	Case No	Age	Sex	Family History	Course and Remarks
Meyer-Betz (1910)	1	13	M	None	History of several minor attacks. In hospital with very severe attack involving whole body. Later two minor attacks while under observation. Complete recovery a year later
Hittmair (1925)	2	41	F	"	Onset with sudden major attack, starting in legs, ascending to trunk and arms. Recovery in 14 days. Second major attack a year later, followed by a lesser attack, and finally minor attack during following year. Recovery
Debré <i>et al.</i> (1934)	3	21	F	"	Major attack with generalized paresis. Febrile. Calves most affected. 10 months later identical attack. Milder attack a year later and a minor attack after a further 3 months. Complete recovery
Huber <i>et al.</i> (1938)	4	4	M	"	Single attack of medium severity affecting lower limbs. Slight fever. Recovery
Louw and Nielsen (1944)	5	4	M	8 members of 5 generations affected by sex-linked recessive muscular disease starting in childhood. ?Progressive muscular dystrophy	History of repeated minor attacks involving calves only. Seen with minor attack at age of 10. Recovery. Myoglobin confirmed
Scherwin (1945)	6	38	M	None	Three attacks with atypical distribution and course. Oedema and red skin over muscles involved. ?Polymyositis. Outcome not known
Elek and Anderson (present case) (1946)	7	41	F	"	Single minor attack. Myoglobin confirmed. Recovery
Hed (1947) ..	8	20	M	3 males of 6 siblings affected; 2 males healthy. No other family history of muscular disease. Mother diabetic	Several minor and some major attacks from age of 15. Attacks related to exertion on fasting. One mild attack observed. Abnormal sugar tolerance curve. Myoglobin in urine confirmed
" " ..	9	19	M	Brother of Cases 8 and 10	History of minor attacks from age of 16. Related to exertion while fasting. Abnormal sugar tolerance curve. Carbohydrate-free diet for 24 hours was followed by severe attack. Myoglobin confirmed
" " ..	10	18	M	Brother of Cases 8 and 9	History of minor attacks consisting of pain in legs and dark urine. Related to exertion
Wissler (1948)	11	6	M	3 brothers suffered from a form of muscular atrophy. 2 died	Single attack of medium severity observed. Slight fever. Myoglobin confirmed
Kreutzer <i>et al.</i> (1948)	12	39	M	None	History of repeated fleeting attacks. 3 attacks of medium severity observed. Attacks could be brought on by stretching of muscles. Myoglobin confirmed. Recovery, but no follow-up available

Differential Diagnosis

The relative ease with which myoglobin can now be identified spectroscopically sets myoglobinuria apart from any form of haemoglobinuria. Although all of them are uncommon, there are several conditions known in which this pigment or its decomposition products appear in the urine. In all these the primary lesion is in skeletal muscle. If there is a sufficiently severe lesion of muscle and enough

circulation for absorption to occur myoglobinuria will ensue. Myoglobin is readily excreted by the kidneys (Camus and Pagnez, 1902); its threshold is stated to be about 20 mg. per 100 ml. Above this value its excretion in dogs is proportional to the concentration in the blood (Yuile and Clark, 1941), which means that myoglobin is cleared about 25 times more rapidly than haemoglobin. The least amount to produce visible discoloration of the urine is about 40 mg. per 100 ml. This rapid excretion explains why in all but the most severe and widespread lesions of muscle the staining of the urine is very transient.

The conditions in which myoglobinuria is one of the cardinal signs may be summarized as follows (modified from Björk, 1949): (1) Paroxysmal paralytic myoglobinuria; Haff disease. (2) Dermatomyositis with myoglobinuria; myositis following carbon monoxide poisoning; myoporphyria. (3) Progressive muscular dystrophy. (4) Traumatic myoglobinuria: (a) "crush syndrome"; (b) electrical high-voltage accidents; (c) arterial occlusion with ischaemia.

Haff disease is undoubtedly the commonest cause of myoglobinuria in man. It occurs in East Prussia (Starfinger, 1924; Ewig, 1924; Meyer, 1924), Sweden (Berlin, 1944), and Karelia (Basharina and Kirochkina, 1949). Its clinical features closely resemble the condition described by Meyer-Betz, and the histological findings, described by Kaiserling (1932), consist of focal lesions of individual muscle fibres. The pigment in the urine has been identified as myoglobin (Assmann *et al.*, 1933; Jeddell, 1939).

Dermatomyositis may also be associated with myoglobinuria, as in the case described by Günther (1924) and possibly also in Paul's (1924) case. In both the disease was characterized by rigors and high fever, and the severity of the muscular lesions was greater in the upper than in the lower extremities. Both terminated fatally. It may be that Scherwin's (1945) case should also be ascribed to this group, since there was oedema of the skin over the affected muscles. Myoglobinuria was not confirmed in any of these three cases, and the clinical picture was unlike that of paroxysmal paralytic myoglobinuria.

Carbon monoxide poisoning causes a severe form of myositis, sometimes with myoglobin in the urine (Günther, 1921, 1940; Brass, 1944).

Myoporphyria is less well established as a disease entity; cases associated with muscle atrophy and loss of myoglobin have been described (Vanotti, 1935-6; De Langen, 1943; Belloni, 1947). Similarly the relationship of progressive muscular dystrophy to paralytic paroxysmal myoglobinuria is at present undefined. The resemblance of the distribution of the lesions was noticed early (Meyer-Betz, 1910; Kreutzer *et al.*, 1948). Louw and Nielsen (1944) found evidence suggestive of progressive muscular dystrophy in the family of their case and a similar family history in another case (Wissler, 1948). Furthermore, some authors are of the opinion that the primary injury in progressive muscular dystrophy is in myoglobin metabolism (Meldolesi, 1937, Meldolesi *et al.*, 1939).

The only group of known aetiology is that of traumatic myoglobinuria. Originally observed in the first world war (Frankenthal, 1916), it was studied by Minami (1923) and Husfeldt and Bjering (1937) and later most extensively by Bywaters and his associates (Bywaters, and Delory, 1941; Bywaters and Beall, 1941; Bywaters, Delory *et al.*, 1941; Bywaters and Popjak, 1942; Bywaters, 1944; Bywaters and Stead, 1944). Severe crush injuries or physical punishment (Langen, 1946) may cause necrosis of muscle, which, if severe enough, terminates fatally through renal failure. High-voltage currents similarly cause damage to skeletal muscle, often to a greater extent than the external injuries would suggest. Myoglobinuria and renal failure have been observed (Fischer and Rossier, 1947; Fischer and Fröhlicher, 1947). Ischaemic necrosis due to arterial thrombosis, embolism, or even spasm may simulate the conditions of traumatic myoglobinuria (Bywaters and Stead, 1945).

Aetiology

Little is known about agents causing acute necrosis of muscle. Myoglobinuria is, however, a common condition in animals (Minett, 1935). One form affecting horses is known as "paralytic myoglobinuria" (Fröhner, 1884; Camus and Pagniez, 1902, 1904; Camus, 1903), and the pigment has been identified (Carlström, 1931). The large muscles of the hind part are most severely affected and the onset is sudden. In "enzootic myoglobinuria" of horses (Wirth, 1921; Hobmaier, 1926; Stang and Wirth, 1928; Deubel, 1932; Bédaride, 1933) the muscles of mastication are affected. There is stiffness and swelling but no paralysis. Draught oxen and young calves suffer from "white muscle disease" (Vawter and Records, 1947), while lambs and young pigs suffer from a form of acute muscular necrosis, but the pigment has not been found in the urine (Hobmaier, 1926).

Foxes suffer from a disease known as Chastek paralysis, while in districts afflicted with Haff disease cats and even birds may suffer from it. The so-called "intermittent paralysis" of horses is said to be due to thromboses in the abdominal aorta (Carlström, 1931).

While the chain of events starting with acute muscular necrosis and leading to myoglobinaemia and myoglobinuria can easily be traced in all these conditions, and in recent years much has been learned about the renal lesions accompanying this sequence, practically nothing is known about the aetiology of acute focal muscular necrosis. In equine paralytic myoglobinuria excessive lactic acid formation was blamed, and this suggestion is reflected by Hed's statement that in his cases abnormal carbohydrate metabolism was responsible. Since the mother suffered from diabetes, the association may well have been accidental. Furthermore, there is no evidence of faulty carbohydrate metabolism in any of the other cases (Kreutzer *et al.*, 1948). Millikan's observation regarding excessive blood potassium levels is likely to be the result rather than the cause. Nor is there convincing evidence that human paroxysmal paralytic myoglobinuria is a hereditary condition. Its course and the long-term good prognosis make it unlikely, but this point cannot be settled until more information is available.

The condition resembles Haff disease in its clinical course, the low incidence of uraemia, and the histological changes found in the muscles, and may be a sporadic form of it. Haff disease is epidemic and so far all the outbreaks have stopped before it could be decided whether a virus or a toxic agent was responsible. Eating tainted fish is believed by many to be the cause. In this respect it may be noteworthy that Chastek paralysis of silver foxes, in which there is severe damage to muscles, is due to feeding on certain raw fish. The symptoms of this disease can be produced experimentally by a diet deficient in vitamin B₁, and recovery follows administration of this vitamin. A substance, probably a protein, has been recovered from fish that inactivates vitamin B₁ (Ågren, 1944). So far intravenous aneurin has not been tried either in Haff disease or in paroxysmal paralytic myoglobinuria, but on the basis of this theory it should bring about rapid recovery. Apart from our case, there is no information available about the lesions in the muscle as they appear in the acute phase, since no biopsy has been taken in any of the other cases. In one of Hed's cases a biopsy between attacks showed no abnormality except for a little diffuse increase of fibrous tissue between the muscle fibres. This suggests that, whatever the aetiological agent, the paroxysms of myoglobinuria represent the onset of necrosis in the muscles, possibly aggravated by exertion.

Summary

Paroxysmal paralytic myoglobinuria is briefly reviewed and a case illustrating the syndrome described.

The disease occurs in minor and major forms, which differ only in the extent of the lesions. Minor forms are characterized by painful tonic spasms affecting the lower

limbs, mainly the calf muscles, followed within a few hours by transient myoglobinuria. This pigment is suggested by the colour and by the absence of red cells or stromata. Major attacks consist of pseudoparalysis of the whole body, and are rarer. The disease has a tendency to recur, but the prognosis is good. The pathological changes in the affected muscles consist of focal necrosis. The aetiology is unknown.

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