EXERTION HAEMOGLOBINURIA

REPORT OF A CASE

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The form of paroxysmal haemoglobinuria associated with exertion is rare and its pathology is imperfectly understood. The clinical features and the results of laboratory investigations undertaken in a case studied by us are here recorded.

Case History

The patient, a European sergeant aged 33, first came under our observation at the end of July, 1944, when he was seen as an out-patient by one of us. He brought with him a sample of almost black urine which he had passed after playing a game of football. He gave the following interesting history.

In civil life he had worked as a stevedore and had never noticed any urinary abnormality or suffered from any illness. In September, 1940, on returning to the U.K. from France, he noticed that after a cross-country run his urine was dark. The same occurrence was noticed on two subsequent occasions under similar circumstances. He then remained free from symptoms until June, 1942, when again after a run his urine was dark. He was admitted to hospital for investigation, the results of which are not known to us, but his medical category was lowered to B. In June, 1943, his category was raised to A again, as he was eager for service afloat. In June, 1944, he arrived in East Africa, and early in July, after a route march, he had his first recurrence of the old symptom. On July 27 he played football, and it was a sample of the urine passed after this game that he brought with him to hospital. Examination of this specimen of urine showed: colour very dark brown; reaction acid; albumin + + + +; benzidine test ++; deposit: a few red blood cells, granular casts +, urates ++, a few calcium oxalate crystals.

He was admitted to hospital on July 31 for further investigation. It was established that a 20-minutes run invariably resulted in a paroxysm of haemoglobinuria lasting several hours. No constitutional disturbance accompanied the paroxysms, but there was some aching in the back and abdomen. The patient was of good physique; no other signs of disease were detected, and before an attack the urine contained nothing abnormal. It was decided to lower his medical category to C for six months, and he was discharged to duty in this category on Aug. 30.

During the next three months the patient reported that the paroxysms were becoming more frequent and that less exertion was required to produce them. Actions such as hauling on ropes were now apt to be followed by an attack, and the condition was becoming a liability in his daily work. He was readmitted to hospital on Nov. 29, and the investigations detailed in Table I were carried out.

An attempt was made to demonstrate the presence of intravascular haemolysins. The patient's red blood corpuscles and serum were mixed and incubated at 37° C. for two hours, with and without previous exposure to a temperature of 4° C. for 30 minutes, and with and without added complement (Donath-

Landsteiner reaction). Foreign group O cells and patient's serum, and patient's cells and foreign serum, were also set up against each other in a similar manner. All these tests were carried out on blood taken from the patient 3 minutes, 15 minutes, and 30 minutes after the beginning of a 30-minute

TABLE I.—Results of Tests Before and Immediately After a 30-minute Run

Test	Before Exercise	After Exercise
Haemoglobin (Sahli)	120%	106%
Red cells	5,750,000/c.mm.	5,320,000/c.mm.
White cells	9,000/c.mm.	8,400/c.mm.
Neutrophils	74%	78%
Lymphocytes	19%	18%
Monocytes	5%	3%
Eosinophils	2%	0.5%
Basophils	—	0.5%
Primitive white and red cells	Nil	Nil
Platelets	545,000/c.mm.	475,000/c.mm.
Coagulation time (at 30° C.)	5 minutes	6 minutes
Bleeding time	60 seconds	60 seconds
Reticulocytes	0.6%	0.4%
Blood group	O	O
Fragility of red cells	Total lysis in 0.34% NaCl; no lysis in 0.42% NaCl (within normal limits)	Total lysis in 0.32% NaCl; no lysis in 0.42% NaCl (within normal limits)
Packed cell volume	41%	40%
Mean corpuscular diameter	6.8μ	6.8μ
" " volume	71 c.μ	75 c.μ
" " average thickness	1.9μ	2.1μ
Van den Bergh reaction	Direct, nil.	Marked haemolysis
Icterus index	Indirect, 1.6 units	6.6

run, and then 45 minutes, 90 minutes, and 7 hours after the exercise was finished. Haemolysis *in vitro* was not demonstrated in any of these tests, or in tests for haemolysin on small amounts of fluid aspirated from muscle during and after exercise. Examination of urine taken at intervals after the beginning of exercise gave the results shown in Table II.

A rising and falling curve of oxyhaemoglobinaemia, which approximately paralleled the curve of haemoglobinuria, was demonstrated by tests on blood taken at intervals during and after exertion. It was possible to make only a rough estimate

TABLE III

Time Since Exercise Began:	During Exercise			After Exercise		
	3 min.	15 min.	30 min.	75 min.	120 min.	450 min.
% Hb (Sahli)	Less than 0.2	0.5	1.5	1	0.2	Less than 0.2
Hb (calculated from Sahli)	Less than 34 mg.	85 mg.	255 mg.	170 mg.	34 mg.	Less than 34 mg.

of haemoglobin by Sahli's method; the figures obtained are shown in Table III. The absorption spectrum for pseudo-methaemoglobin was not found in any of the sera examined.

The following experiment was performed in an attempt to determine if haemolysis occurs locally in muscle during exercise. First, 5 ml. of blood was withdrawn from a vein in the right arm and allowed to clot. A sphygmomanometer cuff was then applied to the left upper arm and inflated to a pressure of 100 mm. Hg. The patient then exercised the left arm, alternately extending and flexing the wrist and fingers for two minutes. At the end of this time blood was withdrawn from a vein in the left arm, with the sphygmomanometer cuff inflated. The serum from these two specimens showed no perceptible difference in colour. The experiment was repeated, this time releasing the cuff just before blood was withdrawn; the specimen presumably contained blood from all parts of the occluded limb, and it, too, showed no trace of haemolysis.

TABLE II.—Results of Urine Examinations

Hours after Exercise Started	Appearance	Spectroscopy	Protein	Sugar	Deposit
1/2	Dark brown, turbid	Oxyhaemoglobin ++; methaemoglobin +++	++++	Nil	Granular casts +++; epithelial and pus cells +
1	Dark brown, very turbid	Methaemoglobin +++	++++	"	Granular casts and epithelial and pus cells +
1 1/2	Dark brown, turbid	Methaemoglobin ++	+	"	Granular casts and epithelial cells +
3	Brown	Methaemoglobin +	+	"	"
5	Pale brown, slightly turbid	Methaemoglobin +	Trace	"	Epithelial cells +
7	Amber, clear	No blood pigment	"	"	Pus cells and epithelial cells +
24	" "	" "	"	"	" "

Finally it was decided to test the effect of posture. The patient stated that 20 minutes' vigorous swimming had not precipitated an attack. In our experiment he was instructed to "cycle" on his back, supporting his buttocks on his hands, his flexed elbows resting on the bed. This position over-corrected any possible lordosis. After 10 minutes' vigorous exercise in this position blood was withdrawn from a vein. The serum from this specimen showed no trace of haemolysis, and urine passed shortly afterwards was also clear of protein and of haemoglobin derivatives.

Discussion

Our experiments support the view that exertion haemoglobinuria results from haemolysis during exertion in the erect or extended position. This agrees with the common view. Cases, however, seem to vary in their degree of dependence on the postural factor. Thus in the case recorded by Makin (1944) haemoglobinuria was strictly postural, and did not occur after exercise on a bicycle, whereas in the case recorded by Witts (1936) running with bent back and work on the bicycle ergometer were followed by haemoglobinuria. The postural factor and the common association with lordosis suggest that the condition is allied to orthostatic albuminuria. Bicycle exercise in Makin's case was followed by albuminuria but not by haemoglobinuria. Orthostatic albuminuria was not present in our case.

The failure to demonstrate circulating haemolysin is of little significance and does not rule out the occurrence of intravascular haemolysis; for unless combination with red cells is prevented by special factors, as it is in the case of cold haemoglobinuria, haemolysin liberated into the circulation is likely to be fixed rapidly. In nocturnal haemoglobinuria all efforts to demonstrate circulating haemolysin have failed (Witts, 1936). The failure to demonstrate local haemolysin in muscle is in keeping with the postural features of the disorder and with the view of Witts, who regards the kidney as the source of the haemolysin. He considers intravascular haemolysis "hardly conceivable" in view of the absence of anaemia and the slightness of systemic changes and of haemoglobinaemia; he regards a local haemolysis in the vessels of the kidney as more probable.

According to Whitby and Britton (1944), in exertion haemoglobinuria "there are neither the constitutional symptoms nor the haemoglobinaemia so characteristic of haemoglobinuria from cold." In our case there was a cherry-red concentration of haemoglobin in the serum, and it would seem that the lowering of the blood haemoglobin level was slight because haemolysis was of short duration only, accompanying tiring exertion in the vertical posture. Whitby and Britton state that in cold haemoglobinuria haemoglobin appears in the urine when the free haemoglobin in the plasma exceeds 100 to 140 mg. per 100 ml. This is higher than the plasma haemoglobin level recorded after exercise in Witts's case (46.5 mg.) but considerably lower than that recorded in ours.

History of an injury is another inconstant feature in exertion haemoglobinuria, which, however, helps to incriminate an abnormal kidney as the immediate cause of haemolysin production. No history of injury was elicited in our case, but the disease had come on rather suddenly shortly after a campaign, when slight injuries might have been ignored. In contrast to the usual history, our case resembled that of Witts in showing symptoms for a period (with intermissions) of considerably more than one year. The age at onset of the complaint was much above the average, and it is of interest that the condition recurred with unusual severity when the patient came to the Tropics.

Summary

A case of paroxysmal haemoglobinuria of exertion is described.

Laboratory investigations, including attempts to demonstrate circulating haemolysin, are described and discussed.

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"TRIDIONE" IN THE TREATMENT OF PETIT MAL

BY

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Tridione, the synthetic anticonvulsant drug (3,5,5-trimethyloxazolidine-2,4-dione), has been extensively used in the treatment of the petit-mal epilepsies by investigators in America since 1944.

A Preliminary Investigation

Recently, when supplies became available in this country, a preliminary investigation was made at St. David's Hospital (for epilepsy), the findings of which are tabulated below. Most of the patients (who are sane males suffering from idiopathic epilepsy, and whose ages range from 17 to 56) have been taking the drug for three months.

Tridione is supplied in 0.3 g. capsules. So far it has been found that the apparently optimum dose in the average case is four capsules daily, in divided doses. One patient aged 17, however, has had his petit-mal attacks abolished by taking only two capsules daily. The drug was given in addition to other medication, such as phenobarbitone and "epanutin" (soluble phenytoin), which the patients had previously been taking.

Convulsive seizures of the grand-mal type did not appear to be reduced by tridione in any case, and one man experienced, possibly as a coincidence, an increase in the number of his fits. All the patients suffered from petit-mal except one whose seizures were of the myoclonic type. This man's condition did not improve. Another, however, who had myoclonic spasms as well as ordinary petit mal, states that he feels better than he has done for years.

It is possible that the patients who showed no improvement might have been benefited had they been given more than six capsules daily. Unfortunately a shortage of supplies precluded an increase of this dose.

No. of patients	23
Entirely free from petit mal	4 (17.4%)
Petit mal reduced by more than half	12 (52.2%)
Definite but slighter improvement	2 (8.7%)
No improvement, or toxic symptoms necessitating withdrawal of drug	5 (21.7%)

Because of the notorious difficulty in obtaining an accurate record of petit-mal attacks each patient was given a notebook, and in this he marked down every attack of which he was aware, or which any fellow patient or member of the nursing staff observed. For the purpose of comparison the patients had kept similar records of their attacks for a period of two months before starting tridione medication.

A few days after beginning to take the drug approximately four-fifths of the patients reported a reduction in the number of their petit-mal attacks. After a week or 10 days no fewer than 19 of the 23 patients mentioned that on walking out of a building into the open air they found the