thrombosis of leg veins, was relieved at operation. We suggest that when there is a *sudden* fall in urinary output in a transplanted kidney with established function, thrombosis of the renal vein may have occurred and an early exploration may enable this to be successfully relieved.

We wish to thank Professor J. R. Batchelor for carrying out the tissue typing.

S. D. Clarke, M.Ch., F.R.C.S.
J. A. Kennedy, M.Ch., F.R.C.S.
J. C. Hewitt, M.D., F.F.A. R.C.S.
J. McEvoy, M.D., M.R.C.P.
M. G. McGeown, M.D., Ph.D., F.R.C.P.Ed.
S. D. Nelson, M.R.C.P.I.
Renal Unit, Belfast City Hospital, Belfast.

References

Khastagir, B., Montandon, A., Nakamoto, S., and Kolff, W. J. (1969). *Archives of Internal Medicine*, **123**, 8.
Owen, K. (1969). *British Journal of Hospital Medicine*, **2**, 1216.
Smellie, W. A. B., Vinik, M., Freed, T. A., and Hume, D. M. (1968). *Surgery Gynecology and Obstetrics*, **126**, 777.
Starzl, T. E. (1964). *Experience in Renal Transplantation*. Philadelphia, Saunders.
Walsh, A. (1969). *Transplantation Proceedings*, **1**, 178.

Studies on March Haemoglobinuria

British Medical Journal, 1970, **1**, 155–156

March haemoglobinuria is a transient disorder which occurs predominantly in healthy young men after walking or running. There is only one reported case of its occurrence in a woman. The average duration is from a few months to two years. Davidson (1964) showed that the haemolysis was due to trauma to circulating erythrocytes in the soles of the feet. No underlying defect has been proved to exist.

Case Report

A healthy 24-year-old soldier presented with dark red urine after an 8-mile (13-km.) road run in thin-soled shoes. This event was recognised as march haemoglobinuria. The condition persisted for 12 months and he remained in positive good health. Haemoglobinuria was preceded by excessive aching in the calves during the run. The onset, about 20 minutes after a 6-mile (10-km.) run, was heralded by a sudden aching in the loins. Running in thick-soled shoes or on grass does not result in haemoglobinuria.

The nature of the disorder was explained to the patient when he first presented. He volunteered to be the subject of further investigations.

Methods

Blood was withdrawn without stasis from large antecubital veins and was gently transferred to heparinized bottles and mixed. After brief centrifugation the plasma was aspirated and either treated immediately or stored at −20°C. Serum complement, red-cell fragility, and autohaemolysis were estimated according to Dacie and Lewis (1963). Plasma haemoglobin was estimated by the method of Vanzetti and Valente (1965). The normal range for the conditions pertaining to the present study is 3-10 mg./100 ml. Plasma haptoglobin was estimated by the electrophoretic method of Louderback and Shanbrom (1968). The normal range for the laboratory is 30-150 mg./100 ml. Urine was examined for cystine by the qualitative cyanide-nitroprusside test according to Varley (1967).

Preliminary Investigations

The haemoglobin was 13·6 g./100 ml. The red blood cell indices, white blood cell count, reticulocyte count, erythrocyte sedimentation rate, plasma protein electrophoresis, and serum bilirubin were normal. Wassermann reaction, Ham's test, Donath–Landsteiner test, and direct Coombs test were negative. Cold agglutinins were not detected. Osmotic fragility of red cells was normal. Fetal cells were not seen in 100 high-power fields, and Singer's test for fetal haemoglobin was negative. No abnormal haemoglobin was found. The red blood cell glucose-6-phosphate dehydrogenase, the serum creatine phosphokinase immediately after a run, and a chest *x*-ray examination were normal. Urine examination showed nothing abnormal except for a period of about six hours after a run.

Investigations on Haemolytic Mechanism

The patient and three controls of similar weight made the same run of 6·4 miles (10·3 km.) on a roadway in about 36 minutes. All wore the same pattern of thin-soled shoes. The patient made the test-run six times with a minimum interval of seven days. In run 1 he wore thin-soled shoes. The serum haemoglobin rose 74 mg. and there was heavy haemoglobinuria. In run 2 he wore thick rubber-soled running shoes. The serum haemoglobin rose only 16 mg. and there was no haemoglobinuria (Table I).

For study of the effect of trauma to the hands the patient performed karate-type exercises. These entailed beating the ulnar borders of the hands fast and hard on a wooden block for 20 minutes. Though the serum haemoglobin rose 40 mg., the haemoglobin-binding power of the haptoglobin was not exceeded and haemoglobinuria did not occur. The results are detailed in Table I.

Table I

		Before test	End of run	2 hours	4 hours	6 hours
Blood:						
Plasma haemoglobin (mg./100 ml.)	Run 1	24	98	60	25	7
	Run 2	20	36	20	29	22
	Karate	8	48	18	8	
Plasma haptoglobin (mg./100 ml.)	Run 1	38	46	11	15	16
	Run 2	32	21	5	2	2
	Karate	52	45	25	19	
Serum complement (units)	Run 1	60	64	60	60	64
Blood sugar (mg./100 ml.)		102	148	62	80	80
Urine:						
Albumin	Run 1	—	+ + +	+ +	±	+
	Run 2	—	—	—	—	—
	Karate	—	—	—	—	—
Haemoglobin (mg./100 ml.)	Run 1	—	400	200	±	—
	Run 2	—	—	—	—	—
	Karate	—	—	—	—	—
Sediment	Run 1	Normal. Haemosiderin −	Granular casts + +. Haemosiderin + +	Granular casts + + +. Haemosiderin +	Granular casts +. Haemosiderin ±	Granular casts ±. Haemosiderin −
	Run 2	Normal	Granular casts +	Normal	Normal	Normal
	Karate	Normal	Normal	Normal	Normal	
Cystine	Run 1	Nil	Nil	Nil	Nil	Nil

The results for the controls are recorded in Table II. In two of them slight haemolysis occurred.

TABLE II

		Before run	End of run	2 hours	4 hours
Blood:					
Plasma haemoglobin (mg./100 ml.)	Control 1	3	13	12	4
	Control 2	5	25	18	10
	Control 3	9	10	8	4
Plasma haptoglobin (mg./100 ml.)	Control 1	70	28	13	21
	Control 2	110	100	74	60
	Control 3	110	90	90	90
Urine:					
Albumin	Control 1	—	—	—	—
	Control 2	—	+	±	—
	Control 3	—	—	—	—
Haemoglobin (mg./100 ml.)	Control 1	—	—	—	—
	Control 2	—	—	—	—
	Control 3	—	—	—	—
Sediment	Control 1	Normal	Normal	Normal	Normal
	Control 2	Normal	Granular casts +	Granular casts ±	Normal
	Control 3	Normal	Normal	Normal	Normal

It was noted that the patient had a serum haemoglobin consistently above normal and a serum haptoglobin consistently at the lower end of the normal range. Eight estimations were made on separate days during his normal daily activity as a clerk. He was then confined to bed for six days and the same estimations were repeated. Both the serum haemoglobin and haptoglobin returned to normal during the rest period. The results are recorded in Table III. At the end of the sixth day he made the test run, when haemolysis was greater than on other occasions. The serum haemoglobin rose by 153 mg., compared with the average of 60 mg. (range 40-70 mg.) for the other runs.

TABLE III

	Normal Activity		Bed Rest					
	Range	Average	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Serum haemoglobin (mg./100 ml.)	8–24	17	14	10	11	11	10	7
Serum haptoglobin (mg./100 ml.)	25–57	43	28	35	35	48	50	57

The standard mechanical fragility test was performed on the red cells of the patient and of a control subject from blood taken immediately before and after a run. The test was repeated but extended to four hours instead of one, with samples examined at hourly intervals. It was again performed over four hours at twice the standard rate of rotation. Under these extreme test conditions the percentage haemolysis in both patient and control fell within the normal range of the standard test.

The autohaemolysis test was performed on the patient and a control who had a compatible blood group. Blood was taken from both runners immediately before and after a run. The erythrocytes of each were incubated in his own serum and the serum of the other runner for 48 hours. The results of all these tests were within the normal range.

The amount of erythrocytes haemolysed during the patient's five haemoglobinuric test runs, expressed in volumes of whole blood, ranged from 12 to 32 ml. As the clearance rate of the haemoglobin–haptoglobin complex for this patient is 11 mg. of haemoglobin per hour the maximum possible range is 14-33 ml.

COMMENT

March haemoglobinuria has the hall-marks of acute intravascular haemolysis—namely, a raised serum haemoglobin, lowered serum haptoglobin, and methaemalbuminaemia. If haemolysis is sufficient to exceed the haemoglobin-binding capacity of the haptoglobins, haemoglobinuria and haemosiderinuria result. The cause of march haemoglobinuria has long been debated. Davidson (1964, 1969) reported three cases and produced evidence that the haemolysis was caused by mechanical trauma to erythrocytes flowing through the blood vessels of the feet during running. Buckle (1965) described one case and produced supporting evidence for Davidson's theory. Streeton (1967) reported one case in which haemolysis and haemoglobinuria occurred after trauma to the hands by karate exercises. He suggested that it was a variant of march haemoglobinuria. The investigations performed on the present subject reinforce the view that march haemoglobinuria is a manifestation of traumatic haemolysis.

That haemolysis is excessive for the amount of surface trauma is shown by the results in the patient and controls under the same conditions. It is unlikely that the running style of patients with this disorder is unduly traumatic as the condition is transient, while running styles remain unchanged. There was evidence in this patient that the minor trauma of normal daily activity produced a low-grade haemolytic state. The protective effect of bed rest was demonstrated. Similar findings have been reported by Flatmark (1963) and Balcerzak *et al.* (1966).

The haemolysis of erythrocytes contained in 12-32 ml. of whole blood is equivalent to 0·24-0·64% of the patient's total circulating red cells. Such a small amount of haemolysis occurring during standard autohaemolysis and traumatic fragility tests would fall within the normal range. It is the rate rather than the amount of haemolysis which determines the clinical recognition of march haemoglobinuria. If a red cell abnormality exists it is unlikely to be found by the methods currently used.

It is interesting that the highest recorded level of haemolysis occurred after a period of bed rest. It implies the accumulation either of a serum factor involved in haemolysis or of abnormal red cells. This finding is complementary to previous observations that haemolysis lessens if walking is prolonged. This also implies a limited amount of a serum factor or abnormal red cells. It seems probable that a small fraction of the total red cells is abnormally susceptible to trauma and is rapidly haemolysed in march haemoglobinuria.

Pare and Sandler (1954) found that the urine of 12 patients who had suffered from march haemoglobinuria contained excessive quantities of the amino-acids cystine and beta-aminoisobutyric acid. Cystinuria did not occur in this patient. Lundquist (1965) reported a case in which there was an abnormal rise in the blood sugar level accompanying haemolysis. Hyperglycaemia was not found in this patient.

I thank Dr. C. Cotton Kennedy, Mr. S. G. Welshman, and Mr. J. F. Bell, senior technician, and their colleagues in the pathology laboratory of the Belfast City Hospital for their advice. I thank the patient for cheerfully enduring a large number of investigations.

A. J. SPICER, M.R.C.P.,

Major, R.A.M.C.; the Military Wing, Musgrave Park Hospital, Belfast BT9 7JB.

REFERENCES

Balcerzak, S., Wheby, M. S., Goler, D., and Crosby, W. H. (1966). *Scandinavian Journal of Haematology*, **3**, 38.
Buckle, R. M. (1965). *Lancet*, **1**, 1136.
Dacie, J. V., and Lewis, S. M. (1963). *Practical Haematology*, 3rd ed. London, Churchill.
Davidson, R. J. L. (1964). *Journal of Clinical Pathology*, **17**, 536.
Davidson, R. J. L. (1969). *Seminars in Haematology*, **6**, 150.
Flatmark, T. (1963). *Acta Medica Scandinavica*, **173**, 307.
Louderback, A., and Shanbrom, E. (1968). *Journal of the American Medical Association*, **206**, 362.
Lundquist, A. (1965). *Nordisk Medicin*, **73**, 536.
Pare, C. M. B., and Sandler, M. (1954). *Lancet*, **1**, 702.
Streeton, J. A. (1967) *Lancet*, **2**, 191.
Vanzetti, C., and Valente, D. (1965). *Clinica Chimica Acta*, **11**, 442.
Varley, H. (1967). *Practical Clinical Biochemistry*, 4th ed. London, Heinemann.