MARCH HÆMOGLOBINURIA

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A GENERAL classification of the paroxysmal hæmoglobinurias is as follows: (1) paroxysmal hæmoglobinuria from chilling (syphilitic type); (2) paroxysmal nocturnal hæmoglobinuria in chronic hæmolytic anæmia (Marchiafava-Micheli disease); (3) favism (sensitivity to the products of the plant *Vicia fave*); (4) myoglobinuria ("paralytic hæmoglobinuria"); (5) march hæmoglobinuria; (6) miscellaneous (toxic) hæmoglobinurias, as in severe acute infections, some poisonings, incompatible transfusions.

March hæmoglobinuria is a form of paroxysmal hæmoglobinuria of unknown cause, occurring in certain individuals following exertion in the erect posture. The condition has been reviewed by Gilligan and Blumgart[1] who found 40 cases in the literature and reported extensive observations on three additional cases. All the cases were males and the onset of symptoms was variously between the ages of 16 and 35 years. The hæmoglobinuria appears suddenly without obvious precipitating cause, and runs a benign course of usually less than two years, though it may persist for 20 years. During this period the patients are in apparently excellent health, but suffer recurring episodes in which bloody urine is passed following erect exertion varying in degree from a short fast walk to runs of several miles. A period of such exertion as short as nine minutes may precipitate an attack. In addition to exertion the erect posture is apparently essential to the production of attacks, and in a number of instances it has been shown that comparable exertion in varying degrees of kyphosis will fail to produce an attack.

Gilligan and Blumgart have shown that the attacks consist of a rise in the free plasma hæmoglobin (hæmoglobinæmia) during the exertion, falling abruptly at the end of exertion, and associated with excretion in the urine of a part of the free hæmoglobin (hæmoglobinuria). In their own cases the amount so excreted was always less than 10% of the amount liberated into the blood plasma, and occurred over a period of one to three hours. In exceptional cases the hæmoglobinuria may last 18 hours[2] and, rarely, for three days.[3, 4] The renal threshold for hæmoglobin has been found low in the studied cases, being about 20 mgm. %, compared to the normal threshold of over 100 mgm. %. By spectroscopic methods the pigment in the plasma and urine has been shown to be oxyhæmoglobin.[1, 2]

The first quantitative studies of both plasma and urine were done by Gilligan and Blumgart who found the amount of hæmoglobin involved in a paroxysm to be small, representative of 6 to 40 c.c. of whole blood, and insufficient to cause any demonstrable change in the peripheral red blood cell count or hæmoglobin.

The etiological factors are still obscure; no abnormalities of blood cells have been shown, or hæmolytic agents found. A slightly greater proteinuria than can be accounted for by the excreted hæmoglobin is passed during paroxysms, but not at other times. Between paroxysms there are no abnormal findings in plasma or urine. In other respects the patients are usually in robust good health, many being athletes; the condition is named from the fact that it has occurred in soldiers during a march. Although in some cases varying degrees of lordosis have been noted, other reported abnormalities are uncommon, mild chronic jaundice in three cases, a palpable spleen in one case, palpable enlargement of the liver in three cases. No evidence of renal disease or abnormalities has been found.

The rather alarming appearance of blood-stained urine is usually the only symptom, though in some cases there have been varying degrees of discomfort in the abdomen and lumbar region during paroxysms. The general belief has been that the raised plasma hæmoglobin is due to hæmolysis of a relatively small amount of blood, induced in some way by exertion in the erect posture, and it has been variously suggested that this may occur locally in the kidneys; that it may be related to orthostatic albuminuria; that extravascular hæmolysis may occur in the spleen; or that there may be venous stasis in the abdominal viscera. Supporting evidence for all these concepts has been completely lacking. Attempts to reproduce the attacks in the same patients by means other than exertion in the erect posture have failed (except for one of the cases reported by Witts[2] in which hæmoglobinuria followed the severe exertion of running up and down one thousand steps, keeping bent over as much as possible. As it is difficult to run downstairs bent forward, part of this exertion may have been erect).

Since early in 1940 there have been admitted to Canadian General Hospitals overseas 4 cases of march hæmoglobinuria in a total of over 75,000 admissions. Owing to its benign course, patients exhibiting the syndrome may not reach hospital, and the incidence is probably greater than the above figures would indicate. In an unselected group of 22 marathon runners Gilligan and Blumgart found three cases of frank hæmoglobinuria and noted that 18 of the 22 men showed plasma hæmoglobin values above normal at the end of a race.

Two patients with this syndrome have been admitted to a Canadian General Hospital in the past year and their findings are to be reported here.

CASE 1

Pte. R.A.P. White Canadian, aged twenty-one years. Infantryman. In excellent health till the end of February, 1942, when during route marches he began to suffer abdominal discomfort "rising from the groins", followed by the passing of blood-coloured urine. Symptoms would last two or three hours, promptly clearing at rest, but have recurred on every route march since. Admitted in March, 1942, general examination and genito-urinary investigations were negative, so he was returned to duty. Re-admitted July 28, 1942, with a history that symptoms had recurred after every route march in the interval.

Enquiry revealed that he had lived all his life in Canada till coming to England in the army. His civilian occupation was poultry ranching and tire repairing, not as energetic as army life. He enlisted in January, 1940. No chronic complaints or past illnesses recalled, except for a minor scrotal injury at football, when twelve years old, when the penis oozed a little blood, but this cleared up in two weeks without recurrence. Family history negative for hæmorrhagic or other chronic disease.

Examination revealed a robust young man, of good colour, energetic, height 5′ 8″, weight 170 lb., pulse 60 to 70, blood pressure 120/80. Spleen palpable for two fingersbreadths below the costal margin; liver not enlarged. Slight left varicocele, otherwise general examination negative. An attack was induced by a march of eight miles and he was cystoscoped. The bladder contained some reddish brown urine and dark smoky urine was seen spurting in a normal flow from each ureteral orifice. This urine contained only rare red blood cells, but gave a strongly positive benzidine reaction.

The patient remained under observation from July 28 to November 10, 1942, during which time the observations detailed below were made. He remained afebrile throughout, felt well, was willing and energetic in assisting about the ward and appeared to be in robust general health. His only symptoms were the passing of red or brown urine as a consistent sequel to a brisk walk of two miles or more, and occasional minor abdominal discomfort during these marches. The spleen diminished in size and was not palpable during October. His weight remained unchanged. Early in November, 1942, it became impossible to induce paroxysms and he was discharged in apparent remission, having exhibited symptoms for over eight months. Prior to discharge his medical category was lowered as a temporary expedient to avoid vigorous exertion until it should become certain that an exacerbation would not occur. This was done because of the theoretical risk that frequently-repeated prolonged paroxysms might result in renal damage from precipitation of the hæmoglobin in the tubules.

LABORATORY FINDINGS

Urinalysis.—(1) At rest (many specimens): usually acid, specific gravity 1.012-30. Negative. (2) After paroxysms: dark red-brown albumin one plus, rare red cells, marked positive benzidine reaction.

Cystoscopy and pyelography.—No evidence of structural abnormality found. X-ray plates in supine and erect postures revealed no evidence of renal ptosis.

Blood count.—July 28, red blood cells 4,600,000; Hgb. 84% (12.2 grm., Hellige); white blood cells 6,300; polymorphonuclears 72; lymphocytes 26; eosinophiles 2. October 26, red blood cells 4,910,000; Hgb. 83% (12.0 grm., Hellige); white blood cells 7,600; polymorphonuclears 70; lymphocytes 25; eosinophiles 1; monocytes 4. No abnormalities of the erythrocytes in stained smears or fresh wet suspensions before or after paroxysms. Rouleaux formation occurs equally rapidly. No evidence of malarial parasites.

Erythrocyte fragility.—Hæmolysis begins at 0.40% saline before and after a paroxysm.

Reticulocytes.—Less than 0.5% with no rise after a paroxysm.

Bleeding time.—Four minutes (normal one to three minutes).

Clotting time.—Eight minutes (normal five to ten minutes).

Blood sedimentation rate (Wintrobe tubes).—Two mm. fall in one hour.

Blood Wassermann and Kahn tests.—Negative.

Plasma protein (estimated by the falling drop method): 6.84 grm. before, 6.90 grm. after a paroxysm.

Blood van den Bergh.—0.6 mgm. % before, 1.2 mgm. % after one paroxysm.

Plasma chlorides.—577 mgm. % before and after one paroxysm.

Donath-Landsteiner test for cold hæmolysins (done in the presence of guinea pig complement).—Negative on blood obtained before and after a paroxysm.

Test for sensitivity to cold (Rosenbach).—Immersion of the four extremities in ice water for forty minutes failed to produce a paroxysm. (Ordinarily the test is done for ten minutes).

Spectroscopic examination of blood plasma and urine following a paroxysm were kindly done by Dr. E. J. King and Mr. G. E. Delory of the British Postgraduate Medical School. Employing the Hartridge reversion spectroscope, the band for oxyhæmoglobin was found prominent in all specimens of blood plasma, no other bands being visible. In the specimen of urine the bands of hæmoglobin could not be distinguished, nor could the band of methæmoglobin be produced with ferricyanide. Several ill-defined bands could be seen which were probably due to a mixture of hæmatin and hæmochromogens formed from altered hæmoglobin (the specimen was unfortunately four days old at the time of the examination).

Quantitative estimations of the blood plasma and urine hæmoglobin were done following some of the paroxysms and at rest and the findings are shown in Table I.

CASE 2

Pte. K.B. Aged 19 years. White, Scottish-Canadian. Infantryman. Admitted November 7, 1942, with a history of good general health except that four months prior to admission following a twelve-mile forced march during a period of about two hours, his urine was dark reddish-brown for about twelve hours. Similar episodes which cleared more quickly followed every march of two miles or more, and were sometimes accompanied by a vague nausea, but he suffered no other discomfort and was not disabled. Prior to admission he noted attacks less frequently. About a month after the onset of this urinary symptom he suffered a minor enteritis for several weeks, had a persistent chest cold for some weeks prior to admission, and has always suffered a tendency to train or car sickness. As a child he had nocturia and in the past two years has noticed some minor burning on urination. Scarlet fever and mumps as a child

were the only illnesses recalled. No family history of hæmorrhagic or other chronic disease.

Examination revealed a slender youth, temperature 98°; pulse 80; blood pressure 130/70; height 5′ 9″; weight 140 lb. Good colour, looks well, apart from some undernutrition; no postural abnormalities. A few firm glands were present in the anterior cervical triangles but there was no general adenopathy. The lungs were clear. A soft systolic murmur confined to the apex was noted. The liver and spleen were not enlarged. General examination otherwise negative.

Urinalysis (resting, several specimens).—Negative.

Blood Kahn (two specimens).—Negative.

Blood sedimentation rate (Wintrobe tube).—Six mm. in one hour.

Blood count.—Red blood cells 4,420,000; hgb. 92% (13.13 grm.); white blood cells 9,800; polymorphonuclears 69; lymphocytes 31.

X-ray of chest.—Negative.

Intravenous pyelogram.—No abnormalities of structure or position.

Test for sensitivity to cold (Rosenbach).—Following immersion of hands and feet in ice water for thirty minutes no hæmoglobin appeared in the urine, and the

TABLE I.

HGB. ESTIMATED IN BLOOD PLASMA AND URINE

Date	*Length of walk*	*Elapsed time*	*Blood plasma Hgb. mgm. %*	*Total Hgb. excreted in urine*	*Remarks*
Oct. 9	Resting	....	3.9	....	
	1 mile	....	13.7	nil	
Oct. 10	Resting	....	6.5		
	2 miles	....	15.4	nil	
Oct. 11	Resting	....	4.2		
	4 miles	....	32.8	2 plus	
	1 hr. after	....	14.9		
	2¾ hrs. after	....	6.7		
	2nd exercise—				
	2 miles	....	17.2	nil	
	1 hr. after	....	11.2		
	2 hrs. after	....	7.8		
	3½ hrs. after	....	8.1		
Oct. 12	4 miles	....	37.0	93.3 mgm.	With abdominal binder.
Oct. 13	2 miles	....	17.54	nil	
Oct. 14	2 miles	....	20.57	trace	
Oct. 15	2 miles	....	13.08	nil	
Oct. 16	4 miles	47 min.	25.5		Standing continuously after exercise.
	1½ hrs. after	....	13.4		
	3 hrs. after	....	12.5	85 mgm.	
	4 hrs. after	....	8.4		
	5 hrs. after	....	7.6		
Oct. 17	4 miles	47 min.	23.0		Lying down immediately after march.
	1½ hrs. after	....	8.5		
	3 hrs. after	....	5.2	13.5 mgm.	
	4 hrs. after	....	4.6		
Oct. 18	Resting	....	4.6		Standing continuously after exercises.
	8 miles	92 min.	22.4		
	45 min. after	....	14.8		
	95 min. after	....	9.5		
	2½ hrs. after	....	5.8		
	3½ hrs. after	....	5.4	18.9 mgm.	
	4½ hrs. after	....	3.2		
Oct. 22	Resting	....	3.7		Lying down immediately after exercise.
	8 miles	100 min.	40.3		
	½ hr. after	....	31.8		
	1½ hrs. after	....	16.6		
	2½ hrs. after	....	8.8	90 mgm.	
	3 hrs. 35 min. after	....	6.2		
Oct. 24	8 miles	92 min.	33.8		Standing after exercise.
	15 min. after	....	28.3		
	95 min. after	....	11.2		
	150 min. after	....	11.8	85 mgm.	
Oct. 25	8 miles	94 min.	35.7		Standing after exercise with abdominal binder.
	1 hr. 35 min. after	....	16.8		
	2½ hrs. after	....	11.0		
	3½ hrs. after	....	7.9	203 mgm.	

blood plasma level was 4 mgm. % by the benzidine method.

Donath-Landsteiner reaction (done without guinea pig complement).—Negative.

Considerable difficulty was experienced in inducing an attack, although the blood plasma was always slightly pink at the end of exertion. Only one typical attack occurred under observation; following an eight mile run in 93 minutes the plasma hæmoglobin was 24 mgm. % and 68 c.c. of reddish brown urine containing 46.4 mgm. of hæmoglobin was passed within two hours. As the patient was apparently entering a remission observations were discontinued and he was discharged, having experienced symptoms less than five months.

DISCUSSION

Case 1 afforded an opportunity for detailed observation and a number of studies were done with particular reference to possible etiological or contributing factors. No abnormalities were noted in the blood cells, ordinary plasma constituents or urine, before or after a paroxysm, apart from the hæmoglobinæmia, hæmoglobinuria and slight albuminuria after erect exertion. Blood counts were not done following each paroxysm, but the fact that the counts were so similar at the beginning and end of the three months' study, during which about 40 paroxysms were induced, is contributory evidence that only small amounts of blood were involved in the episodes (see Table II) and is in keeping with the findings of previous observers.[1] Attempts to reproduce attacks by fever, multiple minor traumata, exercise in recumbency or on a bicycle, or to influence attacks by ascorbic acid, alkalinization of the urine, wearing of a tight abdominal binder, were all negative (see appendix).

TABLE II.

RELATIONSHIPS OF BLOOD PLASMA AND URINARY FINDINGS IN CASE 1.

Date	*Hgb. level in blood plasma mgm. %*	*Total Hgb. excreted in urine. mgm.*	*Calculated % of Hgb. excreted in urine.**	*Calculated total amount of blood involved expressed as c.c. of whole blood.**
1942				
Oct. 9	3.9	nil	..	....
Oct. 11	4.2	nil	..	....
Oct. 10	6.5	nil	..	....
Oct. 9	13.7	nil	..	2.6
Oct. 10	15.4	nil	..	2.9
Oct. 11	17.2	nil	..	3.3
Oct. 14	20.57	trace	..	4.0
Oct. 18	22.7	18.9	2.8	4.3
Oct. 17	23.0	13.5	2.0	4.4
Oct. 16	25.5	85.0	11.1	4.9
Oct. 24	33.8	85.0	8.3	6.5
Oct. 25	35.7	203.0	18.9	6.8
Oct. 12	37.0	93.3	8.4	7.1
Oct. 22	40.3	90.0	7.4	7.9

*Based on an assumed total plasma volume of 3,000 c.c.

Quantitative measurements of the plasma and urine hæmoglobin following some of the induced paroxysms were done, using the benzidine method of Bing and Baker[6, 7] for all estimations except early in the study in the instances referred to in the appendix. Care was taken to avoid hæmolysis in obtaining the plasma specimens and the technique of Gilligan and Blumgart[1] was followed. In Table I are listed all observations done by the benzidine method, and some of these are regrouped in Table II or shown graphically in Figs. 1 and 2. Plasma hæmoglobin values up to 40.3 mgm. % after exertion and resting values from 3.2 mgm. % to 6.5 mgm. % were found. Hæmoglobinuria occurred with plasma hæmoglobin values of 20.7 mgm. % and over (Table II), so that the renal threshold in this case is about 20 mgm. %.

The amount of hæmoglobin excreted in the urine was usually found to be considerably less and never greater than 19%, assuming a total blood plasma volume of 3,000 c.c. and assuming all the hæmoglobin involved to be represented by the value in the plasma at the end of the exertion. The hæmoglobin excretion in the urine usually ended before two hours and always before three hours. The calculated total amount of whole blood represented by the plasma hæmoglobin in solution was always small, varying from 4 to 8 c.c. where hæmoglobinuria occurred (Table II). These findings approximate those of Gilligan and Blumgart, who found, however, some plasma hæmoglobin values representing as much as 40 c.c. of whole blood, and found no urinary excretion greater than 10%.

Fig. 1 shows the time in which hæmoglobin is cleared from the plasma in all the paroxysms that were so observed. The curves show that the plasma hæmoglobin concentration begins to fall as soon as exertion ceases (note a single observation at each of a 15-minute, 30-minute and 45-minute interval) and approaches the normal resting values in about three hours. The higher plasma hæmoglobin values have an initial greater rate of fall. These findings are similar to those of Gilligan and Blumgart and approximate findings in hæmoglobin injection experiments in normal beings.[12]

It has always been assumed that the increased plasma hæmoglobin or the hæmoglobinuria is due to active hæmolysis caused in some unknown manner during erect exertion, although, as in these cases, no contributory abnormalities of blood, urine or tissues have ever been demon-

strated. Watson and Fischer[13] suggest that such hæmoglobinuria may be "an exaggeration exemplified in certain predisposed individuals, of a more or less naturally occurring phenomenon", but they do not enlarge the concept. There is another possible source of the hæmoglobin involved that, as far as we know, has not been explored hitherto. In all individuals there is a continual destruction of senile erythrocytes, liberating hæmoglobin which is apparently rapidly taken up by the reticulo-endothelial system. That some of this hæmoglobin enters the plasma in solution in some stage of this process is suggested by resting plasma hæmoglobin values of about 5 mgm. % in normal persons.[1] In regard to the amount of hæmoglobin that could be available in this normal process no reliable estimates can be made until the normal life span of the erythrocyte is settled. The evidence on this point varies from figures of one to two weeks[8] to one hundred days,[9] though some authorities[10, 11, 14] conclude, following reviews of the literature, that the average life of the erythrocyte is about thirty days under normal conditions. If this were so, in an individual with a total blood volume of 5,000 c.c. there would be a daily destruction of about 166 c.c. Assuming this normal blood destruction to be a continuous process throughout the twenty-four hours, there would be available each hour the hæmoglobin from about 7 c.c. of whole blood. This would be sufficient to produce all the paroxysms in the present cases (Table II).

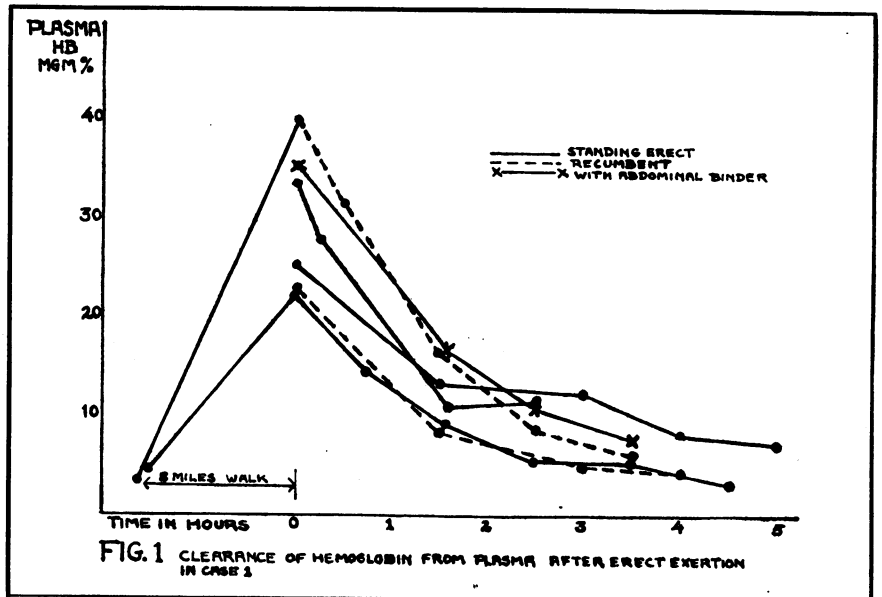

FIG. 1 CLEARANCE OF HEMOGLOBIN FROM PLASMA AFTER ERECT EXERTION IN CASE 1

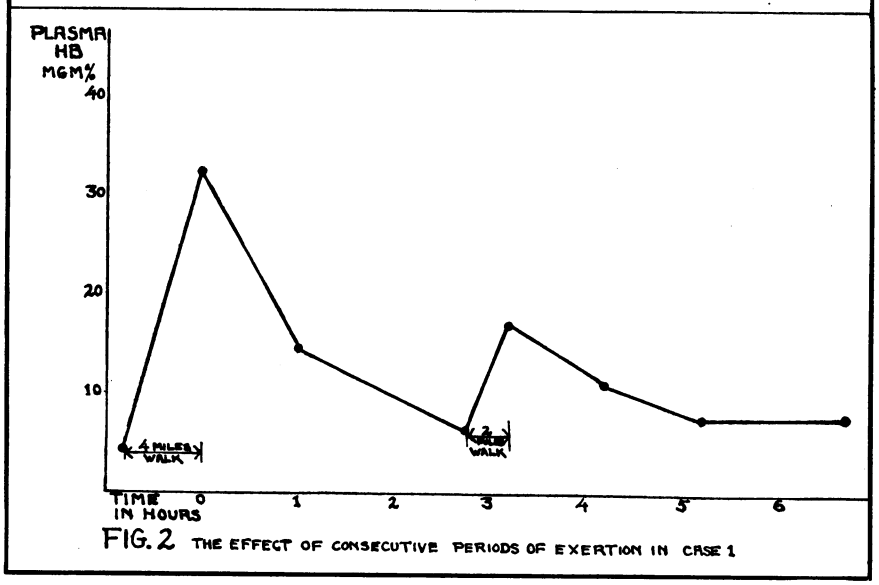

FIG. 2 THE EFFECT OF CONSECUTIVE PERIODS OF EXERTION IN CASE 1

If, as in the case of many other body processes, the rate of normal blood destruction is greater during hours of activity than at rest, this figure may be considerably higher. On the other hand if the average life of the erythrocyte is greater than thirty days these estimated figures for available hæmoglobin through such a process would be correspondingly reduced. Should the average erythrocyte span approach one hundred days the foregoing estimates would be reduced to about one-third, which would be insufficient to supply the observed paroxysms unless the amount of hæmoglobin liberated is greater at periods of increased circulatory activity than at rest.

At all events it seems possible that such a source could contribute largely, if not all, the hæmoglobin involved in the paroxysms. What occurs during erect exertion therefore may not be an active hæmolytic process but rather some

abnormality which permits the accumulation of hæmoglobin in the plasma by interfering with the removal of normally liberated hæmoglobin. Such interference could occur if a part of the circulating blood were not sufficiently exposed to the clearing mechanism, as by a diminished circulatory rate in the viscera or extremities, or, if the clearing mechanism suffered a relative failure of function, possibly by some temporary mechanical interference with the circulation of such major portions of the reticulo-endothelial system as are contained in the liver, spleen or bone marrow. If such a general concept were correct it would imply that cases of march hæmoglobinuria suffer no more hæmolysis than in normals, but that, during erect exertion plasma hæmoglobin rises, due to some interference with its normal removal.

As the urobilinogen of the stool is almost exclusively derived from hæmoglobin, and as usually less than 10% of the hæmoglobin is excreted in the urine, one would expect that a paroxysm due to increased hæmolysis would be followed by an increased stool urobilinogen output. Admittedly, episodes involving such small amounts of blood as 8 c.c. or occasionally up to 40 c.c. may require methods of stool analysis beyond the present limits of accuracy. Stool analyses were not done in our patients, though they were reported by Gilligan and Blumgart[1] who found the stool urobilinogen output within normal limits in the presence or absence of paroxysms. The range in their findings (106 to 156 mgm. of stool urobilinogen per day) is such that, apart from the fact that they are within normal limits, no conclusion can be drawn and more detailed studies are apparently necessary to determine whether significant information about the etiology of the paroxysms can be obtained from this source.

Our attempts to find evidence of such a factor as some local circulatory impairment by observing paroxysms with a tourniquet to one leg (appendix) or applying a tight abdominal binder (appendix and Fig. 1) were without result. Attempts to demonstrate some inefficiency of the reticulo-endothelial system by effecting some change in the rate of hæmoglobin clearance from the plasma were also failures. Reported attempts[1] to produce attacks by prolonged standing in the lordotic posture have been negative, but it was considered possible that after attacks posture might influence the rate at which plasma hæmoglobin is cleared. On different days paroxysms were induced in case 1 and immediately following each exertion the patient was kept either standing in a lordotic posture or put in recumbency. Fig. 1 shows the plasma hæmoglobin values obtained at the end of erect exertion and at subsequent intervals; it would appear that no significant effect of posture was demonstrated. The curves are similar to those obtained by hæmoglobin injection experiments in normal persons[12] and in the previously reported cases of march hæmoglobinuria,[1] which suggests that in these cases at rest the reticulo-endothelial system is normally efficient in this function.

However, Fig. 1 does show one feature that may be of importance, namely, the rather abrupt manner in which plasma hæmoglobin values drop following the cessation of exertion; note some of the values obtained 15, 30 and 45 minutes after the end of exertion. It is reasonable to expect that if the paroxysms were due to increased hæmolysis from some hæmolytic agent liberated during exertion there would be a period of lag following exertion during which hæmolysis would continue, as one would not expect the hæmolytic agent to disappear immediately. On the other hand, if the paroxysms are due to some mechanism which interferes with clearance of hæmoglobin from the plasma during erect exertion one would expect the interference to cease as soon as the erect exertion ended.

The effect of a second period of exertion following paroxysms was observed. It was thought possible that if the reticulo-endothelial system were in some way inefficient a paroxysm might be more easily induced near the completion of hæmoglobin clearance from an initial paroxysm. A paroxysm with a resulting plasma hæmoglobin value of 32.8 mgm. % and unmeasured hæmoglobinuria was induced by a brisk march of four miles. At the end of two hours and forty-five minutes following this, the plasma hæmoglobin value had dropped to 6.7 mgm. % and the urine was clear. The patient was then sent on a brisk march of two miles with a resulting plasma hæmoglobin value of 17.2 mgm. % without hæmoglobinuria (see Table II). The plasma hæmoglobin values are graphically shown in Fig. 2. The results from the second exertion were not materially different from those produced by similar single periods of exertion at other times (see Table I) and afforded no evidence of reticulo-endothelial inefficiency from overloading.

Finally, an opportunity arose to study the plasma hæmoglobin levels in a patient convalescing from splenectomy, following rupture of the spleen. Plasma hæmoglobin values of 3.3 mgm. % before and 3.78 mgm. % immediately after a brisk march of four miles were found, no hæmoglobinuria resulting. This indicates that the loss of such a fraction of the reticulo-endothelial system as is contained in the spleen is not sufficient, even temporarily, to impair the function of plasma hæmoglobin clearance in a normal individual.

It was planned to observe plasma hæmoglobin values at intervals during a period of exertion as it was thought likely that if the paroxysms were due to a hæmolytic process there would be a more or less continuous rise no matter how long exertion were sustained, whereas if the process was one of failure to clear normally liberated hæmoglobin there would probably be a rise to a plateau. Unfortunately, the patients entered remissions before this or other studies could be done.

In conclusion, no evidence of inefficiency of the reticulo-endothelial system, or of failure of the circulating blood to expose itself sufficiently to the action of the reticulo-endothelial system has been found. What evidence we have suggests that at least in the resting state the mechanism of plasma hæmoglobin clearance is normally active. What happens during erect exertion in these patients is still unknown.

Certain considerations lead us to believe that the hæmoglobinæmia characteristic of the paroxysms may not be due to increased hæmolysis. These are: (1) the failure of all observers to demonstrate hæmolytic agents or blood abnormalities predisposing to increased hæmolysis; (2) the amount of hæmoglobin involved in all the paroxysms in our cases and in most of the paroxysms in other reported cases could be liberated in the normal destruction of senile erythrocytes; (3) within fifteen minutes of the end of exertion producing paroxysms the plasma hæmoglobin values begin a significant drop toward the resting normal level, whereas, if some hæmolytic factor were involved one would expect a longer lag; (4) the previously reported observations on fæcal urobilinogen excretion, while not conclusive, suggest that during paroxysms there may be no increase in blood destruction.

SUMMARY

Two cases of march hæmoglobinuria are reported, in one of which some detailed observations were possible. The pathogenesis of the syndrome is still unknown, but a theory is advanced which suggests that the paroxysms are not due to increased hæmolysis but to some unknown abnormality present during erect exertion interfering with the clearing from the plasma of the hæmoglobin liberated in the normal destruction of senile erythrocytes.

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APPENDIX

The following observations were done on Case 1:—

Urine test for hæmolysins.—It was considered possible that a hæmolytic substance might be concentrated in the urine despite the failure to demonstrate the presence of hæmolysins in the plasma. Urine specimens were obtained before and after a paroxysm and in several dilutions up to 1:8 in normal saline were mixed with equal parts of 5% suspension of red blood cells. The suspensions were kept in a water bath at 37° C. for two hours and then allowed to stand at room temperature for fourteen hours. No gross evidence of significant hæmolysis was observed.

Vitamin C saturation.—The finding of a low 24 hour urinary vitamin C output (4.4 mgm.) together with the report that attacks would be prevented by the administration of cevitamic acid[5] suggested the possibility that vitamin C might be a significant factor. Ascorbic acid in dosage of 600 mgm. daily was given for fourteen days at the end of which time the 24 hour urine contained 181.6 and 184 mgm. on two consecutive days. Throughout this period no change in the character of typical paroxysms was noted though hæmoglobin values in plasma and urine were not estimated.

Alkalinization of urine.—A daily dosage of 240 grains of soda bicarbonate for ten days, producing a strongly alkaline urine, was without apparent effect on the paroxysms.

Trauma test.—To investigate the possibility that the multiple minor traumata of vigorous walking might play a rôle, a crude experiment was devised in which the seated patient was passively raised and dropped to produce a bump at the rate of about 100 per minute. This was sustained for two and a half hours

without apparent gross effect on plasma or urine. The fragility of the red blood cells to trauma was found normal by Gilligan and Blumgart.[1]

Vigorous exercise in various postures.—Supervised vigorous exercise in the recumbent posture for two and a half hours was without gross effect on plasma or urine. Strenuous exercise for three and a half hours on a bicycle failed to produce hæmoglobinuria or hæmoglobinæmia, the blood plasma hæmoglobin being 5.3 mgm. % after the test. An attempt was made to determine the degree of kyphosis necessary to prevent a paroxysm, using a plaster jacket as suggested by Gilligan and Blumgart.[1] However, at the time it was done the patient was apparently entering a remission and the findings were inconclusive.

The effect of fever.—The possibility of some abnormal response to raised body temperature as a factor seem excluded by the observation in this case that induced fever of 105° for two and a half hours produced no gross changes in plasma or urine.

The effect of venous stasis.—Gilligan and Blumgart were unable to demonstrate hæmoglobinæmia in a limb which was exercised in the presence of venous stasis produced by a tourniquet. In Case 1 of our group a rubber band was applied above the left knee sufficiently tight to produce engorgement of the distal veins. A typical paroxysm was then induced and blood plasma specimens were obtained from the left antecubital vein, the right femoral vein and the left anterior tibial vein. Plasma hæmoglobin values were determined by a spectroscopic colorimeter and found to be 156 mgm. % in all. This method gives values that are considerably higher than those found by the benzidine method, and was abandoned by us. However, the identical plasma hæmoglobin values from all sources may have some significance and suggests that venous stasis is not a factor in this syndrome.

Abdominal compression. — Some intra-abdominal abnormality permitting venous stasis or interfering with the circulation in important organs as the spleen or liver, have been considered as a possible factor.[1] If so, the application of a tight abdominal binder might have some significant effect either of aggravation or amelioration. The effect of this was observed in Case 1 on several occasions without apparent effect on the degree of hæmoglobinuria as estimated crudely by the use of a Sahli hæmoglobinometer. On the one occasion in which the exact measurements of plasma and urine hæmoglobin were done by the benzidine method, no significant effect on the paroxysms was noted. See Fig. 1 and Table I.

A person with a recently acquired gonorrhœal or syphilitic infection is a most valuable public health asset. . . . Throughout our communities run the ever ramifying, ever multiplying threads of venereal infection —threads of a web, which, hidden by prudery and submerged by sophistry, catches countless men, women and children in its meshes of ill health and death. The patient with a recent venereal infection has touched that hidden net-work somewhere; that is why he is ill; that is why he is seeking help from his physician. This patient has information which can initiate action that will expose a portion of the dank mesh to the wholesome light of modern medical science and public health influence, action which will remove unsavoury community influences which make it easy for healthy persons to touch the foul web of community venereal disease—D. H. Williams: *Canad. J. Pub. Health,* 1943, **34**: 395.

INTERNAL DERANGEMENTS OF THE KNEE JOINT IN THE CANADIAN ARMY (OVERSEAS)

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THE high incidence of incapacitating knee injuries among soldiers on active service led to the investigation upon which this report is based. In order to assay the results of surgical treatment and to evolve a more or less uniform policy of management for such cases, it was obvious that a thorough follow-up study should be undertaken. This task was greatly facilitated by the co-operation of the Department of Records and by the individual efforts of hospital administrative personnel and the medical officers concerned. Direct contact with most of the doubtful cases was established through the A.D.M.S., Canadian Reinforcement Units.

In the opinion of many, the advisability of operating upon soldiers because of internal derangements of their knees has been a moot point. One feels that, in this respect at least, the evidence now available justifies a more conclusive attitude in favour of surgical intervention.

MATERIAL AND FOLLOW-UP

During the two and one-half year-period prior to December, 1942, internal derangements of the knee joint necessitated 463 arthrotomies in General Hospitals* of the Canadian Army (Overseas). At the time this series was reviewed, 370 cases were of sufficiently long standing to warrant assessment. Among these, 39 non-Canadian soldiers were lost to follow-up; the documents of 11 others had been returned to Canada; and 17 were not identifiable in the records. The remaining 303 provided the information which is presented in this text.

Field units yielded 77% of the operative material and Base or Reinforcement units, the balance. The postoperative follow-up period was as follows:

Duration	*Percentage*
3– 6 months	25
7–12 "	24
13–18 "	26
19–24 "	15
25–30 "	10

* The cases under consideration were treated in six Canadian General Hospitals by some two dozen general surgeons, including four orthopædic specialists.