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ADDENDUM.—Two years after completing its first tour, the Northamptonshire Mass Radiography Unit went round the county again. The final results of this survey are not yet available, but a preliminary inspection of the records suggests that the incidence of newly discovered active pulmonary tuberculosis among male boot and shoe operatives is now no higher than among men in other occupations. The exact significance of this finding cannot be appreciated until it is known how many of these men were examined for the first time; how many were new entrants to the industry; what type of case was discovered; and what was the age distribution of the population examined. It is, however, likely that boot and shoe factories in Northamptonshire are already reaping the benefits of having had a thorough comb-out of chronic carriers during 1945-6.

HAEMOPHILIA ASSOCIATED WITH NORMAL COAGULATION TIME

BY

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Haemophilia is a condition which has attracted considerable interest, and the clinical and laboratory features of the typical syndrome are well recognized. The average case presents no difficulty in diagnosis and can be recognized with a high degree of certainty. The means by which this is accomplished are the family history, the clinical picture, and the laboratory findings.

Family History and Clinical Picture

Haemophilia is "an inherited tendency in males to bleed" (Bullock and Fildes, 1911). It is transmitted by apparently unaffected females. No other haemorrhagic diathesis with this type of inheritance has yet been described. The absence of such a history need not exclude the diagnosis, as apparently sporadic cases are not uncommon: they accounted for 39% of cases met with in one series (Merskey, 1950b).

The chief symptom is severe and often almost uncontrollable haemorrhage from even minor injuries. These haemorrhages may occur from skin and mucous membranes, into muscles and especially into joints. It is a severely disabling condition, the patients being constantly exposed to the risk of haemorrhage and often being

crippled by the ankylosis of joints which so constantly follows the repeated haemarthroses. Very few haemophiliacs are able to lead normal lives, and the mortality rate in childhood and adolescence is considerable.

Laboratory Findings

The bleeding time, platelet count, tourniquet test, and plasma prothrombin, factor V, and fibrinogen are all normal. On the other hand, the coagulation time is prolonged and prothrombin is not adequately consumed during coagulation of the blood.

The lengthening of the coagulation time of the blood is the best-known laboratory abnormality of haemophilia. Conflicting views have been expressed about whether a normal coagulation time can occur in haemophilia. Davidson *et al.* (1949) stated that they had never seen it. Birch (1937) stated that in mild haemophilia it might be normal at intervals, and Whitby and Britton (1946) that it might be almost normal between the attacks of bleeding. Quick (1949) reported a series of 24 haemophiliacs, 7 of whom had a Lee and White coagulation time of under 10 minutes, and he commented that in mild haemophilia the coagulation time could be normal; a similar statement was made by Tocantins (1949).

Brinkhous (1939) was the first to demonstrate defective consumption of prothrombin during coagulation of haemophilic blood, and this has since been confirmed (Quick, 1947; Soulier, 1948; Alexander and de Vries, 1949; Merskey, 1950a). By comparing the amount of prothrombin in the plasma with that present in the serum of blood clotted in glass tubes the amount of prothrombin "consumed" during coagulation can be measured. Normally, most of the prothrombin is converted to thrombin and very little remains in the serum. In haemophilia the serum often contains as much as the plasma and, for reasons not at present fully explained, in many cases apparently even more.

Patek and Stetson (1936) showed that there was a substance present in normal blood which was absent or unavailable in haemophilic blood. This substance, sometimes called antihæmophilic globulin, when added in small proportion to haemophilic blood shortened the coagulation time of the latter and also improved its prothrombin consumption defect (Quick, 1947; Soulier, 1948; Alexander and de Vries, 1949; Merskey, 1950a).

The absence of antihæmophilic globulin in haemophilic blood can be used as a diagnostic test for this condition. This can be demonstrated by adding to known haemophilic blood minimal proportions of the blood of a patient suspected of having haemophilia. If the suspected blood proves incapable of correcting the coagulation time and prothrombin consumption defect, the patient probably has haemophilia. If it can correct these defects of haemophilic blood to some extent, but not to that produced by an equal proportion of normal blood, it is probable that the patient has the haemophilic defect, but in less degree.

By the use of this test in a large series of haemophilic patients I was able to show (Merskey, 1950b) that varying grades of the haemophilic defect did exist. At the one extreme there were the classical haemophiliacs with prolonged coagulation time, grossly defective prothrombin consumption, and inability to correct haemophilic blood; at the other extreme patients with normal coagulation time, a much milder prothrombin consumption defect (in some instances no demonstrable defect at

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all), and a partial ability to correct haemophilic blood. Between the two extremes all grades of these defects were found.

It is the purpose of this paper to describe the clinical features of patients in whom the coagulation time was normal or near normal, and whose blood possessed some ability to correct the defects of known haemophilic blood. In no instance was this ability equal to that of normal blood. In the series of 54 patients (Merskey, 1950b) the coagulation time was greatly prolonged in 33, slightly prolonged in 12, and not at all prolonged in 9. The patients to be described belong to the second and third groups.

Case Histories

The family trees in each of the eight families are shown (Figs. 1-8). An analysis of main symptoms in available cases is shown in Table I, and the laboratory findings are summarized in Tables II and III.

Fig. 9 demonstrates the relative inability of the plasma of patients IV 5 of family 1 and IV 6 of family 3 to

correct that of a haemophiliac with prolonged coagulation time. Fig. 10 shows the same phenomenon with regard to patient IV 16 of family 4, while that for IV 3 of family 5 is shown in Fig. 11. This test was carried out on the blood of at least one member of each of these eight families.

Family 1

The inheritance of the disease in this family follows the classical course, and at least seven members show symptoms of haemophilia (Fig. 1).

III 7 and III 8 are affected in much the same way. Cuts and scratches usually bleed little more than normal. Occasionally haemorrhage is troublesome. They both bruise easily and have considerable haemorrhage after dental extraction, when they may bleed for two to three weeks. The elder has had no joints involved, but the younger has had swelling of one ankle, which occurred after only mild trauma, and swelling of the knee-joint following a severe injury.

IV 4, 5, 6, and 7 are all affected in the same way, though IV 6 is even less affected than the others. All except IV 6

TABLE I.—Analysis of Main Symptoms in all Available Cases

Family	No.	Year of Birth	Severity of Bleeding		Bruises	Epistaxis	Bleeding After Dental Extractions	Haemarthroses			Gastro-intestinal Haemorrhage	Haematuria	Personal Interrogation
			Usual	Occasional				No. of Joints Involved	Following Obvious Injury	Residual Ankylosis			
1	III 7	1895	Normal	Excessive	Frequent	?	Severe	0	—	—	Nil	Nil	No
	III 8	1908	"	"	"	?	"	2	No	Nil	"	"	"
	IV 4	1925	"	"	"	Frequent	"	1	Yes	Slight	Once after injury	"	Yes
	IV 5	1930	"	"	"	"	"	1	No	Nil	Nil	"	"
	IV 6	1930	"	Normal	"	"	"	1	Yes	"	"	"	"
	IV 7	1930	"	Excessive	"	"	"	1	"	"	"	"	"
	IV 7	1930	"	"	"	"	"	"	"	"	"	"	"
2	I 1	?	?	"	?	?	?	0	—	—	?	Occasional	No
	III 7	1912	Normal	"	Frequent	?	Severe	2	No	Nil	Once	Nil	Yes
	III 8	?	"	"	"	Nil	"	0	—	—	?	"	No
	IV 1	1939	?	"	?	?	?	?	?	?	?	?	"
	IV 3	1944	Normal	"	Frequent	Frequent	?	1	Yes	?	?	?	"
3	IV 6	1933	"	"	Nil	"	Severe	1	"	No	Nil	Nil	Yes
4	III 19	1908	"	"	Frequent	"	"	0	—	—	"	"	No
	IV 14	1930	"	"	"	Nil	"	0	—	—	"	"	"
	IV 16	1937	"	"	"	Frequent	"	0	—	—	"	"	Yes
5	IV 3	1932	"	"	"	"	"	4	No	Nil	"	"	"
6	V 4	1913	"	"	"	"	"	Multiple	"	Yes	Frequent	Frequent	"
7	III 5	Died aged 45	"	"	"	Occasional	"	4	"	Nil	"	Nil	No
	III 6	Died aged 23	"	"	"	"	—	4	"	"	"	"	"
	III 7	1911	"	"	"	"	Severe	4	"	Yes	Nil	"	"
	III 8	1914	"	"	"	"	"	1	Yes	Nil	Frequent	"	Yes
8	IV 30	1921	"	"	"	"	"	2	No	"	Nil	Once	"
	IV 32	1926	"	"	"	Frequent	"	2	Yes	"	"	Nil	"
	IV 17	1939	"	"	"	"	"	4	No	Slight	"	"	"
	IV 12	1946	"	"	"	"	—	1	"	Nil	"	"	"

TABLE II.—Blood Coagulation Times and Interpretation as Reported by Other Observers

Family	Patient	Year	Coagulation Time (Seconds)	Method	Interpretation
1	IV 4	1928	207	Dale & Laidlaw	Prolonged
	IV 4	1938	180	"	"
	IV 5	1932	220	"	"
	IV 7	1935	220	"	"
2	IV 1	1941	155	?	Slightly prolonged
	IV 3	1943	180	?	Raised
	IV 3	1949	—	—	Normal
4	III 19	1950	450	"Capillary"	Slightly prolonged
5	IV 3	1936	—	?	Normal
	IV 3	1946	200	—	" (!)
	IV 3	1946	330	Dale & Laidlaw	" (!)
6	III 8	1949	—	—	Normal
8	IV 12	1947	660	Dale & Laidlaw	Prolonged

have had at least one severe bleeding episode which continued for days. These episodes usually followed injuries to lips or tongue. Generally cuts have bled little if at all more than would be expected in a normal person, and haemorrhagic episodes of any degree were separated by years. Small bruises were common, and occasional large bruises after injuries have taken weeks to subside. In all four patients haemorrhage occurred when the milk teeth were lost, and considerable bleeding followed tooth extraction. All have had one, and at most two, episodes of haemarthrosis, though with one exception these followed quite severe trauma. The only apparently spontaneous haemarthrosis was in IV 5, who twice had a swollen hip-joint without obvious injury. IV 4 has a little residual ankylosis of a knee-joint; also he once vomited some blood and had a melaena stool following a "heavy fall." IV 7 once fell off a bicycle and bled intraperitoneally, requiring blood transfusion. They have all had frequent epistaxis, but none has had haematuria.

TABLE III.—Laboratory Findings Observed at Radcliffe Infirmary

Family	Patient	Date	Coagulation Time and Method Used				Prothrombin Consumption Index %		
			Lee & White	Dale & Laidlaw	Quick's Test (Seconds)		Source of Serum		
			(Individual Tubes) (in Minutes)	(Seconds)	Slow Spun	Fast Spun	Whole Uncitrated Blood	Citrated Plasma Recalcified	
							Venous	Capillary	
1	IV 4	Nov., 1949	9½, 9½, 9½, 11	205	—	—	60	12	25
	IV 5	Nov., 1949	9½, 10, 11½, 23	—	—	—	—	—	—
	IV 6	Nov., 1949	8, 8½, 9, 11½	200	—	—	47	<5	75
	IV 7	March, 1950	9, 10½, 10½, 12	—	258	547	—	—	—
2	III 7	April, 1949	7½, 8, 8, 8	135	—	—	133	—	—
	III 7	Nov., 1949	8, 8, 8½, 9	165	—	—	115	<5	<5
	III 7	Feb., 1950	9½, 7½, 12, 8	165	172	347	90	—	26
	III 7	Feb., 1950	9½, 7½, 12, 8	165	—	—	—	—	—
3	IV 6	June, 1949	4½, 9, 6½, 8½	—	—	—	24	—	—
	IV 6	Nov., 1949	7½, 8, 8, 8	152	—	—	41	12	—
	IV 6	March, 1950	7½, 7½, 7, 7½	185	204	270	19	<5	13
	IV 6	March, 1950	7½, 7½, 7, 7½	185	—	—	—	—	—
4	IV 16	Feb., 1950	9½, 9½, 9½, 10½	190	225	430	36	<5	45
	IV 16	Feb., 1950	9½, 9½, 9½, 10½	190	—	—	—	—	—
	IV 16	Feb., 1950	9½, 9½, 9½, 10½	190	—	—	—	—	—
	IV 16	Feb., 1950	9½, 9½, 9½, 10½	190	—	—	—	—	—
5	IV 3	Dec., 1946	12½, 12½, 13, 12½	200	—	—	—	—	—
	IV 3	May, 1949	8½, 8½, 8½, 14½	125	—	—	88	—	32
	IV 3	Nov., 1949	5½, 7½, 7½, 8	153	—	—	74	<5	7
	IV 3	Jan., 1950	9, 9½, 9½, 9½	155	187	250	—	—	—
6	V 4	March, 1942	13½	—	165	225	—	—	—
	V 4	Feb., 1946	7½, 8, 8, 9½	—	—	—	—	—	—
	V 4	Aug., 1949	7, 7, 6½, 9	155	—	—	65	—	—
	V 4	Aug., 1949	6½, 6½, 6½, 7	—	—	—	75	—	—
7	III 8	Jan., 1950	12½, 13½, 13½, 13½	—	—	—	—	—	—
	III 8	Jan., 1950	14, 15½, 13, 15½	160	259	353	94	<5	115
	III 8	Feb., 1950	9, 11½, 14, 14	—	—	—	—	—	—
	III 8	Feb., 1950	9, 11½, 14, 14	—	—	—	—	—	—
8	IV 12	Nov., 1947	11½, 13, 26, 46	—	214	364	—	—	—
	IV 12	Nov., 1949	6, 6, 7	255	222	290	113	16	100
	IV 17	April, 1949	9, 10, 10½	170	—	—	44	—	—
	IV 30	Nov., 1949	10½, 11, 10½, 14½	318	—	—	48	6	80
8	IV 32	March, 1950	10½, 12, 12, 12	230	274	500	74	<5	31
	IV 32	March, 1950	11½, 12, 12, 11	260	—	—	83	<5	43

Family 2

The inheritance of the disease in this family is classical, and at least five members appear to be affected (Fig. 2).

I 1 had epistaxis, haematuria, and severe bleeding from cuts, but no joint lesions. He died at the age of 87.

III 7 hardly bleeds at all from small cuts, but on occasion larger cuts have bled for hours. He once bled for a month after extraction of four teeth, and on another occasion

FIG. 1.—Family 1.

FIG. 2.—Family 2.

haematemesis and melaena were severe enough to warrant urgent blood transfusion. He has had two episodes of haemarthrosis (knee and metatarso-phalangeal joint). He bruises easily and has frequent epistaxis.

III 8 bled severely from tooth extraction and also from cuts. He bruised easily but had no swollen joints or epistaxis. During military service he was accidentally shot in the pelvis and died a week later, supposedly from haemorrhage.

IV 1 had two episodes of severe haemorrhage following cuts on lip and tongue. He died at the age of 6 from a "fractured neck."

IV 3 bruises easily and has much epistaxis. On one occasion he had a swollen ankle-joint, and he once bled so severely from a cut lip that he required blood transfusion.

Family 3

Apart from a very doubtful history of bleeding in the second generation there is no family history of haemorrhage (Fig. 3).

II 4 bled severely after tooth extraction and once after injury, but not after severe war wounds.

II 15 had epistaxis on several occasions.

IV 6 bled severely after circumcision and from minor cuts and scratches. He has had repeated epistaxis and bled severely after loss of milk teeth and on extraction of others. On one occasion, after being knocked down by a bicycle, a knee-joint became swollen, but this soon subsided. There is one spider naevus on the left side of his nose.

Family 4

The inheritance in this family is once again classical for haemophilia, at least 10 members being affected (Fig. 4).

FIG. 3.—Family 3.

FIG. 4.—Family 4.

IV 14 bruised easily but had no epistaxis, haematuria, gastro-intestinal bleeding, or swollen joints. Tooth extractions bled for one month despite blood transfusion. He died at the age of 5½ after tonsillectomy. Haemostasis had been secured at operation, but fatal bleeding began seven days later.

III 19 and IV 16 have similar histories. Cuts have often bled very little, but on a number of occasions haemorrhage has continued for weeks. Bleeding for two to three weeks has also followed tooth extraction, while epistaxis has been frequent and severe. They bruise very easily. IV 16 plays cricket and soccer for his school team. III 19 has been an epileptic since the age of 7.

Family 5

It has been possible to trace only one affected member in this family (Fig. 5).

IV 3 bled severely after circumcision. He has also bled for weeks after biting his tongue or cutting his finger or lip and after dental extraction. On a number of occasions his life was saved only by urgent blood transfusion. He has always bruised easily, has had repeated epistaxis, and both ankles and both shoulder-joints have become swollen and painful. These swellings have subsided after a few weeks and left no residual deformity.

Family 6

There is one apparent discrepancy in this large and otherwise typical family history of haemophilia, as III 9 is stated to have been normal (Fig. 6).

FIG. 5.—Family 5.

FIG. 6.—Family 6.

FIG. 7.—Family 7.

FIG. 9.—Shortening of calcium time of known haemophilic plasma produced by blood of patients IV 5 of family 1 and IV 6 of family 3 as compared with that of a normal control. Note the relative inability of the patients' blood to correct the known haemophilic blood. The percentage of plasma added is plotted on a logarithmic scale. The calcium time of the haemophilic plasma alone was 765 seconds.

FIG. 10.—As for Fig. 9. Patient IV 16 of family 4, a normal control, and the mother of the patient. The calcium time of the haemophilic plasma alone was 502 seconds.

FIG. 11.—As for Fig. 9. Patient IV 3 of family 5 and a normal control. The calcium time of the haemophilic plasma alone was 287 seconds.

The readings remained relatively constant over prolonged periods, and the short coagulation times were not due to a fluctuation of a prolonged coagulation time towards the normal range (Tables II and III). Many patients stated that their blood tests had always been found to be normal. There seemed little doubt that the normal coagulation time was a constant feature.

Quick's test for haemophilia measures the increase in the calcium clotting time produced by centrifuging oxalate plasma to precipitate platelets. Quick (1941) claimed that this increase was much greater in haemophilic than in normal plasma. Since the calcium time of normal oxalate plasma may, on occasion, be increased by 100%, Quick's test will be significant only if the increase exceeds this figure. Such increases occurred in only two out of nine tests performed in this series. The test was therefore of little value in the diagnosis of these cases. Similar results were obtained in cases of haemophilia with prolonged coagulation time (Merskey, 1950b).

Prothrombin Consumption Index

With serum from whole clotted venous blood or recalcified citrate plasma the normal range for this test is always under 40% and often under 20% (Merskey, 1950a). In the 14 patients of this series this test gave abnormal readings in 11 instances, while 3 came into the normal range. In the usual case of haemophilia with prolonged coagulation time values of over 100% and even up to 200% are commonly encountered, but such readings were only exceptionally seen in this series. When the test was done on the serum from clotted capillary (finger-prick) blood normal results were obtained in all cases.

Titration of Antihæmophilic Globulin

This test was carried out on the blood of at least one member of each of these families, and the result showed a deficiency of this substance when compared with a normal control. From the fact that these patients could improve to some extent the defects of known haemophilic blood it seemed likely that they had less of the haemophilic defect and possibly more available anti-haemophilic globulin than did cases of haemophilia with prolonged coagulation time. This test was used as the final test in doubtful cases.

Discussion

In these patients the clinical symptoms varied in degree from mild to severe, but remained relatively constant in any particular family. Patients in families 1 to 5 had a mild clinical syndrome, those in family 8 were a little more severely affected, while those in families 6 and 7 were severely incapacitated. Where the syndrome was mild and crippling haemarthroses were absent the patients were able to lead relatively normal lives. One of the adults worked as a lorry driver, and several of the younger patients engaged in strenuous sports.

The symptoms were those of classical haemophilia, but the hæmorrhagic episodes were often widely separated. Small wounds as a rule gave very little trouble, and cuts and scratches bled no more than would be expected in normal individuals. Yet most of the patients had had at least one severe bleeding episode requiring urgent blood transfusion and even seeming to threaten life. Dental extractions were especially troublesome, severe bleeding often continuing for days or weeks. One patient died after tonsillectomy and another bled for many weeks after laminectomy

and required in all 63 blood transfusions to control haemorrhage (Schiller, Neligan, and Budtz-Olsen, 1948). It is possible that surgery is safer in this type of haemophilia than in the type with prolonged coagulation time, but, even so, the risk of haemorrhage is formidable.

Epistaxis and easy bruising were practically invariable. The latter symptom is uncommon in normal males, and more than one intelligent mother in a haemophilic family had diagnosed haemophilia in her infant son on this symptom alone. If the trauma was severe enormous bruises might be produced.

Haemarthroses were infrequent, and this fact provided a very striking difference between this syndrome and that of haemophilia with prolonged coagulation time. If they did occur they were only rarely apparently spontaneous and usually followed severe injury. Frequently only one joint was involved, and the swellings might last for only a week or two and leave slight deformities. As a result most of the adults were not incapacitated by ankylosed joints and were thus able to follow relatively normal lives.

Inheritance.—In the six families, in which there was a familial history this closely resembled the classical inheritance of haemophilia, there being only two apparent discrepancies (family 6, III 9; family 8, I 3). Both these patients were alleged to be normal.

The various members and generations of the same families all seemed to have the same type of clinical picture and degree of laboratory abnormality. The syndrome thus appeared to breed true.

The importance of the recognition that haemophilia can occur with a normal coagulation time cannot be overstressed. Many of these patients had been told that surgery could safely be undertaken, and it was only after alarming haemorrhage had occurred that it was realized that the advice given had been incorrect. These patients must be regarded as haemophiliacs with all the serious implications of that diagnosis.

There are only very scanty references to this syndrome in the literature. The references to haemophilia with normal coagulation time cited earlier also mention a milder syndrome of haemophilia (Birch, 1937; Quick, 1949; Tocantins, 1949). Fowler (1949) stated that some cases of haemophilia are mild, while Sköld (1944) described some cases of haemophilia with normal coagulation time and without haemarthroses. Some of his cases had a normal coagulation time and a mild syndrome, while others in the same family had a prolonged coagulation time and a more severe syndrome. The only extensive papers on this syndrome are those of Davenport (1930) and Haldane (1935), both of which discuss some haemophilic families in whom the clinical picture appeared to be mild. Unfortunately laboratory data are too scanty to be of value.

Summary

The pathology of haemophilia is reviewed. It is pointed out that the disease occurs in varying grades of severity as estimated both clinically and in the laboratory.

Cases occurring in eight families are described in detail because, as part of a larger survey, they were all found to have normal coagulation times, and the other commonly practised blood tests were also normal in the majority of instances. The bloods of these patients were poor at shortening the calcium time and correcting the prothrombin-consumption-defect of known haemophilic blood, however, and clinically there was no doubt whatsoever that these people had haemophilia.

Attention is drawn to the danger of relying on the common bleeding and clotting tests to exclude the possibility of haemophilia.

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THE MYRMECIA

A STUDY OF INCLUSION BODIES IN WARTS

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[WITH SPECIAL PLATE]

The infective nature of warts was first convincingly demonstrated by Jadassohn (1896), who had 33 positive inoculations out of 86 attempted. Ciuffo (1907) found that the infectious agent present in ground wart tissue would pass Berkefeld N, and Serra (1908), Wile and Kingery (1919), and Kingery (1921) Berkefeld W filters. Passage of experimentally produced warts to the second generation was achieved by Tuccio and Coppolino (1912), Kingery (1921), and Ullmann (1923-4). The elementary bodies of human wart virus have never been described, and the evidence for the viral aetiology of warts rests upon the above experiments.

Histological Appearances

On the assumption that warts were due to a virus we looked for inclusion bodies in sections of warts taken from a pilot series of 10 cases. The wart tissue was curetted under local analgesia, and was fixed in formol-Zenker and stained with haematoxylin and eosin. We found that five of the patient's warts contained eosinophilic intranuclear and intracytoplasmic bodies in the prickle-cell layer (Plate, Fig. 1), and in the belief that these were inclusion bodies we named these warts type I, for "inclusion." Warts from the remaining five