THESIS

for the degree of M.D., EDINBURGH UNIVERSITY

on

HAEMOPHILIA

A sketch of our present knowledge of the disease, with results in eight cases of the effect of normal serum on the blood coagulation time.

by

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GENERAL INDEX.

CHARTS.

X ray Photographs, with descriptive notes, in separate volume of Illustrations.

INTRODUCTION.

By the term "Haemophilia", we understand a congenital condition whose main symptom is a tendency to severe bleedings, either internally or externally, affecting generally more than one member of a family, usually the males, and existing during the whole period of the individual's life.

The subjects of Haemophilia are generally known as "bleeders" - a term which was first applied to them by Otto, an American writer.

HISTORY.

Cases of uncontrollable haemorrhage have long been recognized and numerous clinical cases have been recorded. On careful examination, many of these, however, appear not to be cases of true haemophilia, therefore only those which really at all approach the clinical picture of this condition are referred to in this short résumé.

The first of these is to be found in the writings of Abulcasis al-Zaharavi (1), an Arabian surgeon/

surgeon, born in Cordova and living about A.D. 1000. He states that in a certain village there were men who lost so much blood, when injured or "bled", that death would often follow. The boys suffered similarly, if their gums were harshly rubbed, and haemorrhage was a common cause of death amongst them. In 1539, a case was described by Alexander Benedictus (2) of a Venetian barber, who died of haemorrhage from his nose, which he had accidentally cut with his scissors.

In 1674, Philip Hoechstetter (3) described the case of a boy, who at birth bled from the umbilicus and later suffered from epistaxis, bruises and melaena.

In 1743, three cases were described by du Gard (4), Ash (5) and Clopton Havers (6), in the Philosophical Transactions of the Royal Society.

In 1793, an important note, written by an anonymous author - supposed to be a Dr.Consbruch (7)- in the Medicinische Ephemeriden, published at Chemnitz, on this condition, is worthy of special mention, being the first reference to Haemophilia as a disease by itself. The following translation is interesting:-

"On the 4th November, I was called to the "country/

"country to see a boy of 11 years, who two days "before had slightly cut his thumb. All medical "applications proved unable to stem the haemor- "rhage, and before I was able to arrive he had bled "to death. A brother of this boy had a few years "before died from the results of a slight cut, "while several brothers of the mother have similar- "ly met their end. All females in this family are, "so far as I am aware, free from this unhappy "idiosyncrasy; they menstruate normally, and are "quite healthy. The males are extraordinarily "liable to bleed from the nose, when the blood may "readily become abundant and hurry them to the "grave. This, as regards its physiology and patho- "logy, is a curious circumstance, which, as yet, "I am unable to explain fully."

In 1793, a case was described by Alexander Rave (8). About this time American physicians seem to have taken up the study of the subject; thus, in 1803. Otto (9) published "An account of an haemorrhagic disposition existing in certain families", and described amongst others a family of bleeders from New England, in whom the disease could be traced back for 80 years. He stated that "males "only are affected and all are not liable to it; "though/

"though females are free, they are capable of "transmitting it to their children". The word "bleeder" is used in Otto's paper for the first time, "for this is the name given to them". This publication was translated into several languages, and stimulated others to publish similar cases, so that by 1805 Haemophilia had begun to attract attention.

In 1813, Dr. John Hay (10) of Reading, Mass. reported for the first time the now famous Appleton Swain Family, referred to more recently by Osler (11) and Pratt (12), the former of whom states that the tendency to bleeding in this family has shown itself lately in the seventh generation.

In 1817, Drs. William and Samuel Buels (13) described a family from Litchfield, Conn. in the members of whom the condition was well marked.

From this time little is heard of the American physicians, and Germany appears to have taken up the lead, for in 1820, Nasse (14) collected and compiled all the material on the subject which had thus far been written, and published a résumé of all of it that was worth preserving, adding at the same/

same time his own observations on the disease. He was thus the first to give it prominence in medical literature. He asserted that "males alone are the "subjects of haemophilia, and that the disease "is transmitted by normal females through their "marriages with normal males". This assertion is referred to in subsequent publications as "Nasse's Law".

Later, Schönlein proposed a name for the disease, and introduced it for the first time into Systematic Pathology.

In 1849, Wachsmuth (15) added many new observations to the literature, and it was he who first pointed out the prolific tendency met with in Haemophilic families.

In 1854, Virchow (16) wrote upon this disease, and three years later described the post-mortem changes to be found in such cases. The main facts he thought important enough to note were :-

(a) The smallness of the heart.

(b) A condition of narrow, thin-walled blood vessels.

(c) Fatty changes in the endothelium.

(d) Swelling of the spleen.

(e)/

(e) An increased vascular network of the cutaneous capillary vessels.

In 1855, Grandidier (17) published his treatise, which still retains its place as a standard work on the subject, and is still quoted in many papers; though much of his work, and especially his statistics, have now been proved to be inaccurate.

In 1861, Gavoy (18), in France, described the microscopical examination of the blood vessels, and gave an analysis of the blood.

In 1865, Otto (19) reported a further analysis of the blood, and pointed out the effects of climate upon the disease.

In this country, the first to write on haemophilia was Blagden (20), in 1817, who was followed in 1819 by Wilson (21), but very little of a systematic nature was done till 1872, when Wickham Legg (22) published his "Treatise on Haemophilia", and was the first to write a really good critical review of the subject up to this time. Shortly after this, Sir William Jenner described the morbid anatomy of the tissues and joints in Haemophilia.

In 1876, Immermann (23) wrote a most exhaustive and authoritative work on the subject, and brought out a theory depending upon the following/

following four factors, which he maintained produced a condition of plethora, with resultant haemorrhage.

(a) Feeble development of the blood vessels, leading to a diminution in their capacity.

(b) Hypertrophy of the heart, and a consequent high blood pressure.

(c) An increase in the quantity of the circulating blood, and lastly,

(d) An abnormal action of the vasomotor nervous system.

In 1882, Rothschild (24) wrote an interesting article, pointing out that haemophilia must have been known to the ancient Jews. He cites the case of four women who were sisters. The first of these had a male child, who died from haemorrhage after circumcision, likewise the second sister's child had a similar fate, and so also the third. The fourth sister then went to the Chief Rabbi, and got a dispensation from the rite, when her child should have been circumcised. As this Rabbi lived in the second century A.D., it is claimed that this is the oldest/

oldest reference to the disease. A further proof that the condition was not unknown to the ancient Jews is the fact that special dispensations were granted, if two sons of a boy's maternal aunts had died from the operation.

For the last few years, the subject of haemophilia seems to have aroused fresh interest, and a great deal of work is being carried out by both European and American writers, with a view to evolving some theory of causation which will account for all the symptoms met with in this interesting disease.

AETIOLOGY/

AETIOLOGY and PATHOLOGY.

Many theories have been propounded from time to time, to explain the nature of Haemophilia. It may be interesting to briefly review the older, before enlarging upon the modern views held concerning it. Many post-mortem examinations have been recorded, but very few structural changes in the body have been met with. Krimer considered haemophilia a form of "congenital arthritic dyscrasia", while Schliemann (1831) regarded it as a particular modification of scrofula; Grandidier (1855) thought there was a relationship between this disease and the rheumatic disposition, whilst Vogel maintained its identity with scorbutus. Virchow looked to the spleen for an explanation, and this for two reasons, firstly, because he held that this organ was intimately connected with the formation of blood, and secondly, he believed that haemophilia consisted in a defective composition of the blood - this latter view is interesting when compared with modern theories which attribute the disease to an abnormal condition of the blood.

Wachsmuth (15) and others, however, repudiated/

repudiated this theory, for they found in their examinations that "the blood in bleeders is by no means defective, either in its organization or composition, and that when care is taken to collect and test the first blood which flows, the latter is found to coagulate readily and to be no lighter in colour than usual".

Later, Virchow, having abandoned his previous views, attempted to sketch out a mechanical explanation, and pointed out the following facts in support of this:-

(a) The superficial position of the cutaneous vessels;

(b) The thinness of the walls of the arterial vessels;

(c) Abnormal narrowness of the larger arteries;

all these bringing about "a fluxionary diathesis with a tendency to profuse haemorrhage", and he maintained that "the blood supply in these persons is habitually in excess of the capacity of the vessels".

Other writers, again, regarded haemophilia as due to a deranged innervation of the vessels.

In conclusion, Immermann (23) gives the following/

following account of the disease, which may be taken as a résumé of the older views on Haemophilia.

"Haemophilia is, in general, a congenital "and habitual form of the haemorrhagic diathesis, "in which the frequently recurring and readily in- "duced haemorrhages probably, in most cases, owe "their extraordinary vehemence, obstinacy and "danger to an equally congenital and habitual dis- "proportion between the volume of blood and the ca- "pacity of the vascular apparatus, resulting in "an abnormal increase of the lateral pressure "within the vessels. In many instances, moreover, "functional erethism of the heart and hypertrophy "of the cardiac musculature, by inducing a ten- "dency to congestions, also aid to an important "degree in producing the haemorrhages, and in "giving them their abnormal clinical character. "Finally, neurotic influences may perhaps oc- "casionally act as an additional factor, by tem- "porarily increasing the permanent congestive "diathesis."

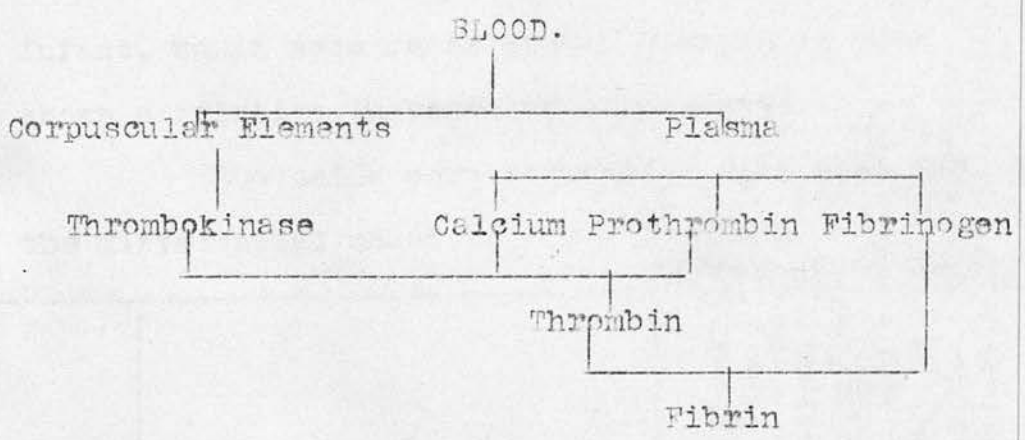
In more recent times, as methods of investigation became more exact and scientific, and more attention was beginning to be paid to the examination of the blood, the older theories on Haemophilia/

Haemophilia began to be modified and new views expounded, until at the present time all modern writers are fairly well agreed that the chief cause of the disease is to be found in some defect in the coagulability of the blood. Opinion, however, is still by no means unanimous as to the factor or factors at work in bringing about this pathological state. Some writers are not satisfied that this is the only cause of the symptoms met with, and maintain that other factors come into play as well.

Wright (25) was the first to definitely prove that there was a delay in the Coagulation Time of the blood in Haemophilia. At first, his opinions were not generally accepted, as similar results were not got by all other workers. These discrepancies, however, were soon rectified by Sahli (26), who explained that the coagulation time should be estimated only during the normal inter-haemorrhagic periods, and not during or immediately after a severe haemorrhage, at which time the Blood Coagulation was more rapid.

The exact nature of the defect in the blood is still a disputed point, and will not be cleared up with certainty until the process of normal blood coagulation has been elucidated beyond doubt./

doubt. At present, the generally accepted view of coagulation is that of Morawitz (27), who attributes it to the presence of a substance - thrombokinase - which is the main connecting link between the calcium salts and the prothrombin in forming thrombin. He does not think the thrombokinase is present normally in the circulating blood, but is got from leucocytes and blood platelets after the blood is shed; while the prothrombin is normally present in solution in the blood plasma. Morawitz's scheme of coagulation, therefore, is as follows:-



Sahli, at first, differed from Morawitz, in that he thought the thrombokinase was either absent or deficient in the tissues, and not the corpuscles, but later came to agree with him. Both Sahli and Wright found a leucopaenia in bleeders - especially/

especially of the polymorphonuclear corpuscles - and the latter further found that this leucopaenia extended likewise to all the other members of a haemophilic family.

In ignorance of this latter assertion, three "non-bleeder" relations of the series of cases under review were examined, with a view to determining the number and differential counts of their white blood corpuscles. Unfortunately, these were seen only once, so that only one result was got in each case, but none of them showed a polymorphonuclear leucopaenia, except the third, who, being just an infant, would even under normal conditions have shown a relative increase of lymphocytes.

300 cells were counted in each case for the differential count.

Date.	"Non-bleeder" Relations.	White Blood Corpuscles.	Differential Count. Polymorphonuclear cells. percentage.	Lymphocytes percentage.	Eosinophiles percentage.
14·6·10.	Sister of Case II. age 15	9,375	70	29	1
5·6·10.	Brother of Case V. age 17	8,125	73	26	1
9·7·10.	Infant brother of Case VI.	14,375	60·5	39	·5

Wright/

Wright states that a polymorphonuclear diminution is associated with conditions in which there is found to be a diminished blood coagulation, and that per contra an increase of these corpuscles is associated with an increased blood coagulation. To show that this is not always so, there may be cited only the case of typhoid fever.

This disease presents a leucopaenia (28) with relative decrease of polymorphonuclear corpuscles (i.e., in uncomplicated cases), and yet Addis (29) found, as the result of a series of tests, that the coagulation time was shorter than normal.

The following results of differential counts taken in the eight cases under discussion likewise do not support this view. (300 cells were counted in each case.)

TABLE/

TABLE of DIFFERENTIAL COUNTS.

CASE I.

Date.	White Blood Corpuscles	Differential Count. Polymorpho-nuclear Cells percentage.	Lympho-cytes percentage.	Eosino-philes percentage.
13·2·09.	6,875	72	27·5	·5
3·4·09.	14,062	75·5	25	·5
5·4·09.	10,313	73	26	1
14·11·09.	13,125	74	25	1
21·11·09.	8,125	73	25	2
28·11·09.	9,400	73	25·5	1·5
12·12·09.	7,167	75·5	24	·5
19·12·09.	8,125	70	29	1
26·12·09.	9,620	71	28	1
9·1·10.	10,200	74	25·5	·5
20·2·10.	11,000	74	25	1
27·2·10.	9,000	75	24	1
6·3·10.	10,800	78·5	20·5	1
13·3·10.	9.687	74	26	0
10·7·10.	15,937	79	20	1
24·7·10.	11,608	72	27·5	·5
14·8·10.	8,750	69	30	1
22·1·11.	10,506	72	26	2
19·4·11.	8,432	70	29	1
20·4·11.	10,312	72	27	1
21·4·11.	8,437	69	30	1
22·4·11.	8,125	72·5	27	·5

SISTER/

Date.	White Blood Corpuscles	Differential Count. Polymorpho-nuclear Cells percentage.	Lympho-cytes percentage.	Eosino-philes percentage.
		SISTER OF CASE II. (Non-bleeder)		
14·6·10.	9,375	70	29	1
		CASE III.		
29·5·10.	7,187	75	24	1
31·7·10.	8,437	74	25	1
		BROTHER OF CASE V. (Non-bleeder)		
5·6·10.	8,125	73	26	1
		CASE VI.		
24·7·10.	5,600	68	30	2
		INFANT BROTHER OF CASE VI. (Non-bleeder)		
9·7·10.	14,375	60·5	39	·5
		CASE VII.		
9·8·09.	14,062	78	21·5	·5
16·8·09.	10,312	76	23·5	·5
31·8·09.	9,000	69	30	1
12·2·10.	10,000	68	31	1
26·2·10.	10,625	68·5	31·5	0
20·9·10.	8,125	69	30·5	·5
7·9·11.	15,000	77	22	1
29·9·11.	11,200	70	30	0
15·10·11.	5,625	68·5	31	·5
22·10·11	5,000	68	31	1
		CASE VIII.		
12·2·10.	10,200	65	34	1
26·2·10.	9,194	70	29	1

Wright/

Wright has shown that a local thrombosis may be produced by an intravenous injection of nucleo-albumin - thus increasing the venosity of the blood to that area, and he was of opinion that this thrombosis was caused by an increased content of CO_2 in the blood, or, in other words, that this condition induced an increase of blood coagulability. Thus may be explained the frequent onset of haemorrhage in haemophilia during the night, the CO_2 content in the blood being diminished, with consequent decreased coagulability. Most of the cases recorded here showed this nocturnal onset very markedly. It was a common occurrence for these patients to wake in the morning with some swollen and painful joint, bleeding gums, or some other haemophilic manifestation. In Case I., this is especially well illustrated, for recently he has bled from a tooth stump for over a week, and he says that, though the bleeding frequently stops during the day, it always starts again at night when he is in bed, so much so, that he shrinks from going to sleep, and being an observant patient, he has himself often remarked that his symptoms, more frequently than not, come on during the night without obvious cause. Case VI. likewise illustrates this fact very markedly, for example./

example, he developed during the night, without obvious cause, a painful swelling of the left ankle on the 8th July 1910, the right hand on the 27th July 1910 and the right wrist on the 15th September 1910.

Case VII. - the left ankle on the 6th September 1910 and Case VIII. - the gums, on the 31st August 1909.

Wright also showed that, in cases where there was a delay in the coagulation time of the blood, there was also a deficiency of calcium salts, later, however, he modified his views on this subject, and admitted that the administration of these salts did not invariably have the desired effect of reducing the blood coagulation. In many cases it has a beneficial effect, in small doses, but if given in large doses, it tends to have an opposite effect. Addis (30) made extensive researches in this connection, and got results which were directly opposed to Wright's views on the subject.

Finally, Wright, while refraining from stating any definite theory of blood coagulation, nevertheless gives the following as a working hypothesis, to account for the decreased coagulation in Haemophilia.

(a)

(a) Some defect in calcium metabolism.

(b) A diminution in the number of leucocytes.

(c) A lack of fibrinoplastic substances in the tissue fluids, which mix with the escaping blood.

(d) A decreased content of CO_2 in the blood.

Sahli (26) agrees that the diminution in the blood coagulating power is the constant character of Haemophilia. As to the cause of this phenomenon, he found that it was the absence of thrombokinase, and that traces of normal blood or serum could, if added to haemophilic blood, restore the power of coagulating. Morawitz found similar results. Sahli pointed out that the substance existing in normal blood and wanting in haemophilic blood was affected by heat, as thrombokinase ought to be, and that the difference between normal and haemophilic blood resided in the blood corpuscles, because normal blood corpuscles had a strong coagulating effect on haemophilic blood, whereas haemophilic blood corpuscles had much less. In this way, he established his theory of a cellular anomaly, namely, an absence of thrombozyme, both of/

of the blood corpuscles and of the endothelial cells of the vessels. In answer to criticisms, that his blood corpuscles might have been enveloped with plasma, and that that contained the thrombokinase, he stated that they had been thoroughly washed in oxalate solution and afterwards in physiological saline.

Sahli in his cases found no morphological changes in the blood, and only very unimportant changes in relation to the number of corpuscles. The blood platelets were rather fewer than normal, and there was a leucopaenia, with relative lymphocytosis, (which was also noted by Wright, but not found by Morawitz and Lössen). He found that the blood pressure in several of his patients was low (whereas Schönlein and Schneider, quoted by von Recklinhausen, state that a high blood pressure is the cause of haemophilia). The pulses in all his cases showed a low pressure. As already noted, he was the first to show that the blood coagulation of haemophilics was hastened during haemorrhagic attacks, and retarded only in the interhaemorrhagic periods.

Sahli's theory does not explain the fact that sometimes uncontrollable bleeding may not appear/

appear till several days after an injury, or that a small wound may bleed profusely, while a large one may behave in almost normal fashion.

1906. Weil (31) was the first to discover that blood could be taken from the veins of haemophilics by puncture, without dangerous results, and this fact was also confirmed by Baum (32) in his researches.

Unlike Sahli, he thinks that haemophilia can be entirely explained by changes in the blood alone, which he says are quite sufficient to account for the delay in coagulation found in this condition. In support of this contention, he states that the intravenous injection of 15 to 20 cc. of normal serum renders normal, both in form and time, the coagulation in his "sporadic" cases. Further, he had also produced locally a haemophilic state in man, by the application of leeches, the wounds thus caused going on bleeding for a prolonged period, and forming clots similar in every respect to those got in haemophilics. In vitro this blood also behaved in exactly the same way as haemophilic blood.

Weil divides the disease into two forms, viz., an accidental or Sporadic Form, and a Family Form, which latter he further subdivides into Severe/

Severe and Mild Varieties.

In the Sporadic Form, which usually shows itself after childhood, he says there is an absence or alteration of the thrombokinase, and that the blood is normal both morphologically and chemically, for the addition to it of a few drops of normal serum (which contains the thrombozymic ferments which are wanting in haemophilic blood) renders it normal, the coagulation time in vitro being much more markedly influenced by this addition than is the case with true haemophilic serum. On the other hand, this sporadic form of haemophilic blood does not contain any substance preventing coagulation, for the addition of a few drops of this serum to normal blood does not modify it in any respect.

The blood is very fluid, and the flow from the vein is rapid, and it coagulates in an hour at most, the time being less prolonged than is the case with the blood of the family form. In this sporadic form, there is usually a short haemorrhagic leucocytosis, followed by a leucopaenia, with mononuclear predominance.

In/

In the Family Form, Weil finds that there is an excess of antifibrin ferment, and the fibrinogen is modified either quantitatively or qualitatively. The addition of a few drops of this form of haemophilic serum to normal blood, results in a prolongation of the coagulation time of the latter, but in some cases may have no effect at all. The same result is got from adding normal blood to that of a dog rendered incoagulable by the injection of peptone.

The blood is surprisingly viscid; being increased beyond the normal, and being less fluid, it does not flow so rapidly from the vein, and the needle soon gets clogged. The coagulation time in vitro is more prolonged and less complete, - owing to its viscosity - but, nevertheless, takes place in the same way as in the sporadic form, and the clot, once formed, is normal in appearance.

The blood morphology shows no change as regards the red blood corpuscles, but there is a constant leucopaenia, varying between 3,400 and 4,500, of which polymorphonuclear cells account for 60%, mononuclear cells (especially the large ones) for from 38% to 39%, and eosinophiles for from 1% to 2%.

This/

This family form may suddenly show itself in a family where there are no antecedent bleeders, and such are not to be confounded with haemophilics of the sporadic form.

The viscosity was estimated in four out of the eight cases recorded here. Taking the normal viscosity of the blood as between 4·8 and 5·6, that of water at the body temperature (28), the following results were got.

Case I.	Viscosity of Blood	6·06
		6·25
		6·103
		5·86
	Viscosity of Plasma	2·2
		2·06
	Viscosity of Serum	1·902
Case VI.	Viscosity of Blood	4·24
Case VII.	" " "	3·45
Case VIII.	" " "	5·2

Thus Case I. is the only one which shows an increased viscosity. That of Case VIII. may be said to be normal, while those of Cases VI. and VII. are below normal - all these cases, however, could be classed under Weil's Family Form of Haemophilia.

Morawitz/

Morawitz and Lössen (33) came to the following conclusions. They found that haemophilic serum was nearly three times as strong as normal active serum, when tested by seeing the effect on the coagulation of Hammerstein's Fibrinogen. This paradox they explain by saying that it shows that the amount of antifibrin ferment in haemophilic blood is diminished; it is an attempt at a natural cure. (This result is interesting when compared with the directly opposite conclusions arrived at by Weil.)

They made an attempt to find if there were any changes in the vessels, by finding what amount of pressure was necessary to produce a haemorrhage into the skin. A small glass bell, about 4 cm. in diameter was connected with a suction pump and with a quicksilver manometer, and applied to the skin surface. The diminished pressure was maintained for 60", and they found that in haemophilic subjects bleeding occurred at a pressure of 100 mm. of Mercury, whilst in healthy people it occurred between 60 and 158 mm. of Mercury.

They found that the addition of Calcium Chloride made no difference to the coagulation time of haemophilic blood, but that the addition of thrombokinase/

thrombokinase (from the human kidney) caused the coagulation time to become as quick as that of normal blood, and the clot was quite normal. They conclude, therefore, that Haemophilia is due to a deficiency in thrombokinase, due to a chemical (or fermentation) change in the formed elements of the blood, and perhaps also of the tissues. It is not due, they say, to an increase in antiferment, which seems to be rather diminished, and Morawitz further states that because haemophilic serum contains more "metathrombin", it therefore cannot contain so much antifibrin ferment.

In 1901, Gilbert and Lerebouillet (34), in their theory of the disease, attribute the cause to the liver, and in favour of their opinions it is pointed out, that experiments have proved the important part played by this organ in the incoagulability of certain bloods - e.g., peptone blood, leech blood, and organic extracts. On the other hand, lesions in the liver have been shown to be one of the factors in purpuric haemorrhages. Thus they maintain that in haemophilia there is either a functional disturbance, or a lesion, to be found in the liver.

All authors admit that peptone, which

has/

has no direct anti-coagulating action on the blood, acts, nevertheless, by exciting the production of an anti-coagulative substance. Delezenne (35) has shown that it is the liver which gives this out by stopping, among the substances let loose from the destruction of leucocytes, the coagulating substances, and thus allowing the anti-coagulative substances to circulate freely in the blood.

The injection of peptones produces a destruction of leucocytes in the body, thus giving rise to a condition of leucopaenia, and most writers state that a condition of leucopaenia exists in Haemophilia. In 1908, Esmein (36) described the post-mortem changes which he found in a haemophilic subject. He laid stress on the liver condition found, and stated that it was fatty and smooth, its general yellowish appearance being marked with small irregular zones. On microscopical examination, a section of the liver showed that normal hepatic tissue was present around the portal spaces only, around the hepatic veins were found large masses of necrosed liver tissue, the hepatic cells having here disappeared, and having been replaced by means of brown pigment, of blood pigment and of fat globules, and he/

he believes that these liver changes were the cause and not the result of the haemophilia.

Both these results of Gilbert and Esmein are interesting, in connection with the work (1910) of Nolf and Herry (37), who do not agree with the Morawitz theory of the coagulation of the blood. They consider that the interaction of fibrinogen, prothrombin and thrombokinase (thrombozyme) gives origin to fibrin and thrombin, and that thrombokinase is not found in the skin or muscles, though it is abundant in leucocytes, blood platelets and vascular endothelium. The blood contains all the elements necessary for the formation of a clot. It remains fluid in the vessels, because the liver produces antithrombin, and in normal conditions there is an equilibrium maintaining fluidity. In certain intoxications, the liver may secrete antithrombin in great excess. They conclude that the Vascular Endothelium plays an active part in secreting thrombozyme, and the cause of haemophilia is the functional insufficiency of this thrombozyme; along with this defect there is an associated friability, which accounts for the many slight accidental haemorrhages in haemophilia, which are not accounted for by mere incoagulability of the blood.

Von/

Von Arnsperger (38) 1910, bases his theory of haemophilia, like Sahli and Morawitz, upon a want of thrombokinase.

Alderhalden (39) found that wounds of the skin did not bleed excessively in a case reported by him, while wounds of mucous membranes did so, and concludes that haemophilia is due to disease of the small vessels and capillaries.

1904. Geyer (40) found an enormous number of nucleated red cells in one case, and considers that clotting is prevented by the degeneration products of such cells, but thinks that thinness of vessel walls, their inability to retract, their want of muscle fibres and the scarcity of elastic fibres in the skin are all factors of importance!

Faludi (41) 1904, in the case of a boy of 6 years of age, could find no anatomical ground to explain the condition.

Goodall (42) 1905, found no anatomical peculiarity of the vessels or tissues in a post-mortem examination on a haemophilic boy, and considers that the essential pathology of haemophilia consists in a delayed coagulability of the blood.

Finally, Addis (43) attributes the defective coagulability to an inherited peculiarity in the constitution of the prothrombin, whereby its activation into thrombin is retarded.

The/

The writer of this thesis was associated with Dr Addis in this experimental work, and was able to put at his disposal several of the cases here described. As the results of these investigations have already been published, it remains only to refer to them in a few words in this more clinical study. The process of coagulation in normal people was compared with that in haemophilic subjects, and it was found to be essentially the same in both cases. The four factors necessary for coagulation are, fibrinogen, prothrombin, calcium and thrombokinase - the first three,being already in the blood, are constant, whereas the last, which is derived after injury to the tissues, is variable, and upon the quantity of this substance depends the rate of change of prothrombin into thrombin. The more thrombokinase present, the more rapid is the production of thrombin. The thrombokinase in normal and haemophilic blood was found to be equal in amount. The point to be settled was whether there was delayed thrombin formation, or whether the fault was to be found in the reaction between thrombin and fibrinogen. Normal and haemophilic thrombin were found to be equally active, and normal and/

and haemophilic fibrinogen were both readily coagulated by thrombin. No quantitative defect could be made out in haemophilic fibrinogen. It was ascertained that the rate of thrombin formation in haemophilic wounds was slower than that in wounds of normal people, so that the cause must be found in delayed thrombin formation. Calcium additions made no appreciable effect on the coagulation time, and a deficiency of thrombokinase was found not to be the cause. No quantitative deficiency in haemophilic prothrombin was made out, but a qualitative change was noticed, for in the presence of calcium and thrombokinase, the change into thrombin was greatly delayed. On adding small quantities of normal prothrombin, however, the thrombin formation was found to become instantaneous. It was therefore concluded that haemophilic prothrombin was normal in amount, but abnormal in some quality, preventing its rapid formation into thrombin. The following coagulation tests, carried out in Case VII., are interesting, as showing <u>in vivo</u> the correctness of the above experiments <u>in vitro</u>. These coagulation results were obtained with Addis Coagulometer - at a constant temperature of 20°C.

12·2·10./

	Start.	Finish.	Coag. Time.
12·2·10.	3·25· 0	4·11· 0	46 m.
	Blood taken from same puncture $9\frac{1}{4}$ minutes later.		
	3·34·15	3·52·15	18 m.
12· 3·10.	5· 0· 0	6· 4· 0	64 m.
	Blood taken from same puncture 12 minutes later.		
	5·12· 0	5·28· 0	16 m.
	Blood taken from same puncture 15 minutes later.		
	5·15· 0	5·21· 0	6 m.
	No more blood could be expressed.		
19·3·10.	4·32· 0	5·51· 0	60 m.
	Blood taken from same puncture 5 minutes later.		
	4·37· 0	4·57· 0	20 m.
	Taken 10 minutes later.		
	4·42· 0	4·54· 0	12 m.
	Taken 15 minutes later, had to be squeezed out from puncture wound.		
	4·47· 0	4·53· 0	6 m.
	No more blood could be expressed.		

26·3·10./

	Start.	Finish.	Coag. Time.
26·3·10.	3· 4· 0	3·52· 0	48 m.
	Blood taken from same puncture 6 minutes later.		
	3·10· 0	3·35· 0	25 m.
	Taken 12 minutes later.		
	3·16· 0	3·26· 0	10 m.
	No more blood could be expressed from same puncture wound.		
25·6·10.	3·26· 0	4·34· 0	72 m.
	Blood taken from same puncture wound 4 minutes later.		
	3·30· 0	3·50· 0	20 m.
	Taken 8 minutes later.		
	3·34· 0	3·40· 0	6 m.
	No more blood could be got.		
9·7·10.	4·15· 0	5·39· 0	84 m.
	Blood taken from same puncture wound, 5 minutes later.		
	4·20· 0	4·50· 0	30 m.
	Taken 10 minutes later.		
	4·25· 0	4·42· 0	17 m.
	Taken 15 minutes later, had to be expressed.		
	4·30· 0	4·43· 0	13 m.

6·9·10./

	Start.	Finish.	Coag. Time.
6·9·10.	3·24· 0	4· 6· 0	42 m.
	Blood taken from same puncture wound 4 minutes later.		
	3·28· 0	3·58· 0	30 m.
	Taken 8 minutes later.		
	3·32· 0	3·48· 0	16 m.
	Taken 12 minutes later, had to be expressed.		
	3·36· 0	3·45· 0	9 m.
	No more blood could be got for accurate testing.		
20·9·10.	3· 4· 0	3·36· 0	32 m.
	Blood taken from same puncture, 6 minutes later.		
	3·10· 0	3·30· 0	20 m.
	Taken 12 minutes later.		
	3·16· 0	3·28· 0	12 m.
	No more blood could be got.		

These results show that the first specimen of blood from a wound takes longer to coagulate than the successive specimens, until the last, which does so instantaneously. The first is ejected before it has time enough to come long into contact with/

with the thrombokinase set free in the surrounding tissues, whilst the later specimens, being subjected longer to its influence, produce more thrombin, with consequently more rapid coagulation. But the formation of thrombin is never instantaneous, however much thrombokinase be present, and it is only when pre-formed thrombin is added, that it coagulates at once. Such pre-formed thrombin is found to be present in these wounds, being derived from the blood which has previously coagulated, and this fact accounts for the immediate coagulation of the last specimen of blood.

PATHOLOGY of HAEMOPHILIC JOINTS.

Considered from a pathological standpoint, there are three stages to be met with in haemophilic joint affections, and according to Koenig (43a), these consist first of a:-

(a) Haemarthrosis, or simple exudation of blood into the joint cavity, later:-

(b)/

(b) an Arthritis develops. As the blood is being absorbed, fibrous tissue may pass into the clots from each side, resulting in organisation of the entire clot; and often in fibrous union, to a greater or less extent, of the opposed surfaces. At the same time, erosion of the cartilage and lipping of the joint may begin, leading lastly to a condition of:-

(c) Arthritis deformans.

All the present cases show haemarthrosis of their affected joints, but only Case I. shows a condition of arthritis.

(Vid. X ray photographs and description of changes seen, in separate volume).

INFLUENCE/

INFLUENCE of RACE.

Race has little bearing upon the disease. It has been said that Jews were more liable to it than other races, but Bulloch, who has gone very fully into this subject, is inclined to attach little importance to this statement. He cites the case of the London Hospital, where 10% of the total admissions are Jews. From 1900 to 1909, the total admissions were 137,676, of which 15,600 were strict Jews, and of these, only two cases of haemophilia in brothers are recorded. Bulloch (44) states also that the Teutonic races account for the majority of cases. In France, very few authentic cases have been noted. In Japan, it is thus far unknown. Only three cases in negroes have been recorded, and none of these are undoubted cases of haemophilia. The number of cases recorded does not depend so much upon the frequency of the disease in a given country, as upon the previous education of the medical man, and the interest he takes in this condition.

INFLUENCE of CLIMATE.

Cold and damp weather seems to predispose to attacks of haemorrhage, whilst the occurrence of warm, dry weather has the opposite effect. The joint affections appear also more liable to occur in spring and autumn, especially if the weather is cold and damp.

'INFLUENCE of SOCIAL POSITION.

Social Position has no influence upon the occurrence of the disease - both rich and poor being equally affected - and even Royalty is not exempt from it. It is true, of course, that the leisured classes are less liable to traumatic haemorrhages than the working classes, but this is due to their having to work for their living, and often taking up risky occupations.

PROLIFIC NATURE of HAEMOPHILIA.

When the disease exists in a family, if there is marriage, it becomes rapidly propagated. Wachsmuth, who was the first to point out this prolific nature, mentions as an example, that in twelve families/

families which he collected, there were born no fewer than 114 children - an average of 9·5 children per family - and more recently, the "Mampel" family, recorded by Lössen, shows this same fertility, in even more marked a degree. Ralph Stockmann (45) states that haemophilics are twice as prolific as normal individuals.

The families here recorded demonstrate this well-marked fertility, as follows:-

---

Case I. whose parents had 5 children.

Case II.)
(whose parents had 11 children.
Case III.)
(
Case IV.)

Case V. whose parents had 7 children.

Case VI. whose parents had 8 children.

Case VII.)
(whose parents had 8 children.
Case VIII.)

Bulloch (44) states in a general way, that only one girl in every three or four, who has sons at all, will have them free from haemophilia.

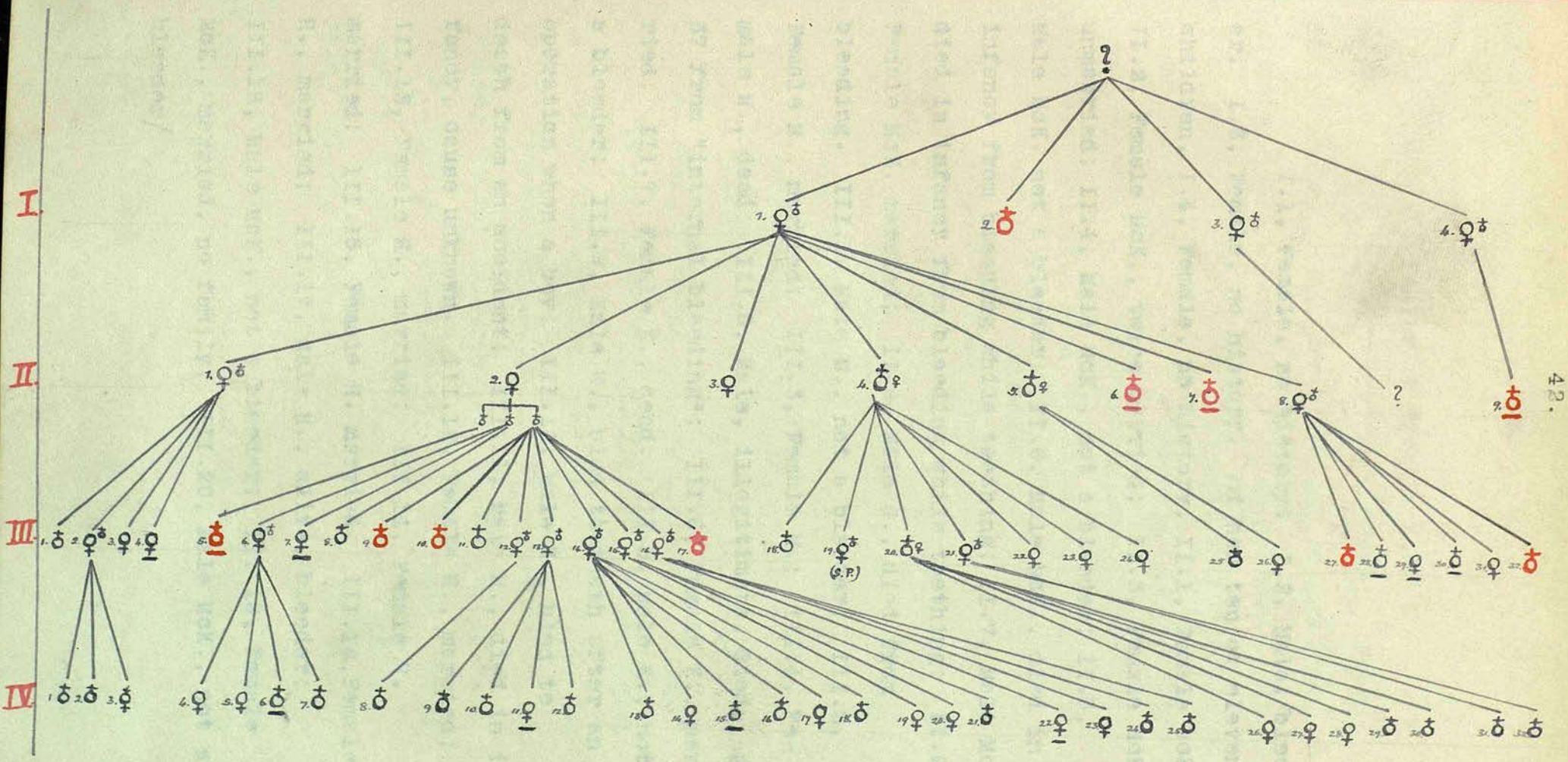
TRANSMISSION/

TRANSMISSION and THE QUESTION of FEMALE HAEMOPHILICS.

Otto was the first to note that, though the males were usually affected, it was the females only who transmitted the tendency to bleed to their children, being rarely themselves ever affected. This law is well illustrated by the three accompanying Family Charts, belonging to the eight cases of haemophilia here recorded.

If a haemophilic man marries a non-haemophilic woman, his children are usually non-bleeders, but if they do show the tendency, it is always in a severe form, and it has been further noted that direct transmission from a father's generation to a son's is more common where the father's brothers have been affected, while the father himself has escaped.

FAMILY/



— denotes haemophilic subjects.
— denotes healthy subjects.

Family Pedigree, I.

(Unpublished.)

III. 32. is Case I.

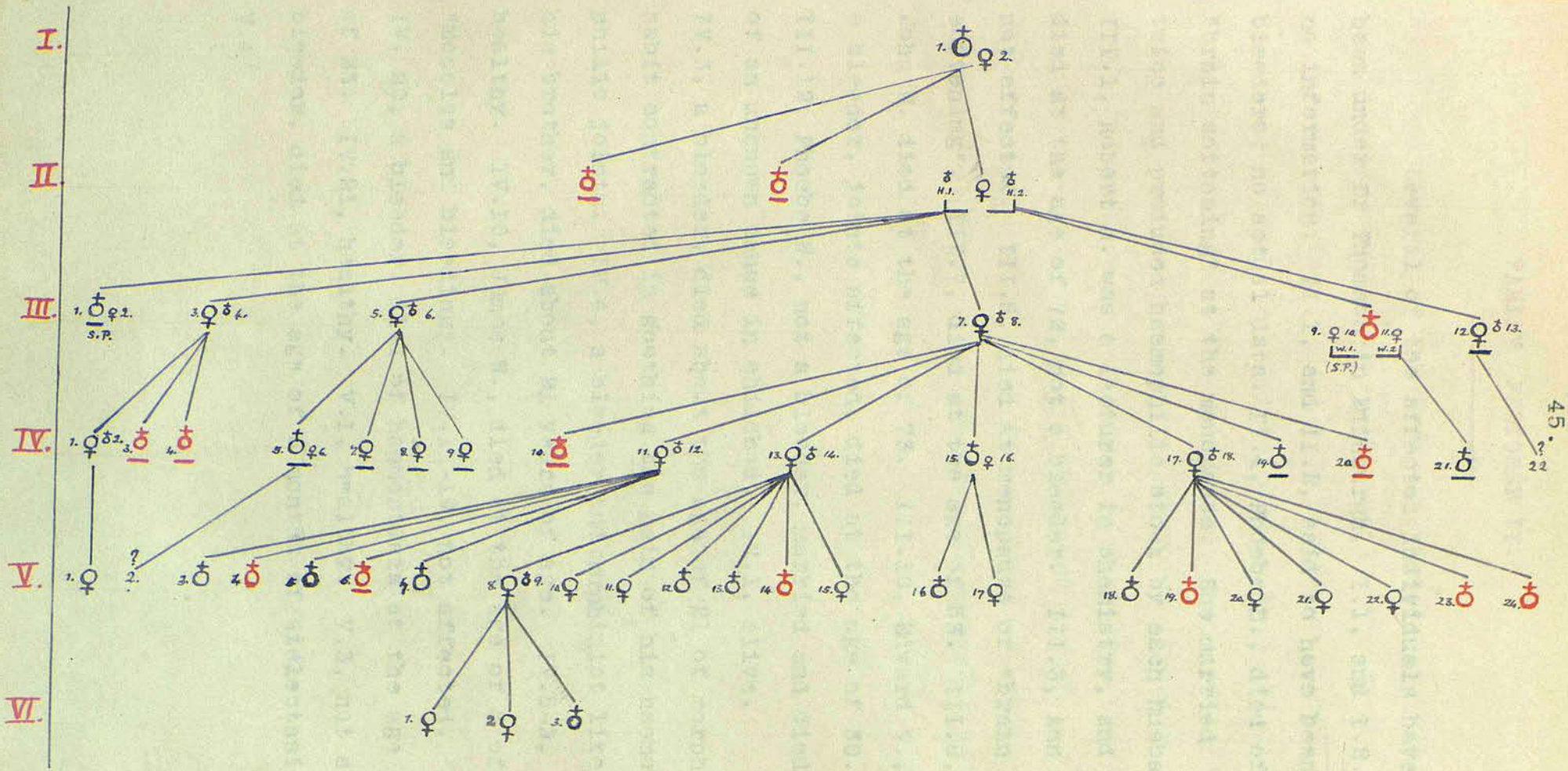
III. 17. is described under Case I. p. 130

FAMILY PEDIGREE I.

I.1, Female, no history; I.2, Male, bleeder; I.3, Female, no history. of her ten or eleven children, I.4, Female, no history; II.1, Female McK.; II.2, Female McK., twice married; II.3, Female McK., unmarried; II.4, Male McK., not a bleeder; II.5, Male McK. not a bleeder; II.6, Male McK., died in infancy from bleeding while teething; II.7, Male McK. died in infancy from bleeding while teething; II.8, Female McK. married; II.9, Male G., died from bleeding. III.1, Male M., not a bleeder; III.2, Female M., married; III.3, Female M.; III.4, Female M., dead; III.5, Male, illegitimate, died, age 37 from "internal bleeding"; III.6, Female K., married; III.7, Female K., dead. III.8, Male K., not a bleeder; III.9, Male H., bled to death after an operation when a boy; III.10, Male H., bled to death from an accident; III.11, Male H., died in infancy, cause unknown. III.12, Female H., married; III.13, Female H., married; III.14, Female H. married; III.15, Female H. married; III.16, Female H., married; III.17, Male H., alive, bleeder; III.18, Male McK., not a bleeder; III.19, Female McK., married, no family; III.20, Male McK., not a bleeder/

bleeder; III.21, Female McK., married; III.22, Female McKay, no history; III.23, Female McK., no history; III.24, Female McK., no history; III.25, Male McK., not a bleeder; III.26, Female McK., no history; III.27, Male W., bleeder; III.28, Male W., dead, 20 months, cause unknown, not a bleeder; III.29, Female W., dead, whooping cough, unmarried; III.30, Male W., dead, 6 months, cause unknown; III.31, Female W., alive, unmarried; III.32, William W., bleeder, age 27. IV.1, Male J., age 3; IV.2, Male J., age 2; IV.3, Female J., age 6 months; IV.4, Female; IV.5, Female; IV.6, Male, burnt to death in childhood; IV.7, Male, no history; IV.8, Male, no history; IV.9, Male; IV.10, Male; IV.11, Female, dead, teething and convulsions; IV.12, Male; IV.13, Male; IV.14, Female; IV.15, Male, died after circumcision, bleeder (?); IV.16, Male; IV.17, Female; IV.18, Male; IV.19, Female; IV.20 Female; IV.21, Male; IV.22, Female, stillborn; IV.23, Female; IV.24, Male; IV.25, Male; IV.26, Female; IV.27, Female; IV.28, Female; IV.29, male; IV.30, Male; IV.31, Male; IV.32, Male.

FAMILY/



45.

—. denotes haemophilic subjects.
—. denotes healthy subjects.

Family Pedigree II.

(Unpublished.)

V. 4. is Case V.
V. 19. is Case III.
V. 23. is Case IV.
V. 24. is Case II.

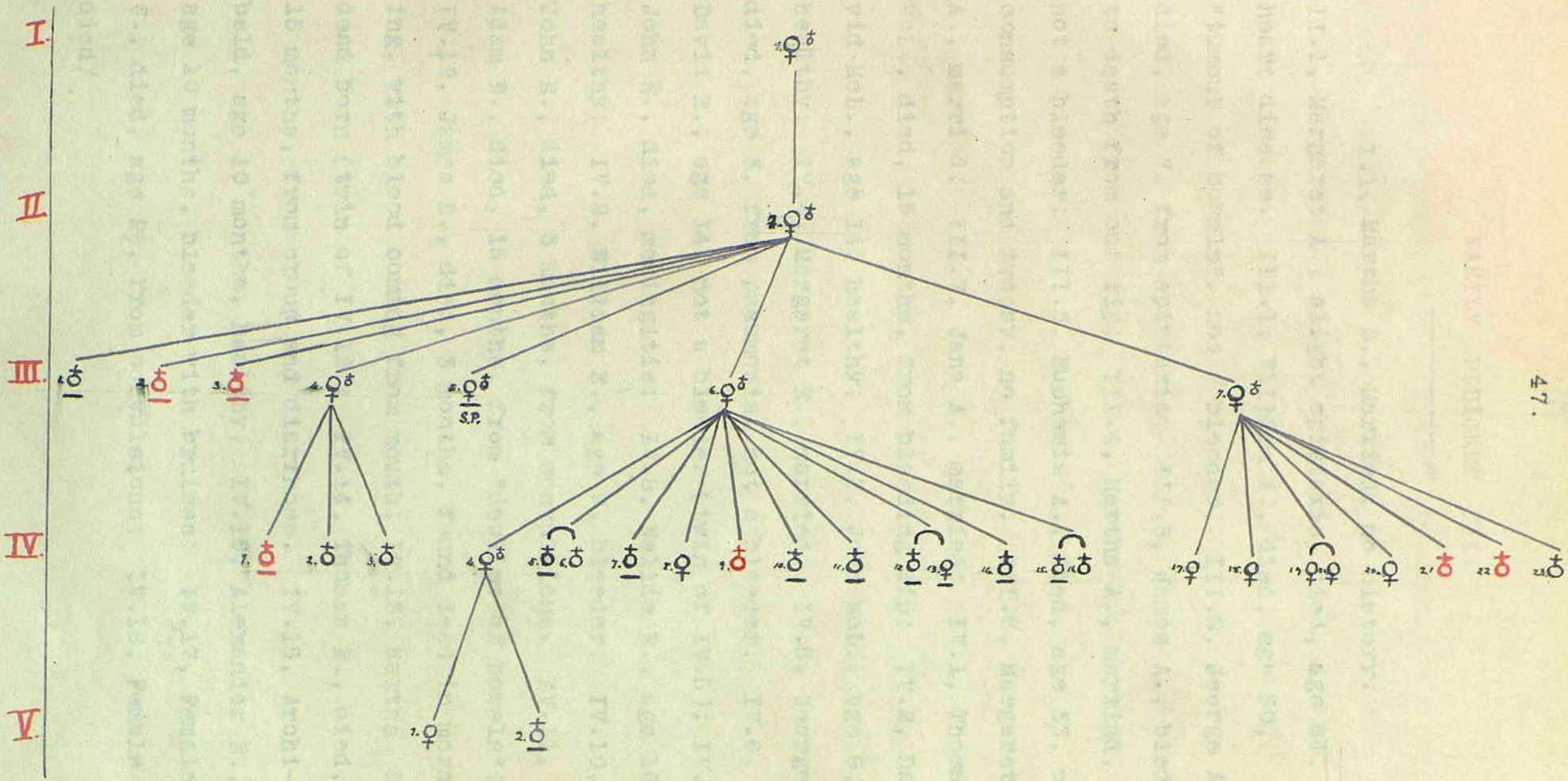
FAMILY PEDIGREE II.

Several of the affected individuals have been under Dr Thomson in Edinburgh. I.1, and I.2., no information. II.1, and II.2, said to have been bleeders; no actual data. II.4, Phoebe D., died of "brain softening" at the menopause. She married twice and produced haemophilic stock by each husband. III.1, Robert M. was a lecturer in chemistry, and died at the age of 72, not a bleeder. III.3, Ann M., not affected. III.5, died at menopause of "brain softening". III.7, died at the age of 53. III.8, John W. died at the age of 73. III.10, Edward W., a bleeder, joints affected, died at the age of 30. III.12, Phoebe W., not a bleeder, married and died of an unknown cause in childbed. IV.1, alive. IV.3, a bleeder, died about the age of 21 of morphia habit contracted in soothing the pain of his haemophilic joints. IV.4, a bleeder and morphinist like his brother, died about 21 years of age. IV.5-9, healthy. IV.10, James W., died at the age of 5 of "measles and bleeding". IV.11-19, not affected. IV. 20, a bleeder, died of haemoptysis at the age of 23. IV.21, healthy. V.1, healthy. V.3, not a bleeder, died at the age of 9 months of atelectasis(?)

V.4/

V.4, James S., alive, aged 25, a bleeder, no details. V.5, Archibald, died at the age of 18 of fits and jaundice; not haemophilic. V.6, died of bleeding in childhood. V.7-13, not affected. V.14, William W., aged 13, a bleeder, no details. V.19, John McD., aged 25, a bleeder, affected with joint troubles. V.20, alive, aged 23, healthy. V.21, aged 18, alive and healthy. V.22, aged 15, alive and healthy. V.23, aged 11, a bleeder, joints affected. V.24, aged 6, a bleeder with haemarthroses; mentally deficient.

FAMILY/



— denotes haemophilia subjects.
— denotes healthy subjects

Family Pedigree III.

(Unpublished.)

IV. 9. is Case VI.
IV. 21. is Cases VII.
IV. 22. is Case VIII.

FAMILY PEDIGREE III.

I.1, Martha B., Married, no history. II.1, Margaret A., slight epistaxis, died, age 64, of heart disease. III.1, William A., died, age 50, "tumour of bowels", not a bleeder; III.2, George A., died, age 7, from epistaxis; III.3, James A., bled to death from cut lip; III.4, Martha A., married, not a bleeder; III.5, Euphemia A., died, age 33, of consumption and dropsy, no family; III.6, Margaret A., married; III.7, Jane A., married; IV.1, Thomas McL., died, 15 months, from bleeding lip; IV.2, David McL., age 14, healthy; IV.3, John McL., age 9, healthy; IV.4, Margaret E., married; IV.5, George, died, age 3, from pneumonia, not a bleeder; IV.6, David E., age 14, not a bleeder (twin of IV.5); IV.7, John E., died, meningitis; IV.8, Nellie E., age 10, healthy; IV.9, William E., age 9, bleeder; IV.10, John E., died, 3 months, from convulsions. IV.11, Adam E., died, 15 months, from "decline of bowels"; IV.12, James E., died, 3 months, found dead in morning, with blood coming from mouth; IV.13, Martha E., dead born (twin of IV.12); IV.14, Thomas E., died, 15 months, from croup and diarrhoea. IV.15, Archibald, age 10 months, healthy; IV.16, Alexander E., age 10 months, bleeder with bruises; IV.17, Female C., died, age $2\frac{1}{2}$, from convulsions; IV.18, Female C., died/

died, age 8, from glands in neck and pneumonia; IV.19, Female C., died, age 2 days; IV.20, Female C. died, age 7 hours (twin of IV.19); IV.21, James C., age 9, bleeder; IV.22, David C., age 7, bleeder; IV.23, John C., age 3, not a bleeder; V.1, Margaret A., age 1½, healthy; V.2, Samuel A., died, age 3 days, from convulsions, instrumental labour. IV.20a., Female C.

Many/

Many cases have been published which show a departure from the classical description, as regards sex and heredity; thus Pearson (46) in 1904, recorded a case of haematuria, where the female members of a family were affected, and showed the transmission through the male line. Another such case is the one published by Pritchard (47) in 1905, of a girl in whom the tendency to spontaneous haemorrhages had been handed down in the male line for two generations, and in the third generation was evidenced in a severe form in the case of a female. Bulloch, on the other hand, does not admit that the disease is ever transmitted through the male line, and he has made a digest of all the well-authenticated pedigrees of haemophilic subjects, with the following results. He finds that out of a total of 171 recorded instances of transmission, 160 conform to the so-called "law of Nasse", that the disease is transmitted by the unaffected female - the "conductor" - of the 11 remaining, 7 cases are apparently through the alleged affected male, and the rest through unaffected males. These Bulloch explains as probably due to intermarriage, for he states that a number of haemophilic families occur among people socially and geographically isolated,

so/

so that a woman, presumably normal, but in reality a "conductor", may marry a man in a bleeder family, or one who is normal, and be responsible for his bleeder sons.

The question, as to the immunity of the female sex from haemophilia, is one on which opinion is divided. Some maintain that the disease is sex-limited to males only, whilst others assert that females are not immune, and may be attacked with comparative frequency. Lange in 1849, stated that the ratio of female to male bleeders was 1 to 7, and a few years later Grandidier gave it as 1 to 14. Numerous cases of so-called haemophilic manifestations in females have been described; these have usually been confined to bruisings, disorders of menstruation, and haemorrhage in connection with childbirth. The most important of these monographs in recent times is that published by Fraenkel and Böhm (48), who give a report of 151 cases of haemophilia in women. Out of these, 30 proved fatal, or about 20%. In 29 of these, the bleedings were on no occasion from the genital tract, and 6 of this sub-series ended fatally, again about 20%. The purely genital cases numbered 122, with 24 deaths, once/

once more about 20%, not higher than in the 29 non-local series.

Legg makes the statement:-

"I have never seen a case of true hae-
"mophilia in a woman, and I am inclined to think
"that the diagnosis of cases of haemophilia in
"women is founded on mistaken observation."

Bulloch, who went into this question very fully, came to a similar conclusion, that the case for haemophilic females had not been proved, and states that, in no case yet published, does the description bear more than a superficial resemblance to the disease as found in man.

SYMPTOMS/

SYMPTOMS.

Haemophilic infants are usually healthy and vigorous, and seldom show evidence of their inherited peculiarity before the first year of life. Holt (49) observes that haemorrhage of the new-born usually has no relation to Haemophilia. Larrabec (50), in an important article, dealing with haemophilia neonatorum, likewise states that uncontrollable haemorrhages in the newly born are seldom due to haemophilia. These are usually of septic origin, and many organisms have been found in the blood of these infants, or at the necropsy. Epidemics have been known to occur in hospitals, thus proving the infectivity of the condition. Larrabec, however, maintains that cases of true haemophilic origin do occur, and has collected a series of 37 cases, each of which had a family history of bleeding, and in later life proved to be "bleeders". The sex incidence was according to the general rule of those who admit haemophilia in females. Out of 33 cases, only six patients were females; on the other hand, where the haemorrhage was clearly shown to be due to infection, the sexes were about equally divided.

John/

John Thomson (51) considers the condition extremely rare in infants.

Apart from a history of doubtful and slight tendency to bruise, none of the present series of cases showed any severe symptoms till after the years of infancy had been passed.

Case	I.	showed	no	symptoms	till	he	was	6	years old.
Case	II.	"	"	"	"	"	"	3	" "
Case	III.	"	"	"	"	"	"	5	" "
Case	IV.	"	"	"	"	"	"	3	" "
Case	V.	"	"	"	"	"	"	5	" "
Case	VI.	"	"	"	"	"	"	$3\frac{1}{2}$	" "
Case	VII.	"	"	"	"	"	"	2	" "
Case	VIII.	"	"	"	"	"	"	2	" "

On the other hand, there is a tendency in many cases for the symptoms of haemophilia to become less severe and pronounced as years advance. Cases III. and V. are evidence of this, for both admit that they now suffer less frequently and severely than they did when they were children.

In the older accounts of the disease, it is frequently stated that "bleeders" have unusually fine skins, and are of fair complexion, giving them rather a refined appearance, but there is nothing in/

in the physiognomy or temperament which can be said to be at all symptomatic; indeed, Case IV. has a particularly dark complexion.

The constitution is usually good. During the intervals, when free from active symptoms, these patients show a peculiar recklessness of their dangers, which is so common a feature, as to deserve mention under symptomatology. Case I. illustrates this fact well, and admits it himself; for whenever he is in this condition, he feels able for anything, and goes out either for a whole day's golfing or a long walk in the country, or over-exerts himself in some other way, regardless of any consequences.

Fever and general constitutional symptoms during attacks are the exception. Cases I., II., and VI. have occasionally shown rises of temperature during acute stages, as shown by the accompanying temperature charts.

Wright (35) and others have described the occurrence of prodromal symptoms in haemophilia. The patient is said to be in a plethoric condition, with headaches and palpitations, slight dyspnoea and a feeling of tightness in the chest, slight puffiness of the face, a feeling of lassitude, an increased/

DISEASE.

Notes of Case.

Name

Age

Diet

Case Book No.

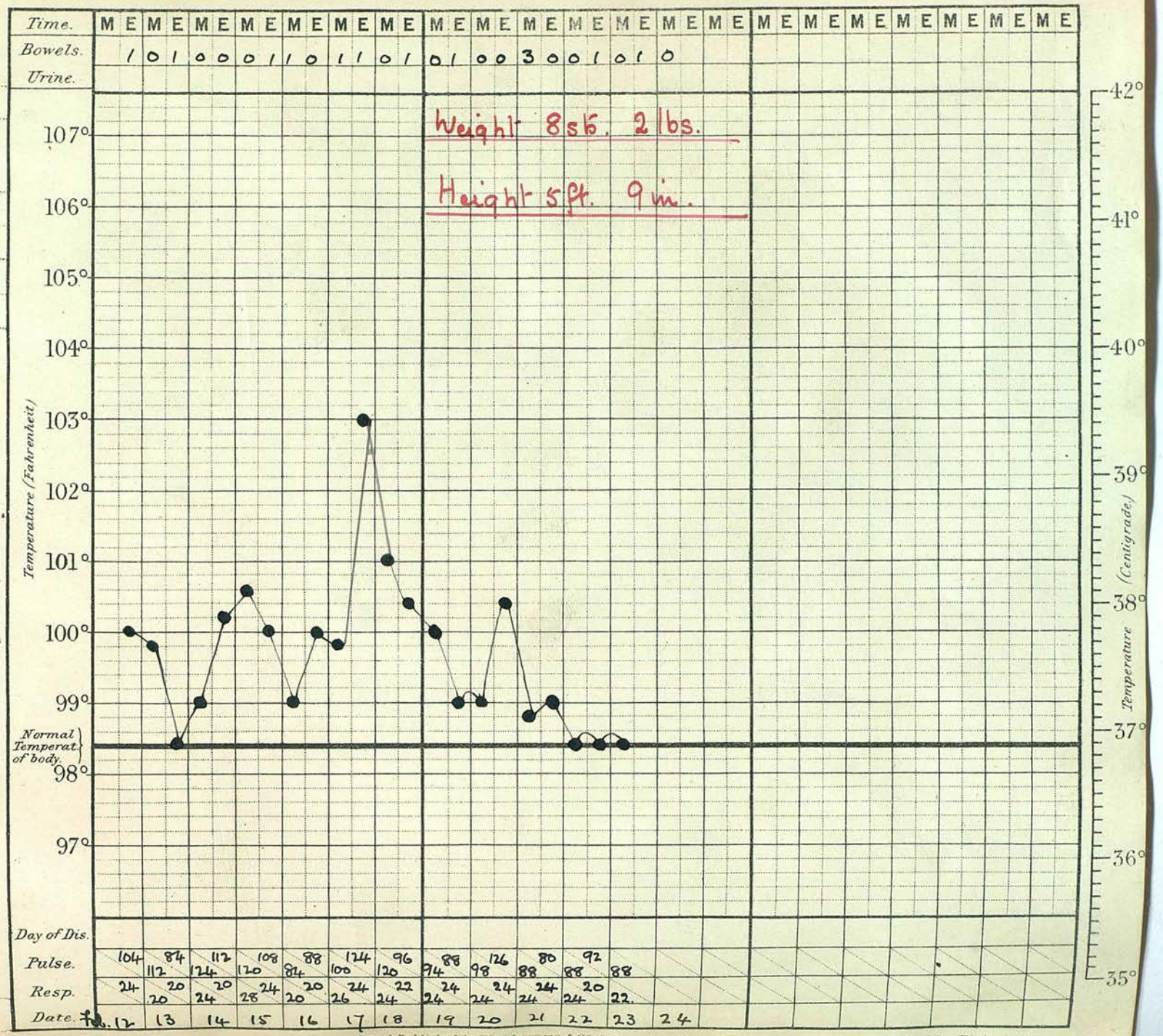
Case I.

12th February 1909
to
24th February 1909.

Left Knee swollen and painful 17-2-1909. Right Knee swollen and painful

Date of admission.
12th. Feb. 1909.

Result



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DISEASE.

Notes of Case.

Name

Age

Diet

Case Book N°

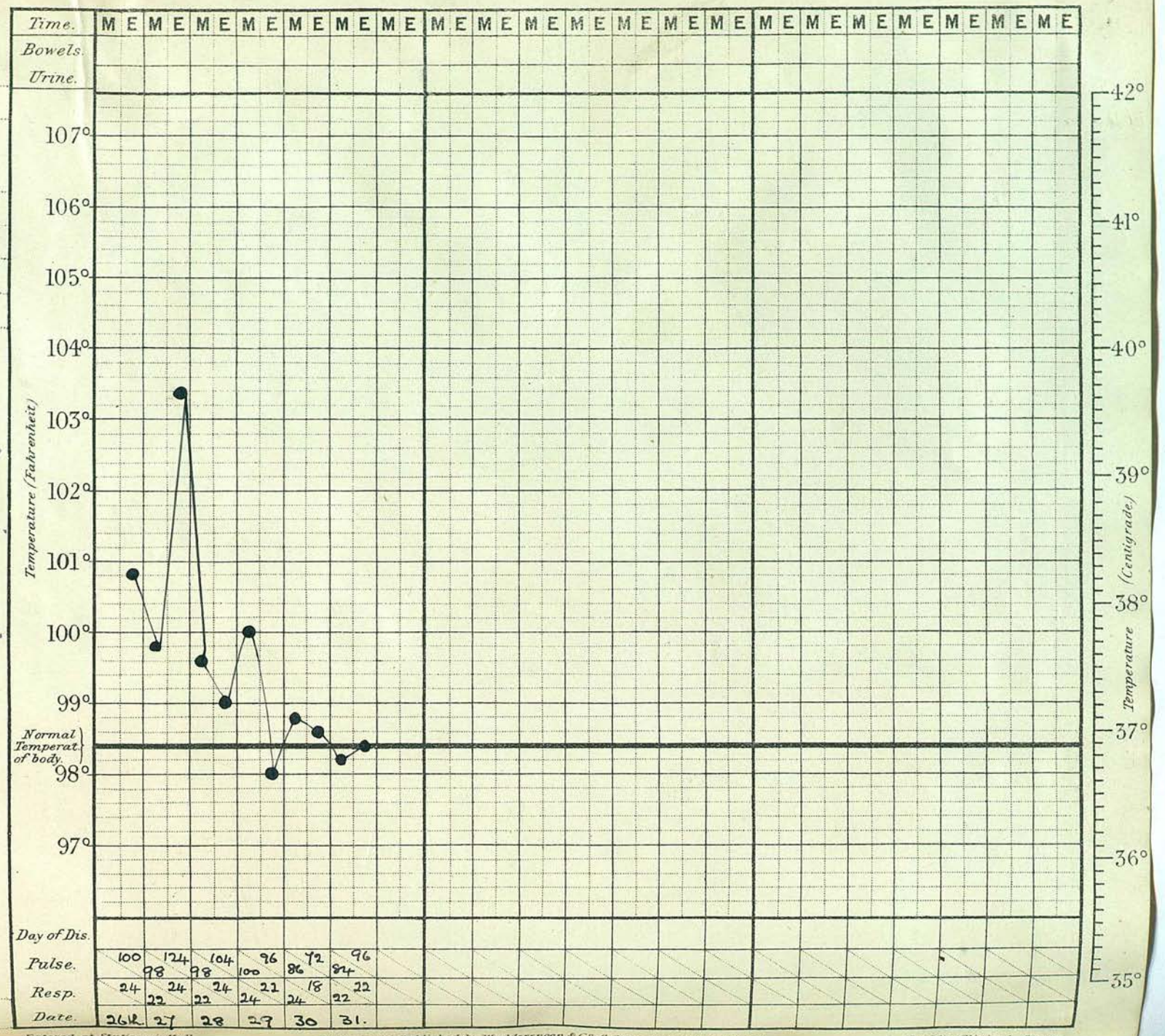
Case I.

26th March 1909
to
31st March 1909.

Haematoma of finger becomes septic.

Date of admission.
26th. March 1909.

Result



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DISEASE.

Notes of Case.

Name

Age

Diet

Case Book No. (1)

Case I.

23rd January 1911

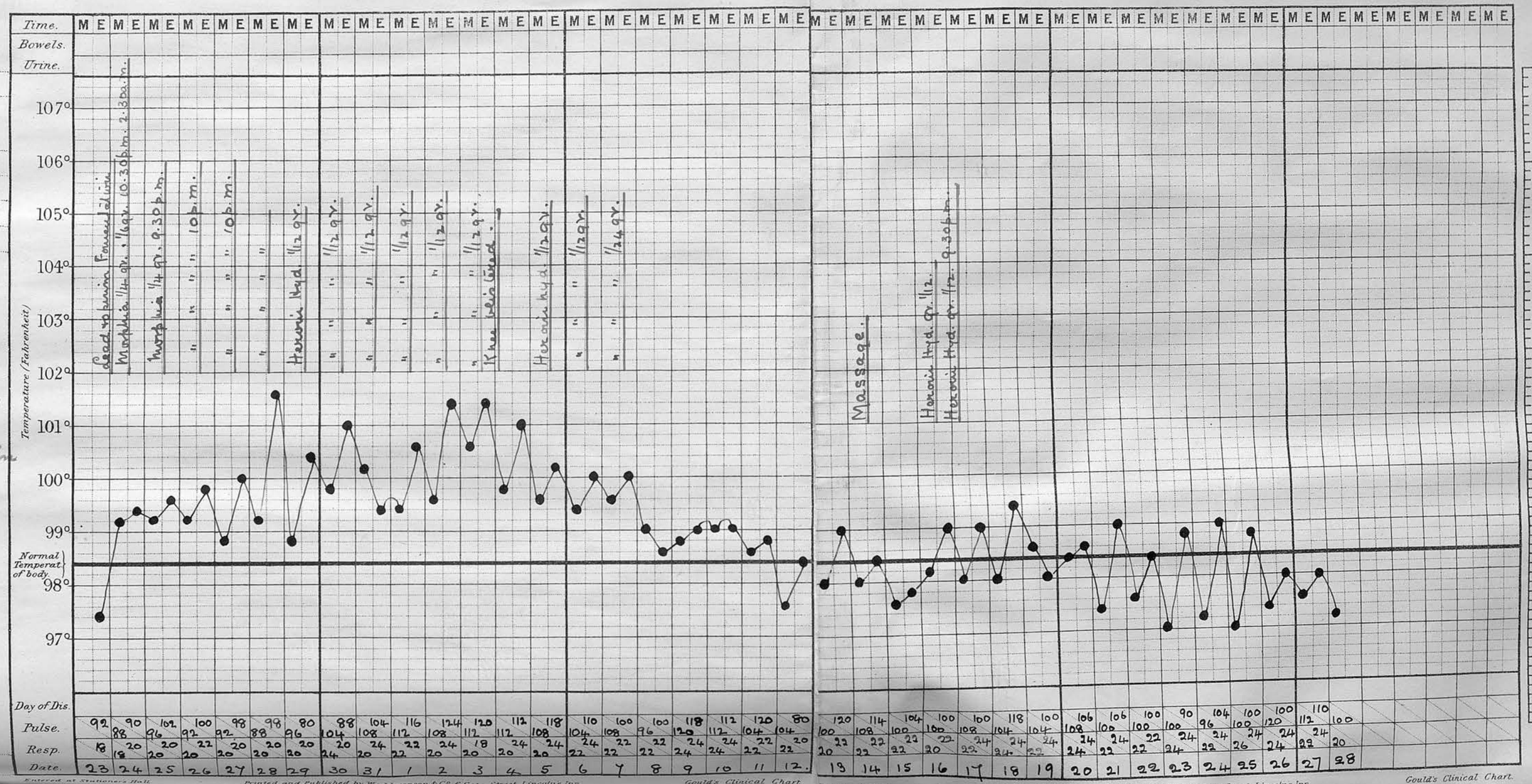
to

28th February 1911

Right Knee swollen and painful

Date of admission.

Result



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DISEASE.

Notes of Case.

Name

Age

Diet

Case Book No.

Calc. Chlor. gr. iii t.i.d.

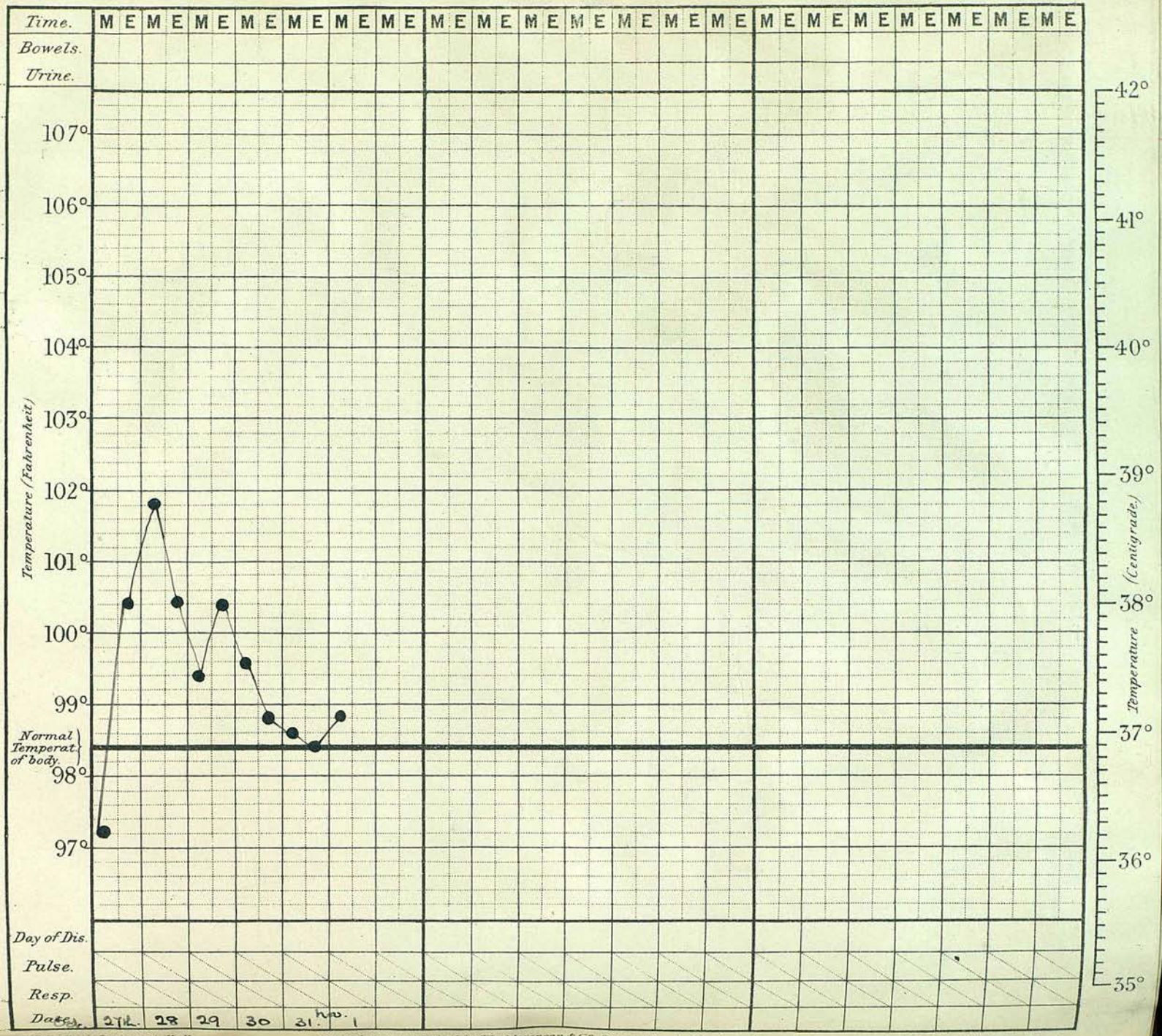
Case II

27th October 1906
to
1st November 1906.

Haemorrhage from the tongue

Date of admission.
27th. Oct. 1906.

Result



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DISEASE.

Notes of Case.

Name

Age

Diet

Case Book No.

29. 6. 10.

Horse serum

10 cc. daily.

8. 7. 10.

Lead + potassium applied locally to ankle.

Case VI.

21st June 1910

to

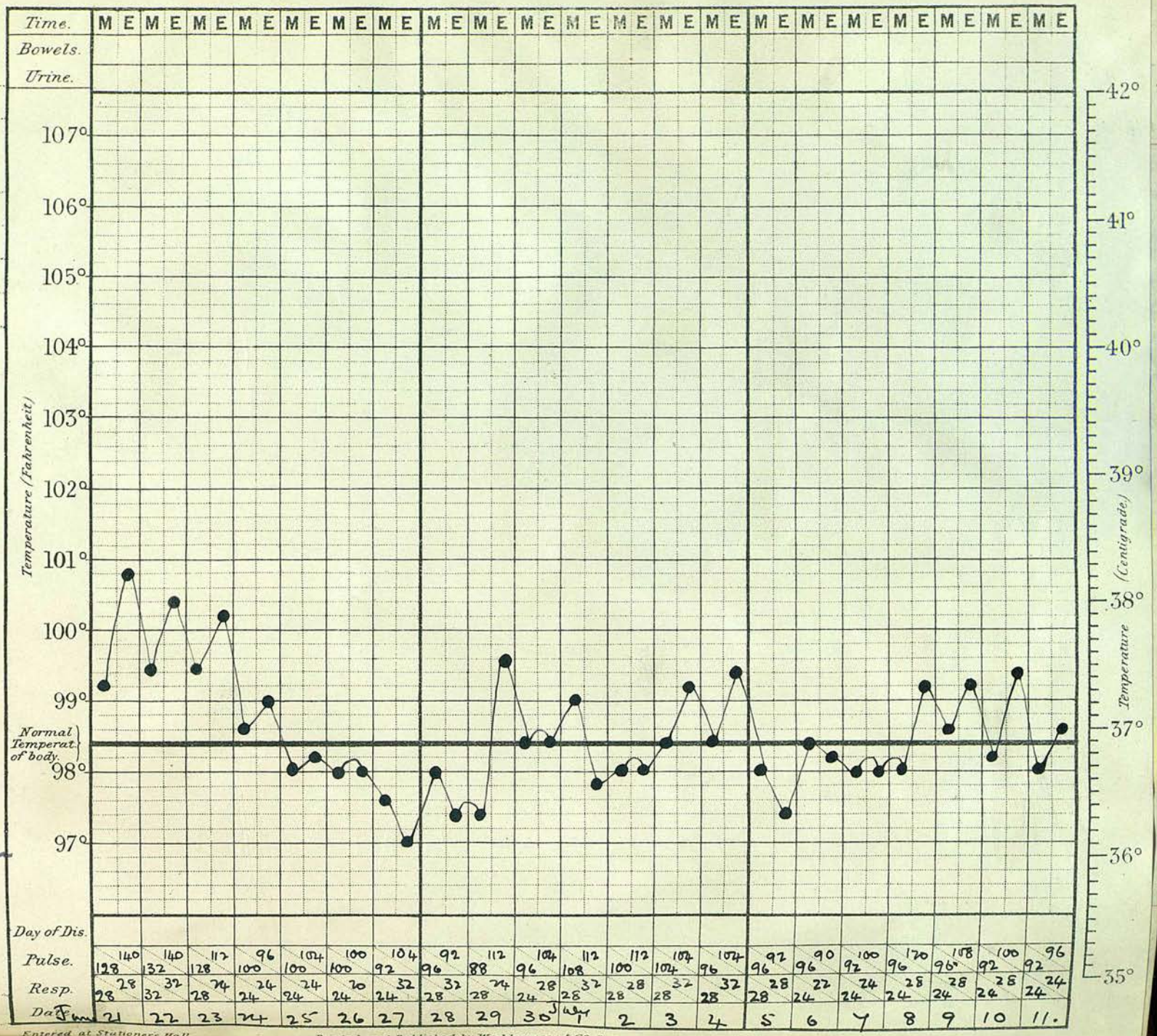
11th July 1910

Right ankle swollen + painful, also epistaxis

Date of admission.

21st. June 1910.

Result



Entered at Stationers Hall

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Gould's Clinical Chart.

increased fulness in the joints and a hysterical irritability. None of the present cases show such prodromal symptoms. Case I. usually feels nervous and gets flushed after his joints begin to swell, but never before.

There appears to be a certain degree of periodicity in onset of symptoms in this disease. Case I. finds that he can usually count on "something happening" about every five weeks or so.

Early dental caries, and a peculiar depraved appetite for eating grit and chalk, are described by Wright (35), the latter, he says, being possibly due to a craving for calcium. He has also frequently met with urticaria and chilblains in haemophilic subjects.

Weil/

Weil (31) sees in his cases two different clinical pictures, which has led him to divide the disease into two groups. In his "sporadic" form, he notes that the haemorrhages are less severe and frequent, these may be in the form of spistaxis, bleeding from the gums, haemoptysis, haematuria or cuts, which often do not show themselves except at intervals of years. More intense trauma is necessary to produce symptoms in this form, and there is also freedom from visceral and articular attacks, and absence of a hereditary tendency to bleed. In his "family" form, he describes the symptoms as being more severe and frequent, haemorrhages occurring from the least injury, and even from no apparent cause. Violent muscular exercise may bring them on. The coagulation time is more protracted than in the former variety of the disease. Joint troubles are very common, and there is always a well-marked family history of "bleedings".

The constant feature of Haemophilia is the tendency to bleed. The application of trauma, which in a normal person would never be noticed, gives rise in this condition to a haemorrhage which, once started, does not stop in the usual way, but is apt to go on, in spite of treatment, reducing the/

the patient, if he survives at all, to a state of profound anaemia. This liability to haemorrhage is always chronic, commencing in childhood, and continuing, more or less, throughout the patient's natural life; making his existence a truly wretched one. It has been pointed out already that these haemorrhages frequently come on during the night. Variations in intensity to bleed have been noted. At one time a haemophilic may bruise inordinately from a slight knock, whereas at another time, an equal degree of violence may not show any appreciable result. The more intense the symptoms, the more retarded is the coagulation time of the blood. Needle pricks seldom bleed more than normal, and haemorrhage from veins is almost never seen.

The haemorrhagic symptoms may, for convenience, be classified under three headings.

I. External Haemorrhages.

II. Internal Haemorrhages.

III. Joint Haemorrhages.

Under the first heading may be noted those haemorrhages coming from the skin, mucous membranes of the nose, mouth, stomach, bowels and bladder. Skin lesions may vary from a slight discolouration to/

to an extensive haematoma, or there may be a continual oozing of blood, where there is an abrasion. Bruising was noted in all the present series of cases. The application of a tight bandage may frequently bring about a well-marked ecchymosis. Case VII. always showed this, if his arm was bandaged at any time. On the other hand, Case I. never showed any such bruising, though his arm was repeatedly bandaged, previous to being bled from the median basilic vein.

Haemorrhage following the cutting of milk teeth, and especially during the eruption of the second dentition, is said to be a constant feature of the disease. None of the cases under review had any trouble in their early years from the cutting of their teeth. The only examples of teeth bleeding in the present cases are those of Case I., who, when 10 years old, had a tooth extracted, and bled for two or three days afterwards, when the bleeding atopped spontaneously, and Case III., who knocked out his left upper incisor tooth, owing to a cycle accident, and had to be treated in hospital for the resultant haemorrhage. The most frequent seat of bleeding, especially in children, is from the mucous membrane/

membrane of the nose; Epistaxis, according to Grandidier, being four times more common than haemorrhage from any other situation. Goodall's case (42), already referred to, had persistent epistaxis for over three weeks, and,in spite of treatment, died from the resulting anaemia. Cases V., VI., VII. and VIII. have suffered from epistaxis at various intervals. Bleedings from the gums were noticed in Cases I., VI., VII. and VIII; Haematemesis in Cases I. and VII. Melaena was got in Cases I. VI. and VIII., but in them it was always after attacks of epistaxis or haematemesis. Haematuria developed several times in Case I. In Pearson's Case (46), haematuria occurred, no local cause being discovered. The first attack was said to be due to "Mental worry", and though this was formerly given as a cause of haemorrhage, by the older writers, it seems to be the only one recorded in recent times. This patient further illustrated well the effect of climate upon the disease, for the haematuria was always better in warm weather,returning during the colder months.

By Internal Haemorrhages, we understand those that occur beneath the skin, between or into the/

the muscles, or into serous or synovial cavities. In such cases the temperature may be raised and the pulse quickened; the blood tumour may cause the most intense pain, and lead to extensive areas of anaesthesia. An excellent example of this nature is that suffered by Case I., and described at length on pages 156 to 160. This was a haemorrhage into Scarpa's triangle, travelling down Hunter's Canal, causing the most intense pain, for which morphia had to be given. At first, there was hyperaesthesia of the affected leg, followed by a gradual descending anaesthesia, with loss of power in the limb. An X ray photograph was taken of this region, and is shown and described in the separate volume of illustrations (X ray photograph No. 7).

In these internal haemorrhages, at first there may be fluctuation, but later this passes off, as the blood tumour coagulates and gradually becomes absorbed, during which time there may be some discolouration of the skin - a state of affairs, which, according to Wright, is due to a diapedesis of red blood corpusles into the tissues, as well as to a transudation of blood fluids through the capillary walls. On the other hand, instead of absorption of the clot taking place, it has been stated/

stated that calcification of the altered blood may occur, resulting in masses similar to phleboliths, sometimes found in the veins of the pelvis. The occurrence of these is interesting, for it may have been their presence which led the older writers to connect haemophilia with gout,on the assumption that these hard masses were of a gouty nature. Haemorrhages into serous sacs have been known to occur, but are extremely rare in haemophilia. Immermann (23) records two cases where there was bleeding into the peritoneum, and four in which it occurred into the meninges. Cases of meningeal haemorrhage in haemophilia have been reported from time to time, but Arkwright (52), from an analysis of such cases, comes to the conclusion that this cannot be considered a recognized cause of death in this disease. There is reasonable ground for presuming - in Case II., whose family history shows no tendency to insanity - that his mental state may be accounted for by some cerebral haemorrhage of a haemophilic nature in his early infancy, for symptoms of the disease showed themselves in him at an earlier age than in any of the other members of his family, for example, bruising was noticed in him as soon as the third month, long before the first year, as is the general rule for the appearance of haemophilic manifestations.

JOINT HAEMORRHAGES.

These appear usually in one joint at a time, and are by far the most characteristic phenomena of Haemophilia. They are said to occur as later symptoms, usually about the twelfth to the fourteenth year of life.

It appears from the present eight cases, however, that these arthritic troubles start earlier than is generally supposed.

Case I. at 8 years.
Case II. at 5 years.
Case III. at 5 years.
Case IV. at 5 years.
Case V. at 5 years.
Case VI. at 5 years.
Case VII. at 6 years.
Case VIII. at 5 years.

The attack generally comes on suddenly, with swelling of the joint - a point to be remembered when dealing with diagnosis - for haemophilic joints have been not infrequently mistaken for other conditions, often with disastrous results, if operated/

operated upon. (This was nearly so with Case I., who narrowly escaped having an incision made into his knee joint.)

The frequency with which the joint swellings come on during the night has already been mentioned, several of the present cases having shown this peculiarity. There is always pain, and it has been said that the first haemorrhage into a joint is more painful than the subsequent ones. The part may be red and inflamed, but this is not a constant feature. There is usually fluctuation, where the bleeding is not excessive, and the patient is utterly unable, on account of the pain, to move the joint; along with this there may be a rise of temperature. (Vid. Temperature Chart of Case I., page 56). The pulse may become accelerated, and the patient looks ill and has sleepless nights.

Ths joints most commonly selected are naturally those in most common use. In order of frequency, in the present series, by far the most common joint affected was the knee joint, then perhaps the ankles and elbows, wrists, finger and hip/

hip joints.

The joint effusions were at one time thought to be serous in character, but are now definitely known to be haemorrhagic.

The joint swellings usually subside rapidly, (well shown in the present cases - especially Case I. - who was seldom off work for more than three days at a time).

It is probable that very few, if any, bleeders who live to adult age ever escape some degree of crippling from articular lesions. (Case I. cannot fully bend his knee joints).

Only a few cases of fractures have been reported in haemophilic subjects. These are accompanied often with extreme swelling and a steady rise of temperature; the point to guard against is, not to mistake this condition for a secondary inflammatory process, as was nearly done in the case of a boy, aged 8, reported by Monsarrat (53). Another important fact to bear in mind is that union of fractures is in no way delayed by the haemophilic tendency.

RÉSUMÉ/

RÉSUMÉ of SYMPTOMS in EIGHT CASES.

	Prodromal.	Joint Haemorrhages.	Other Haemorrhages.
Case I.	None	Left hip Left knee Right knee Left ankle Big toe Left elbow Left wrist Middle finger Small finger	General Bruising Cuts on head Cuts on fingers Bleeding teeth Bleeding gums Haematemesis Melaena Haematuria Haematoma of thigh Haematoma of leg
Case II.	None	Right ankle Left elbow Right hand	General Bruising Right ear Tongue Melaena
Case III.	None	Left knee Left ankle Right ankle Left wrist Right wrist	General Bruising Bleeding teeth Bleeding tongue Cut fingers
Case IV.	None	Left knee Right ankle	General Bruising Cut forehead Cut thumb Crushed finger
Case V.	None	Left knee Right knee Right elbow	General Bruising Epistaxis

Case/

	Prodromal.	Joint Haemorrhages.	Other Haemorrhages.
Case VI.	None	Left ankle Left hand Right hand Left wrist Right wrist	General Bruising Epistaxis Bleeding gums Melaena Haematoma (Right thigh)
Case VII.	None	Right knee Left ankle Right ankle Finger joints.	General Bruising Epistaxis Cut head Cut fingers Bleeding gums Haematemesis
Case VIII.	None	Left knee Left elbow	General Bruising Epistaxis Bleeding gums Melaena.

DIAGNOSIS/

DIAGNOSIS.

The diagnosis of haemophilia is frequently made on insufficient grounds, and many cases of haemorrhage have been published as haemophilic, which, on closer investigation, have proved to bear no relation at all to this disease. It is very important, therefore, to note what signs and symptoms one ought to lay stress upon, in arriving at a definite diagnosis. The main characteristics are briefly, as follows:-

(a) Inheritance. Only those cases showing a hereditary tendency to bleed should be included as haemophilic, and in investigating this point, it is well to bear in mind that the study of the collateral branches of a family is as important in this connection as that of the direct line.

(b) Delay of Blood Coagulation Time. This is always a constant and marked feature.

(c) Transmission This is always through the female members of haemophilic families.

(d)/

(d) Sex. The males, with rare exceptions, are the only members affected.

(e) Chronicity of Symptoms. The haemorrhages are always chronic in character, starting in childhood, and occurring at intervals throughout the patient's life.

(f) The haemorrhages, as a rule, appear singly, but vary in position at different times. Bleedings restricted to one site alone, though hereditary in character, are not to be confounded with haemophilia. Osler has shown this in a case of recurrent epistaxis, which was hereditary in a certain family, and which he proved to be due merely to a local cause - an inherited condition of the nasal mucous membrane.

With regard to other allied diseases:-

(a) Haemophilia neonatorum. This is a very rare condition. The vast majority of cases, published as such, have now come to be recognized as syphilitic or/

or micro-organismal in character. Umbilical haemorrhage is of no importance in diagnosis, unless it occurs at birth, and there is evidence of a haemorrhagic inheritance.

(b) Infantile Scurvy is distinguished from haemophilia by the appearance of the patient; the lack of implication of the gums, the absence of subperiosteal haemorrhages, and general tenderness; in haemophilia the bleedings are, as a rule, subcutaneous.

(c) Simple bruising, as a rule, is less extensive and less easily brought on than is haemophilic bruising, and there is no accompanying swelling.

(d) Haemorrhagic purpura. Here the coagulation time of the blood is normal, and the bleeding is due to some abnormality of the vessel walls. The bruising occurs as purpuric spots of a deep inky blue colour, and there is no swelling.

(e)/

(e) Chronic purpura, a condition mentioned by Osler as likely to be confounded with haemophilia, for here epistaxis, purpuric spots and bruising are very commonly met with, and any slight abrasion is followed by haemorrhage.

In dealing with the joint manifestations of Haemophilia, these must not be mistaken for:-

(a) Rheumatic Joints, which are always, as a rule, multiple, whereas haemophilic joints are single in onset.

(b) Tubercular Joints, which closely simulate haemophilic joints, and cases have been known where operative interference has led to uncontrollable haemorrhage and death. In haemophilia the onset is sudden, the pain and swelling often extreme, and the recovery remarkably rapid.

The taking of X ray photographs of joints may prove to be a help in diagnosis, for the depth of the shadow cast by fluid in a joint is in direct proportion to its density. In ordinary normal traumatic joint haemorrhages, this shadow is very distinct, with well-defined edges, whereas reference to/

to the photographs of haemophilic joints in the accompanying volume of illustrations show that in haemophilia the shadows cast by the haemorrhagic effusions are all very faint and ill-defined. This may be due to a possible difference in density in haemophilic blood, compared with that of normal blood, a point which, if shown to be correct, might prove important with regard to the aetiology of the disease.

PROGNOSIS/

PROGNOSIS.

The prognosis, though necessarily not always fatal, is nevertheless far from cheerful. The patient is never sure of being free from attacks of haemorrhage at any time, which means that he has to be off work often, and in many cases is thus unable to secure constant employment. On the other hand, there seems to be a tendency for the condition to become less severe and frequent as adult life is reached, and the risk of fatal haemorrhage diminishes in like proportion. This latter fact is probably due to two causes, firstly, to an alleged improvement in the coagulation time of the blood as age advances, and secondly, to the patient getting to realize the risks he runs, and becoming more careful to avoid dangers than he was in his more irresponsible days.

Should the joint manifestations, however, continue to appear, the ultimate result may bring about deformities of the limbs, with consequent crippling of the patient.

TREATMENT.

Before one can treat a disease with much hope of success, one must first know the cause of that disease, and it is exactly for this reason that one is so handicapped in the treatment of haemophilia. Many means have been tried, some of which have proved useful in temporarily arresting the symptoms, but none so far can be said to have cured the condition entirely.

The only recorded case which has been treated antenatally, was by Ballantyne (54), who gave a patient 10 grs. of Calcium Chloride twice daily till her confinement, in the hope of her giving birth to a non-haemophilic child, and it is interesting to note that the patient did give birth to a non-haemophilic male child, unlike her two previous children, who were both "bleeders". How far this is a pure coincidence, it is difficult to say, for it does not always follow that all the male children of a mother of a haemophilic stock should be bleeders. This case is interesting, but it is an isolated one, and more cases with similar results are necessary/

necessary before any definite conclusion can be arrived at on the subject of the antenatal treatment of haemophilia.

With regard to postnatal treatment, the first consideration that has to be attended to, is that of prophylactic measures. When the condition is present, it should be made known to the sufferer, if he does not already realize it, for many haemophilics have been known to submit themselves to operation unwittingly, with disastrous results from uncontrollable haemorrhage. Case I. is a case in point. This patient was in hospital when a boy, with a swollen knee joint, and was about to be operated upon for it by a surgeon. His doctor happened to mention casually to his father, who had just retired from practice, that he was just going out to see the operation, when the father remembered suddenly that this patient came of a haemophilic family, and sent his son off in haste to stop the operation. The latter arrived at the hospital just in time to warn the surgeon, as the patient was being wheeled into the operating theatre. The operation was abandoned, and the patient was kept in bed with complete rest to the swollen knee, which subsided naturally

in/

in the course of a few days, and enabled him to return home cured, having run the grave risk of an untimely death.

Haemophilic patients should lead a quiet life, and avoid excess of stimulants. Their occupation should be a sedentary one, or, at any rate, one free from obvious risk of injury. They should take exercise in moderation, and never over exert or fatigue themselves unduly. Case I. suffered from a swollen and painful ankle joint, and was laid up in bed for several days, merely owing to having played two rounds a day of golf over a hilly golf course two days running. On the other hand, Case III. asserts that since he took up cycling he has never suffered from any joint troubles, whereas before this he was being continually laid up with swollen joints.

Children especially should be carefully looked after, and guarded against possible injury or accident.

Haemophilic patients, who can afford it, should live in warm climates.

The/

The females of a haemophilic stock ought not to marry, even when they show no signs of the disease. As an example of the efficacy of this means of prevention, Fagge (55) relates that among two families in Tenna, haemophilia had been known to exist for about a century. In 1855, the female members resolved not to marry, and in 1879, there were no well-marked cases in the community. The men, however, who are not "bleeders", may be allowed to marry healthy females.

As regards Diet, substances which reduce the blood pressure, such as ale, tea, coffee and tobacco should be avoided.

Operations not absolutely necessary should also be avoided. Great care should be taken of the teeth. The bowels should be kept open, with salines, preferably, when necessary.

LOCAL TREATMENT.

To stop bleeding, local pressure may be applied, but must be moderate, to prevent injury to the surrounding tissues. Bandages, when used, should be firmly, but not tightly, applied. Dr. Lewis of Folkestone (56) says he can safely control cases/

cases of epistaxis in ten minutes, by applying pressure with the finger and thumb, from half an inch anterior to the line of junction of the cartilaginous with the bony part of the nose. This method was tried in several of the present cases, but with no effective result.

Various styptics have been tried, but found to be of little use. Alum, Tannic Acid and Adrenalin, have all been tried. The local application of ice sometimes does good, and for bleeding gums a paste consisting of phenol dr.iii., resin dr.iv. and chloroform dr.ii. may be tightly applied. Liquor Ferri perchlor. Adrenalin Chloride, Tinct. Benzoini Co.,were all tried in Case VII., for a severe cut in the head. Human blood also was resorted to, but the clot which formed was always washed away by the oozing of blood below. The only good result was derived from the use of the Thermocautery, which seemed to stem the haemorrhage for a time at least. Weil advocates the local use of Normal Horse Serum, which, he says, contains the thrombozymic ferments wanting in haemophilic blood. This seemed to stay bleeding on two occasions in Case VIII. A plug of cotton wool soaked in serum was tightly applied to the gums, and at another time/

time a similar plug arrested an uncontrollable epistaxis, but how far the action of the serum was beneficial, it is doubtful to say, for the sites of haemorrhages, being suitable to pressure applications, the good result might have been got equally well by simple plugging. Normal Horse Serum was of no use locally in Case I. or Case VII.

Turpentine is recommended by Eustace Smith (57), in cases of bleeding from the bowels. Plugs soaked in it were applied to stop bleeding from a tooth in Case III., while in the Royal Infirmary in 1908, but patient says it had practically no effect. Gelatine has been loudly praised by some as a local styptic. Sahli used bandages soaked in 2% gelatine solution, and thought that possibly by the pressure some of the gelatine or some of the thrombin in the clot may have reached the wounded vessels. Schmidt tried the local application of thrombokinase, and Morawitz (58) also thought of this, but says that thrombokinase in a few days becomes inert; he managed, however, by vacuum distillation at 30°C. to obtain a permanent preparation. When this is used, it should be pressed into the wound by a tight bandage. Calcium Chloride locally, has been advocated by Wright. Sahli is very doubtful about his results, but/

but recommends its local application in 1% to 2% solutions. It was tried frequently in the present cases, but always found useless. Wright also strongly recommends the use of his "physiological styptic"; it is applied, soaked in cotton wool, and firmly held in contact with the bleeding surface. The preparation of this substance is as follows:-

"Obtain two or three thymus glands, or tes-
"tes of a calf. Free them from fat, and pound or
"mince them as finely as possible. Mix the gland
"substance with saline solution (·9% NaCl in tap
"water) to which a trace of sodium carbonate has
"been added. The proportion of gland to fluid
"should be about 1 to 10. Filter through calico,
"and then add 5% $CaCl_2$, crystaline, and 1% carbolic.
"If time does not press, a more potent styptic is
"obtained by allowing the extraction of the gland
"to proceed for 24 hours in the presence of 1% car-
"bolic. The calcium chloride is then added, after
"straining through calico."

In joint affections Complete Rest is indicated. Lead and opium fomentations may be tried, but are not of much use in relieving the pain.

It is a common practice among haemophilics to rub their affected joints with methylated spirit, and Case III. has found that the application of a liniment, consisting of "Menthol ($\frac{1}{6}$ oz.) and methylated spirit (1 gill)", always gives him relief when his/

his joints are swollen. Later on, when the pain has disappeared from an affected area, gentle massage often does good, and helps to hurry on the process of absorption of the blood clot. For large subcutaneous ecchymoses, ichthyol and collodion are very useful.

TREATMENT by INTERNAL ADMINISTRATION.

For pain, morphia may have to be given. It is stated that it should never be given by hypodermic injection, as it always gives rise to a haematoma at the seat of puncture. Case I. has frequently required morphia, to relieve the pain during his joint attacks, and he has never had it otherwise than subcutaneously, and on no occasion, when a haematoma developed, was it any larger than the size of a small pea. The same may be said about the other cases, who occasionally received hypodermic injections of morphia. The number of drugs, which have been used in the attempt to control haemophilic haemorrhages, is very great, and only a few of the more important ones need be referred to here. They may be classed under three headings - drugs, organic extracts and serums.

Antipyrine/

Antipyrine is mentioned, because it has proved beneficial in the case of a doctor - an undoubted haemophilic - who tried it and was good enough to furnish me with the following details. He found that he could invariably stop his attacks of epistaxis by taking antipyrine in 10 grs. doses, three or four times a day, but the effect was not of long duration. When he had joint haemorrhages, he was in the habit of taking 20 to 30 grs. t.i.d., for a day or two, followed by 10 to 15 grs. t.i.d., till symptoms of antipyrine poisoning began to show themselves.

Ergot has been tried, but its action is doubtful.

Gelatine is said to have proved very useful in controlling haemorrhage. It may be given by subcutaneous injection, as was done with good results in a case reported by Heymann (59). It has been recommended as a cure for haemophilia by Hess (60). Sahli, on the other hand, thinks it too dangerous a drug to give, and does not advise its use. It must be got pure and untainted, and obtained from recently killed calves, making sure that the solutions are perfectly sterile. Lancereaux states that 15 grammes of gelatine, divided into four doses, produces/

produces a remarkable effect in Haemophilia. Abt (61), on the other hand, has observed great prostration and collapse in three healthy children, to whom he gave it subcutaneously, and says it contains toxic properties, given thus, but he warmly approves of its use, given locally or by the mouth.

Wright recommends the administration of one gramme of a mixture of calcium lactate and magnesium carbonate, equal parts, followed by half a gramme daily, and for adults four times this quantity, but the blood most be carefully examined during this treatment, as excess of the drug tends to produce a condition of decreased blood coagulability.

Calcium lactate has also been tried alone, in doses of 30 to 80 grs., two or three times daily. It has been stated, however, that calcium salts, given in too large doses, have an opposite effect to reducing the blood coagulation time.

Wright also suggested inhalations of CO_2 as a treatment in haemophilia - the theory upon which this is based has already been discussed, under Aetiology and Pathology, where it was pointed out that the nocturnal onset of symptoms might be due to a diminished CO_2 content of the blood. He suggests the/

the use of gas from an ordinary Kipps' apparatus, fitted with a wash bottle and a rubber tube passing to the patient's mouth.

Various Extracts have been described as being useful, such as Ovarian, Thyroid and Suprarenal extracts.

Grant (62), being impressed with the rarity of the disease in females, thought of trying Ovarian Extract, on the principle that the ovaries undoubtedly exert a profound influence on the adult female, possibly through an internal secretion, and that this influence might be a factor concerned in the prevention of the disease in women. He gave it in $2\frac{1}{2}$ gr. doses twice daily, in the case of a boy, aged 10 years, who had a severe cut in the foot, and was successful in arresting the apparently uncontrollable bleeding in a few days.

Wright states that he has seen the tendency to bleed in a haemophilic held in check by the administration of thymus tabloids, with a view to remedying the defect in leucocytes. On the other hand, Thyroid Extract in 5 grs. doses has been tried, with much success. Fuller (63) reports a case of haematuria in a Jewish boy, where other means had failed, and where thyroid cleared up the symptoms in a couple of/

of days, and remained cured till the time of writing, nine months later. The haemophilic doctor, already referred to, also tried this remedy, after personally extracting one of his own teeth, and he was able thus to at once arrest the profuse haemorrhage which ensued. Weil (31), on the other hand, found thyroid was of no use.

Suprarenal Extract, according to some, has been reported to be of value in successfully controlling haemorrhage, and Schäfer advises its use along with calcium as a local styptic. In an article on the action of organic extracts upon the blood of haemophilics, Weil summarises their effects, as follows:-

I. Dosage and species of animal selected are of no moment.

II. They affect in a similar way both his "family" and "sporadic" cases.

III. They do not all act in the same way.

(a) Those which cause a constant prolongation of the coagulation time are, Extracts of Thyroid, Spleen, Duodenum, Liver, Pancreas, Suprarenal body, the whole Pituitary body in the case of sheep, but only the anterior lobe in the case of the ox.

(b)

(b) Those which have various effects are Extracts of Ovary, testis, thymus and kidney.

(c) Those which hasten coagulation are serums, and the posterior lobe of the pituitary body of the ox.

The therapeutic agent which was employed in the present series of eight cases was normal horse serum, first suggested by Emile Weil (31), and the effect of this on the blood coagulation time was noted by a series of coagulation tests, taken while these patients were under treatment.

The method employed at first for testing the coagulation of the blood was that of McGowan (64), which,briefly stated, consists in partially filling a capillary tube 6 ins. long, and 1·5 mm. in diameter with blood, under certain precautions, sealing up one end, and at intervals of a minute breaking off a small part, until a fine fibrin thread is seen, on slowly drawing the fractured ends apart. The coagulation time is the time elapsing between the filling of the tube and the first appearance of fibrin. McGowan believed that, for clinical purposes, it was unnecessary to have an apparatus to maintain his glass tubes at a constant temperature, since variations/

variations between 15°C. and 20°C. did not appreciably affect the coagulation time - but Addis (65) showed this idea to be erroneous, and stated that a constant temperature was most important for accurate results, and devised a modification of McGowan's method to remedy this defect. This consists of a cylindrical vessel, placed in the centre of a similar, but considerably larger, vessel; both are filled with water, at a temperature of 20°C., and McGowan's tubes are inserted into metal receptacles made to exactly fit them, and introduced into the inner vessel, - thus being kept at a constant temperature. On reference to the Blood Coagulation Chart of Case I., (page 111), it will be seen how inconstant were the results got by McGowan's method, especially noticeable in the control estimations, compared with those arrived at by the use of Addis' Coagulometer, which was therefore uniformly used for all subsequent estimations. It was found that, to obtain accurate results, the temperature of the finger from which the blood was taken, should not be too cold, and where this was the case, the patient was made to warm up his hand by bathing it in hot water. Tests were also performed, to see if previous bandaging of the proximal end of the finger to be punctured/

punctured caused any alteration in the coagulation time, but these proved negative. As a rule, six estimations were made each time the test was applied, making a separate and fresh puncture, for each result, and the average of these taken to be the coagulation time of the patient's blood. In doing so, it was found that, in the majority of cases, the times obtained varied often considerably, some sets showing more divergent results than others. In only one case, out of over 500 estimations made, were they all exactly the same - this was with Case VII., whose blood was tested on the 15th October 1911, with the following uniform result.

No.1.	6· 2· 0	6·32· 0	= 30 m.
No.2.	6· 5·30	6·35·30	= 30 m.
No.3.	6· 9· 0	6·39· 0	= 30 m.
No.4.	6·11· 0	6·41· 0	= 30 m.

The control estimations, on the other hand, seldom varied more than about one or two minutes on each occasion they were taken, for example, on the 22nd April 1911, they showed the following times:-

No.1.	9·30· 0	9·40· 0	= 10 m.
No.2.	9·32· 0	9·42· 0	= 10 m.
No.3.	9·36· 0	9·47· 0	= 11 m.
No.4.	9·40·30	9·49·30	= 9 m.
No.5.	9·43· 0	9·54· 0	= 11 m.
No.6.	9·45· 0	9·55· 0	= 10 m.

Those/

Those of the "non-bleeder" relations of these patients likewise showed similarly constant results.

"Non-bleeder" sister of Case II., estimated on the 14th June 1910.

No.1.	4·13· 0	4·23· 0	= 10 m.
No.2.	4·15· 0	4·25· 0	= 10 m.
No.3.	4·17· 0	4·27· 0	= 10 m.

"Non-bleeder"brother of Case V., estimated on the 5th June 1910.

No.1.	3·45· 0	3·53· 0	= 8 m.
No.2.	3·47· 0	3·55· 0	= 8 m.
No.3.	3·48· 0	3·56· 0	= 8 m.

So that it is evident that these variations in the coagulation time of haemophilic blood must be due to some cause other than to mere experimental error.

Before stating the results arrived at from the administration of normal serum, the effects noted by Weil in his researches must first be summarized.

He used serum from the rabbit, horse, and man, with equal effect, but states that the serum of/

of bullock's blood must never be used, as it has been known to cause serious symptoms of "serum disease", always temporary, but at times intense,and accompanied by hyperpyrexia, rigors, headaches, cyanosis and vomiting. Normal serum, according to Weil, contains the thrombozymic ferments, which he says are wanting in haemophilic blood. It may be given by the mouth, in doses of 20 cc. to 40 cc, subcutaneously in doses of 20 cc. to 30 cc., or by intravenous injection in 10 cc. to 20 cc. doses. The serum does not take effect till 48 hours after administration, and its influence does not last for a very prolonged period - a matter of a few weeks. It becomes less potent, the longer it is kept, and should not be used older than 15 days, if a full therapeutic action is desired. Nolf and Herry (37) on the other hand, state that serum, which has been kept, is just as efficacious as fresh serum, although no thrombin is contained.

Weil affirms that it acts differently in his two forms of the disease, thus in the "sporadic" form, serum given intravenously in doses of 15 cc. to 20 cc. renders the coagulation of the blood normal, both in time and form, bleeding from the skin surface goes on and stops like that of a normal person, and the skin reacts to traumatism in

a/

a normal way. The effect is transient, lasting about five weeks, when the Coagulability "goes back", in time, but not in form. He mentions the following examples. In one case, a tooth was drawn 25 days after injection, in another a perinephric abscess was incised 2 days later, and in yet a third case an operation for empyema was performed, all without notable bleeding.

In the "family" form, intravenous injection of serum modifies coagulation of the blood considerably, but never brings it down to normal. It is only a suitable therapeutic agent against symptoms, and does not reach at the cause of the condition. Thus a case of haematuria, having lasted for a whole month, stopped in three days after an injection of serum. Likewise, a patient who was in the habit of bleeding for 12 hours after cutting himself in shaving, did so for only two minutes after getting serum. Weil, however, admits that normal serum is not always effective in this form of the disease, and certainly does not appear to have much action <u>in vitro</u> (a fact which was gone into and confirmed by Addis).

Toussaint found antitetanic and antidiphtheritic serums equally efficacious in the prevention/

prevention of bleeding in cases of haemophilia.

Broca was successful in arresting haemorrhage from the socket of a milk tooth in a haemophilic boy, by plugging the cavity with gauze soaked in anti-diphtheritic serum, and injecting 20 cc. of the serum subcutaneously.

Rosenau and Anderson (66) have written a paper on "serum disease", following the injection of horse serum, and after describing in detail the symptoms met with, state that, though such serum injections are usually innocuous in man, they have found from experiments in rabbits and guinea-pigs, that it may often cause sudden death.

Dejardin (67) supports Weil's views on the pathology and treatment of haemophilia, and gives details of cases which, previous to surgical interference, were treated by him with serum, with excellent results.

The Serum used in the present cases, with very few exceptions, was procured direct from a reliable firm in London. It was administered in various ways in the eight cases: Intravenously, for the most part, in Case I; subcutaneously, in Case II., and by the mouth in all the other cases. It was found impracticable to give it otherwise than by the mouth in the younger cases, who became very nervous and upset at the sight of the injecting syringe/

syringe. The serum appeared in all cases to have a general constitutional effect, in that the patients admitted that they felt a "sense of well-being" (as one of them expressed it), while they were taking it, and in that sense they derived benefit from it, but the results shown by the effect on the coagulation time of the blood were found to be uncertain, slight and transient, never bringing about a sudden fall, and as often as not having no effect whatever. In only one case did a serum rash develop - Case II. - but the symptoms were not severe.

Several estimations were made to test the result of normal serum on haemophilic blood in vitro, and it was found that the serum had no effect in diminishing the coagulation time, but tended rather to increase it. For example, in Case I., on the 20th March 1910, two sets of estimations were made, one set done with tubes through which normal horse serum had been run, and another set through which no serum had been passed.

1st Series, having serum previously passed through the coagulation tubes.

No.1./

No.1.	9·2 · 0	9·53· 0 = 51 m.		
No.2.	9· 4· 0	9·52· 0 = 48 m.		
No.3.	9· 6· 0	10· 0· 0 = 54 m.		
No.4.	9· 8· 0	10· 0· 0 = 52 m.		51 m.
No.5.	9· 9· 0	9·55· 0 = 46 m.		
No.6.	9·10· 0	10· 5· 0 = 55 m.		

Average coagulation time being 51 minutes.

2nd. Series, without serum having been previously passed through the coagulation tubes.

No.1.	9·59· 0	10·30· 0 = 31 m.		
No.2.	10· 0· 0	10·30· 0 = 30 m.		
No.3.	10· 3· 0	10·35· 0 = 32 m.		
No.4.	10· 4· 0	10·40· 0 = 36 m.		32 m.
No.5.	10· 7· 0	10·40· 0 = 33 m.		
No.6.	10·12· 0	10·45· 0 = 33 m.		

Average coagulation time being 32 minutes.

A similar test was later attempted in the same case <u>in vivo</u>, the patient not having had any serum for a prolonged time. The coagulation time was taken first, before any serum had been given, 10cc. of normal serum was then injected into the median basilic vein, and the coagulation time later re-estimated at intervals of several hours.

2·10·10.

No.1.	3·36· 0	4·42· 0 = 66 m.		
No.2.	3·38· 0	4·43· 0 = 65 m.		
No.3.	3·42· 0	4·41· 0 = 59 m.	61 m.	
No.4.	3·44· 0	4·45· 0 = 61 m.		
No.5.	3·47· 0	4·43· 0 = 56 m.		
Cont.	3·50· 0	3·59· 0 = 9 m.		

Six hours later, 10 cc. Normal Serum injected intravenously.

No.1.	9·30· 0	10·39· 0 = 69 m.		
No.2.	9·32· 0	10·45· 0 = 73 m.		
No.3.	9·34· 0	10·44· 0 = 70 m.	70 m.	
No.4.	9·37· 0	10·41· 0 = 64 m.		
No.5.	9·40· 0	10·55· 0 = 75 m.		
Cont.	9·45· 0	9·55· 0 = 10 m.		

3·10·10. Twelve and a half hours later.

No.1.	10· 0· 0	11· 7· 0 = 67 m.		
No.2.	10· 2· 0	11·14· 0 = 72 m.		
No.3.	10· 4· 0	11· 3· 0 = 59 m.	68 m.	
No.4.	10· 6· 0	11·15· 0 = 69 m.		
No.5.	10·10· 0	11·25· 0 = 75 m.		
Cont.	10·15· 0	10·25· 0 = 10 m.		

4·10·10/

4·10·10. Thirty-six hours later.

No.1.	9·30· 0	10·32· 0	= 62 m.	
No.2.	9·32· 0	10·26· 0	= 54 m.	
No.3.	9·35· 0	10·43· 0	= 68 m.	65 m.
No.4.	9·38· 0	10·56· 0	= 78 m.	
No.5.	9·41· 0	10·46· 0	= 65 m.	
Cont.	9·44· 0	9·53· 0	= 9m.	

Forty-eight hours later.

No.1.	9·32· 0	10·39· 0	= 67 m.	
No.2.	9·36· 0	10·24· 0	= 48 m.	
No.3.	9·38· 0	10·32· 0	= 54 m.	60 m.
No.4.	9·40· 0	10·50· 0	= 70 m.	
No.5.	9·41· 0	10·43· 0	= 62 m.	
Cont.	9·43· 0	9·53· 0	= 10 m.	

It will be seen, therefore, from both these series of tests, that the serum given intravenously was practically inert in vivo, as well as in vitro. In none of the cases did the administration of normal serum bring about a sudden fall in the blood coagulation time, the greatest reduction being one of twenty minutes in Case II., where in three days, after a subcutaneous injection of 10 cc. of normal serum, the coagulation time altered from 85 minutes to 60 minutes, but did not long remain at/

at this, for two days later it was up to 73 minutes, and in seven days more it reached 80 minutes. In fact, a general survey of the coagulation results, taken during the three weeks the patient was under observation, gives the impression that the serum injection had no therapeutic effect, and that the same coagulation results might have been got even in the absence of the serum.

Before			(Serum)	After		
70m.	65m.	85m.	(Injection)	60m.	73m.	80m.

If there was any effect at all, it was only transient and very slight.

Case IV. showed a reduction of 31 minutes in coagulation time in three days (from 58 to 27 minutes respectively), but serum in 10 cc. doses had been taken daily by mouth for as long as seven days before this drop occurred. After the serum was stopped, the coagulation time showed signs of becoming prolonged again, so that it may be admitted that in this case there was some effect caused by the serum, though not sufficient to be of any practical value in treatment.

	(10.cc.)						
	) serum (					(stopped)	
52 m.	(by mouth)	50 m.	58 m.	27 m.	25 m.	(serum.)	36 m.
	) daily. (						

Numerous/

Numerous examples are seen in these results of reductions in coagulation time during periods when serum was not being given. Thus, Case VIII. showed a reduction of 20 minutes, dropping from 68 minutes to 43 minutes, in the course of several days.

In some cases the administration of serum showed a retarding effect on the coagulation of the blood, thus that of Case III. rose from 68 to 106 minutes, while 10 cc. serum was being given daily by mouth, and went on being prolonged even after the

68 m.	(10 cc.) (serum) (daily)) (by mouth)	64 m.	63 m.	106 m.	(serum) (stopped) 144 m.

serum was stopped. It is a question, whether this result would not have been got, even without serum, for the prolongation was not accompanied by any symptoms pointing to excess or harmful effect of the serum.

Case VII., under serum treatment, showed, at first, a similar delay in coagulation time,

40 m.	(10 cc.) (serum) (by mouth) (daily.)	63 m.	104 m.	(stopped) (serum.)	95 m. 95 m.

on subsequent occasions, however, when serum was again given, no such excessive delay occurred.

Case/

Case I. showed a delay of from 42minutes to 70 minutes, after an intravenous injection of 10 cc. of serum, when he was first seen, but never on any subsequent occasion did a similar result occur. Given by the mouth in 10 cc. doses daily, the coagulation time of his blood gradually reduced from 70 minutes to 13 minutes, but when stopped, it rose again to 52 minutes; on starting the serum once more, the coagulation time was brought gradually down to an average of 25 minutes, never any further. During a prolonged time, when the serum was stopped, the delay in coagulation again showed itself, but, on resuming the treatment, the coagulation again showed signs of becoming hastened. Each time he was taking the serum, the effect was of a very gradual nature, and out of all proportion to the amount of serum taken. He never showed the least symptom of serum excess.

In all these cases the administration of serum seemed to have no therapeutic effect upon the symptoms of the disease, for joint troubles and other haemorrhages occurred in the same proportions during treatment, as when serum was not being given.

SHORT/

SHORT RÉSUMÉ of the EFFECT of NORMAL SERUM.

Case I. Given intravenously not much good, showed better results by oral administration, but took a long time to produce any appreciable reduction in coagulation time.

Case II. Given subcutaneously very little effect, and not lasting. Caused a mild attack of serum disease.

Case III. Applied locally was of no use. Given by the mouth showed no effect at first, but later greatly delayed the coagulation time.

Case IV. Given by the mouth had a slight effect, but not sufficient to be of any practical value in treatment.

Case V. Given by the mouth showed no result worth noting. This was a very mild case, and only seen on two occasions.

Case/

Case VI. Given by the mouth showed no result, the coagulation time being much the same with serum as without, and did not seem to be influenced by presence of symptoms.

Case VII. Given by the mouth showed no appreciable effect, beyond a delayed coagulation on its first administration. The coagulation time was reduced by half during haemorrhagic symptoms.

Case VIII. Given by the mouth showed no result. The coagulation time did not appear to be affected during haemorrhagic symptoms.

CASE/

CASE I.

RÉSUMÉ of COAGULATION RESULTS.

25·2·09.	Coagulation Time 42 mins. Control 16 mins. Given 10cc. Normal Horse Serum intravenously.
26·2·09.	Coagulation Time 32 mins. Control 10 mins.
14·3·09.	" " 70 " " 20 " Started 10cc. Normal Horse Serum daily by mouth.
18·3·09.	Coagulation Time 40 mins. Control 16 mins.
1·4·09.	Stopped Normal Horse Serum. Put on 10 grs. Calcium lactate, but had to be stopped in 3 days, owing to gastric intolerance.
3·4·09.	Coagulation Time 58 mins. Control 14 mins.
22·5·09.	Started Normal Horse Serum again, 10cc. daily by mouth.
23·5·09.	Coagulation Time 40 mins. Control 9 mins.
30·5·09.	" " 44 " " 10 "
13·6·09.	" " 38 " " 11 "
27·6·09.	" " 35 " " 15 "
18·7·09.	" " 31 " " 12 "
1·8·09.	" " 24 " " 12 "
8·8·09.	" " 19 " " 6 "

28·8·09./

MACGOWAN'S METHOD.

28·8·09. Stopped Normal Horse Serum.

29·8·09. Coagulation Time 13 mins. Control 9 mins. (McGowan's Method).

14·11·09. Started Normal Horse Serum 10cc. daily by mouth.

21·11·09. Coagulation Time 52 mins. Control 10 mins.
" " 41 " " 8 " (Addis. Method)

28·11·09. Coagulation Time 32 mins. Control 12 mins.

12·12·09. " " 27 " " 10 "

Normal Horse Serum reduced in dose to 5cc. daily by mouth.

19·12·09. Coagulation Time 33 mins. Control 9 mins.

26·12·09. " " 25 " " 10 "

27·12·09. Started again on full 10cc. dose of Normal Horse Serum daily.

9·1·10. Coagulation Time 26 mins. Control 9 mins.

23·1·10. " " 25 " " 10 "

6·2·10. " " 28 " " 8 "

13·2·10. " " 29 " " 7 "

Stopped Normal Horse Serum for one week.

20·2·10. Coagulation Time 36 mins. Control 10 mins.

Normal Horse Serum 10cc. injected intra-venously.

27·2·10. Coagulation Time 28 mins. Control 10 mins.

6·3·10. " " 32 " " 12 "

13·3·10./

13·3·10.	Coagulation Time	37	mins.	Control	8	mins.
20·3·10.	"	"	32	"	"	10	"
	Normal Horse Serum 10cc. injected intra-venously.						
27·3·10.	Coagulation Time	31	mins.	Control	10	mins.
3·4·10.	"	"	31	"	"	10	"
13·4·10.	"	"	48	"	"	9	"
20·4·10.	"	"	37	"	"	10	"
1·5·10.	"	"	39	"	"	8	"
8·5·10.	"	"	32	"	"	10	"
15·5·10.	"	"	37	"	"	9	"
22·5·10.	"	"	61	"	"	10	"
29·5·10.	"	"	52	"	"	10	"
5·6·10.	"	"	61	"	"	9	"
12·6·10.	"	"	60	"	"	9	"
19·6·10.	"	"	61	"	"	7	"
26·6·10.	"	"	58	"	"	9	"
10·7·10.	"	"	66	"	"	11	"
19·7·10.	"	"	53	"	"	8	"
24·7·10.	"	"	54	"	"	12	"
1·8·10.	"	"	40	"	"	10	"
7·8·10.	"	"	56	"	"	9	"
14·8·10.	"	"	56	"	"	10	"
18·8·10.	"	"	42	"	"	8	"
23·8·10.	"	"	57	"	"	9	"
4·9·10.	"	"	52	"	"	11	"
26·9·10.	"	"	61	"	"	9	"

10cc. Normal Horse Serum injected intravenously.

9·10·10. Coagulation Time 50 mins. Control 10 mins.

2·2·11. Normal Horse Serum 5cc. daily by mouth night and morning.

28·2·11. Normal Horse Serum stopped.

19·4·11. Coagulation Time 57 mins. Control 11 mins.

10cc. Normal Horse Serum daily by mouth.

20·4·11. Coagulation Time 61 mins. Control 9 mins.

21·4·11. " " 51 " " 9 "

22·4·11. " " 48 " " 10 "

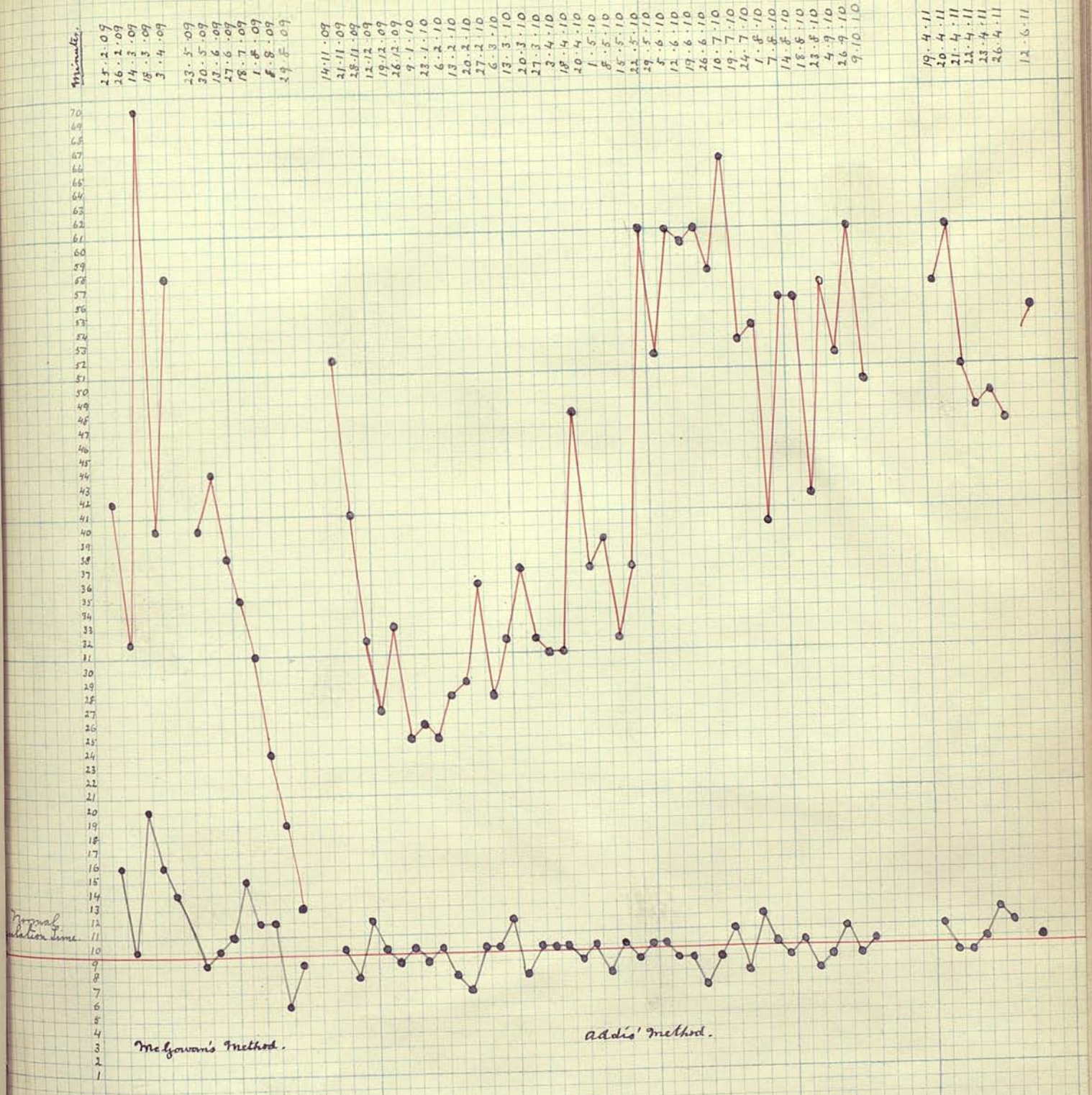
23·4·11. " " 49 " " 12 "

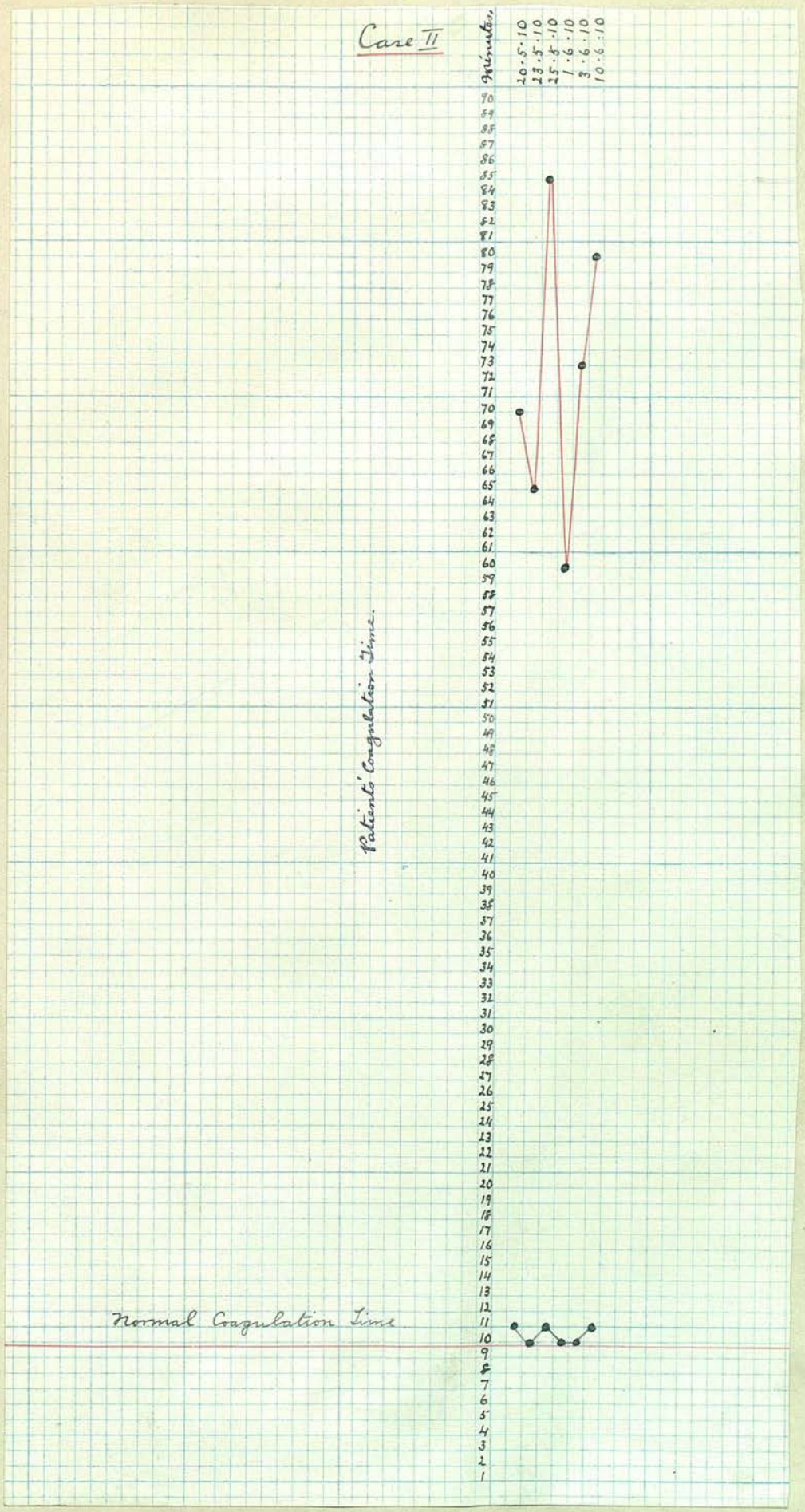
26·4·11 " " 47 " " 11 "

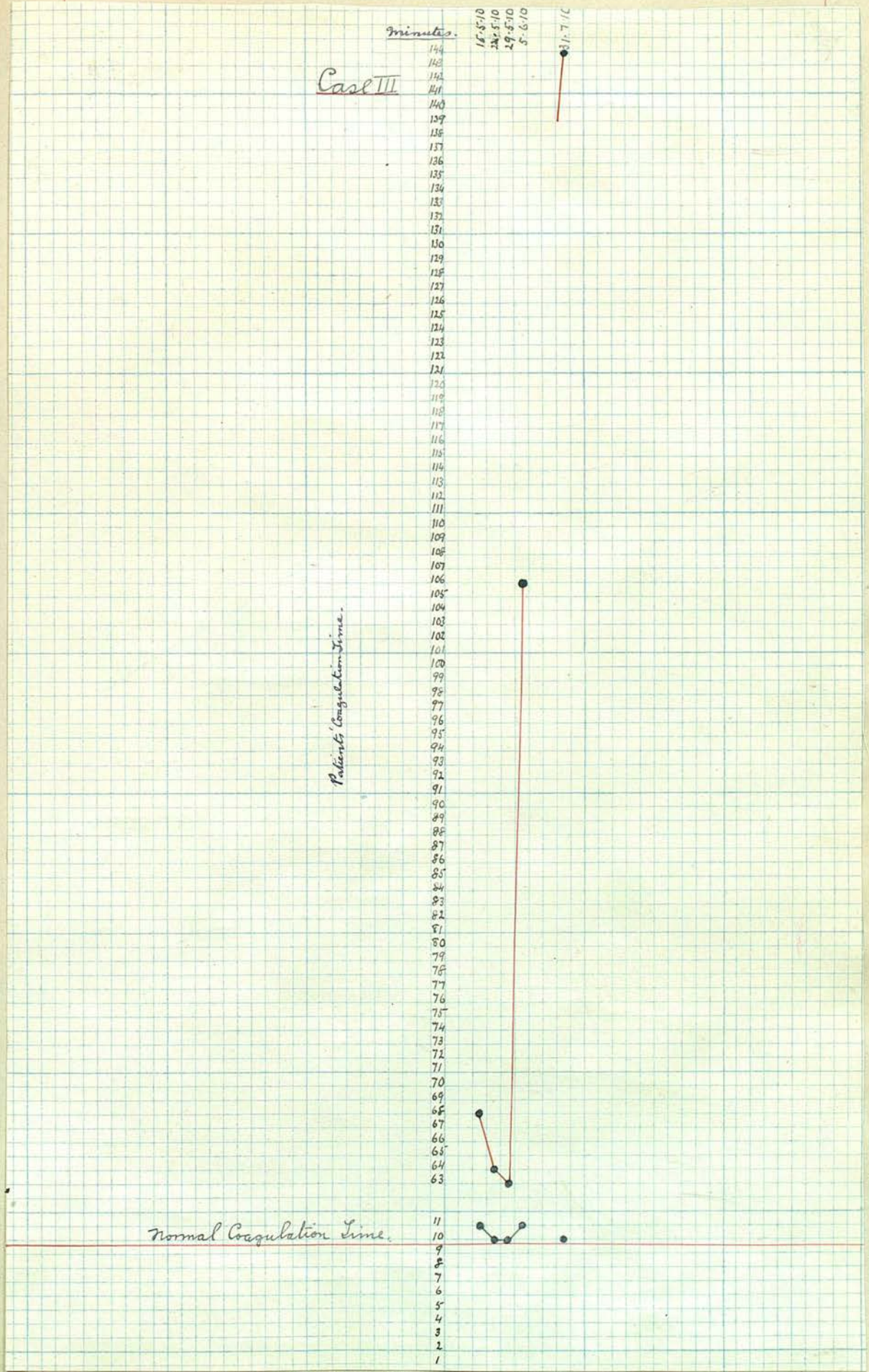
Stopped Normal Horse Serum.

12·6·11. Coagulation Time 55 mins. Control 10 mins.

Case I


Minutes.
25.2.09
26.2.09
14.3.09
16.3.09
3.4.09
23.5.09
30.5.09
12.6.09
27.6.09
18.7.09
1.8.09
8.8.09
29.8.09
14.11.09
21.11.09
28.11.09
12.12.09
19.12.09
26.12.09
9.1.10
23.1.10
6.2.10
13.2.10
20.2.10
27.2.10
6.3.10
13.3.10
20.3.10
27.3.10
3.4.10
18.4.10
20.4.10
1.5.10
8.5.10
15.5.10
22.5.10
29.5.10
5.6.10
12.6.10
19.6.10
26.6.10
10.7.10
19.7.10
24.7.10
1.8.10
7.8.10
14.8.10
18.8.10
23.8.10
4.9.10
26.9.10
9.10.10
19.4.11
20.4.11
21.4.11
22.4.11
23.4.11
26.4.11
12.6.11
Normal Ovulation Time.
McGowan's Method.
Addis' Method.


Case II
Minutes.
20.5.10
23.5.10
25.5.10
1.6.10
3.6.10
10.6.10
Patients' Coagulation Time.
Normal Coagulation Time.


Minutes.
Case III
Patient's Coagulation Time.
Normal Coagulation Time.
15.5.10
24.5.10
29.5.10
5.6.10
31.7.10

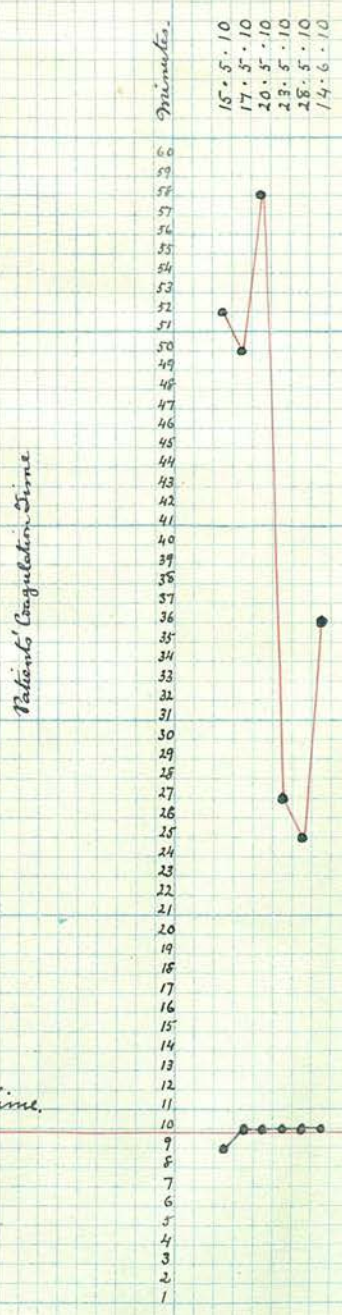
CASE IV.

RÉSUMÉ of COAGULATION RESULTS.

15·5·10.	Coagulation Time	52	mins.	Control	9	mins.
	Put on Normal Horse Serum 10cc. daily by mouth.						
17·5·10.	Coagulation Time	50	mins.	Control	10	mins.
20·5·10.	" "	58	"	"	10	"
23·5·10.	" "	27	"	"	10	"
28·5·10.	" "	25	"	"	10	"
	Stopped Normal Horse Serum.						
14·6·10.	Coagulation Time	36	mins.	Control	10	mins.

CASE/

Case IV


Minutes.
15 · 5 · 10
17 · 5 · 10
20 · 5 · 10
23 · 5 · 10
28 · 5 · 10
14 · 6 · 10
Patients' Coagulation Time.
Normal Coagulation Time.

CASE V.

RÉSUMÉ of COAGULATION RESULTS.

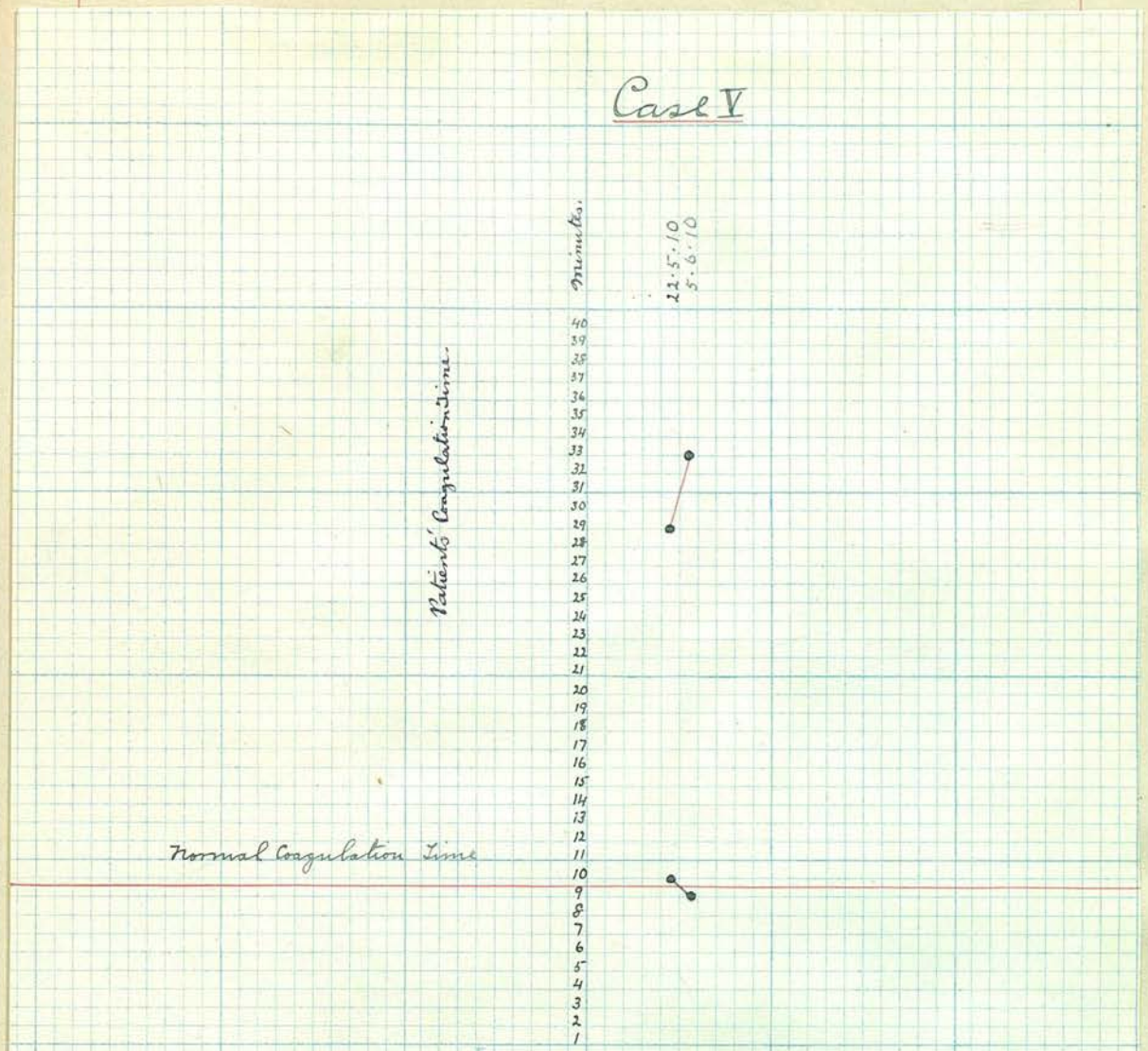
22·5·10. Coagulation Time is 29 mins. Control 10 m.
Put on Normal Horse Serum 10cc. daily by mouth.

5·6·10. Coagulation Time 33 mins. Control 9 mins.

NON-HAEMOPHILIC BROTHER.

5·6·10. Coagulation Time 8 mins. Control 9 mins.

Case V


Minutes.
40
39
38
37
36
35
34
33
32
31
30
29
28
27
26
25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
Patient's Coagulation Time.
Normal Coagulation Time
22.5.10
5.6.10

CASE VI.

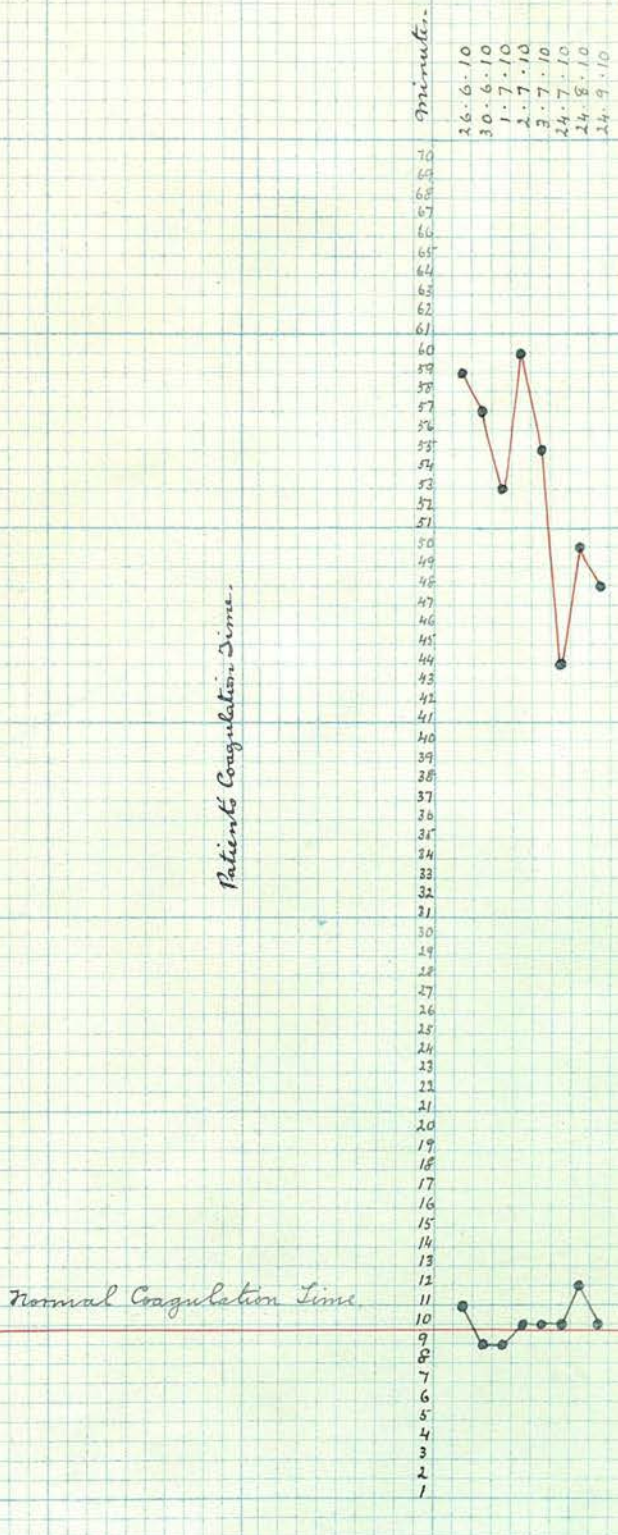
RÉSUMÉ of COAGULATION RESULTS.

26·6·10.	Coagulation Time	59	mins.	Control	11	m.	
29·6·10.	Put on Normal Horse Serum 10cc. daily by mouth.						
30·6·10.	Coagulation Time	57	mins.	Control	9	mins.	
1·7·10.	"	"	53	"	"	9	"
2·7·10.	"	"	60	"	"	10	"
3·7·10.	"	"	55	"	"	10	"
24·7·10.	"	"	44	"	"	10	"
29·7·10.	Normal Horse Serum stopped.						
24·8·10.	Coagulation Time	50	mins.	Control	12	mins.	
24·9·10.	"	"	48	"	"	10	"

NON-HAEMOPHILIC BROTHER.

9·7·10. Coagulation Time 12½ mins. Control 10 mins.

Case VI

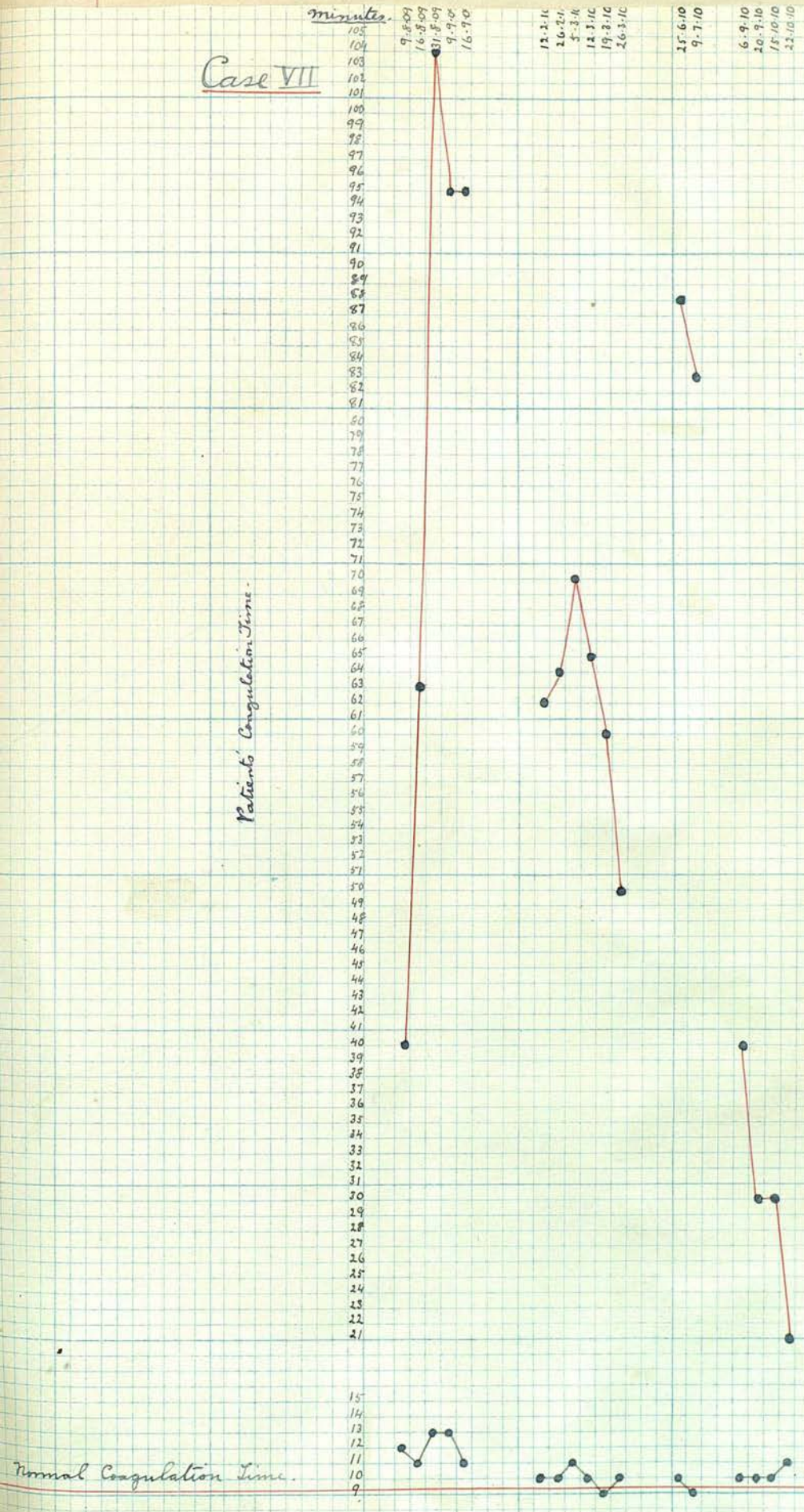

Minutes.
26.6.10
30.6.10
1.7.10
2.7.10
3.7.10
24.7.10
24.8.10
24.9.10
Patient's Coagulation Time.
Normal Coagulation Time.

CASE VII.

RÉSUMÉ of COAGULATION RESULTS.

9·8·09.	Coagulation Time 40 mins. Control 12 mins.	MOGOWAN'S METHOD.
	Normal Horse Serum 10cc. daily by mouth.	
16·8·09.	Coagulation Time 63 mins. Control 11 mins.	
31·8·09.	" " 104 " " 13 "	
	Normal Horse Serum stopped.	
9·9·09.	Coagulation Time 95 mins. Control 13 mins.	
16·9·09.	" " 95 " " 11 "	
12·2·10.	" " 62 " " 10 "	
17·2·10.	Normal Horse Serum 5cc. daily by mouth.	
26·2·10.	Coagulation Time 64 mins. Control 10 mins.	
5·3·10.	" " 70 " " 11 "	
12·3·10.	" " 65 " " 10 "	
19·3·10.	" " 60 " " 9 "	
	Normal Horse Serum stopped.	
26·3·10.	Coagulation Time 50 mins. Control 10 mins.	
25·6·10.	" " 88 " " 10 "	
	Normal Horse Serum 5cc. daily by mouth.	
9·7·10.	Coagulation Time 83 mins. Control 9 mins.	
6·9·10.	" " 40 " " 10 "	
20·9·10.	" " 30 " " 10 "	
15·10·10.	" " 30 " " 10 "	
	10 grs. Calcium Lactate intramuscularly.	
22·10·10.	Coagulation Time 21 mins. Control 11 mins.	

Case VII


minutes.
9.8.09
16.8.09
31.8.09
9.9.09
16.9.09
12.2.10
26.2.10
5.3.10
12.3.10
19.3.10
26.3.10
25.6.10
9.7.10
6.9.10
20.9.10
15.10.10
22.10.10
Patients' Coagulation Time.
Normal Coagulation Time.

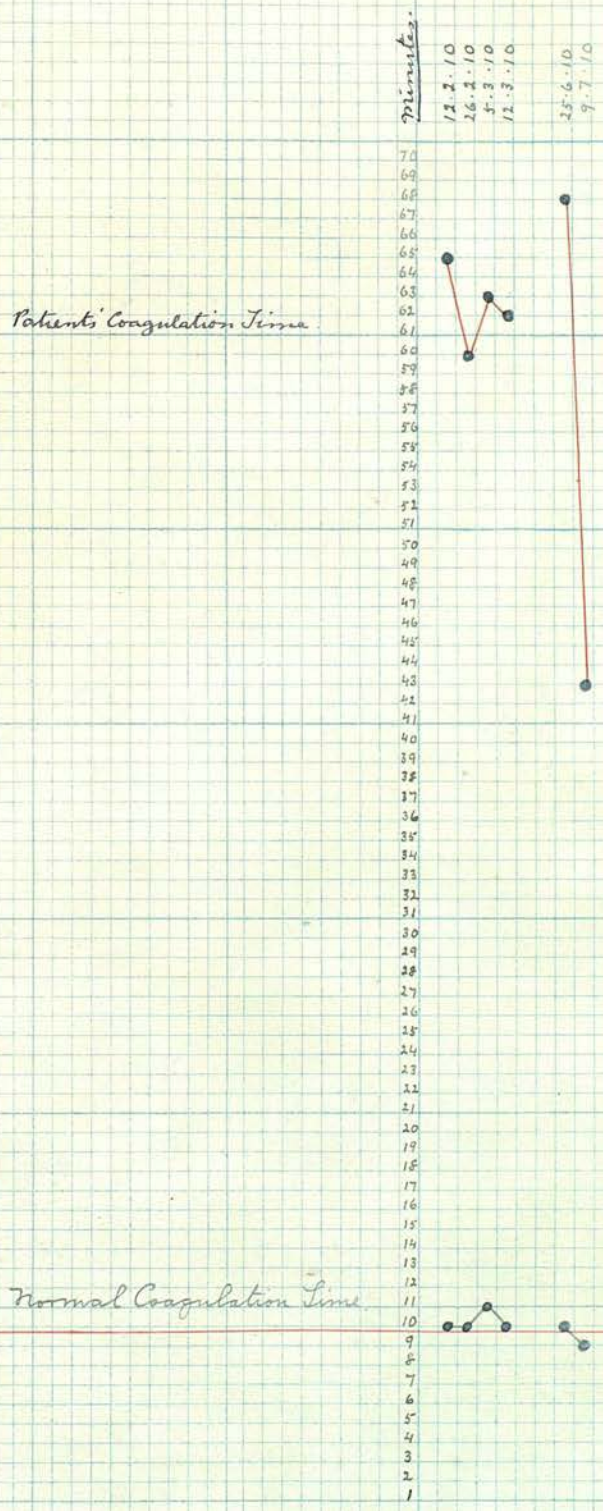
CASE VIII.

RÉSUMÉ of COAGULATION RESULTS.

12·2·10.	Coagulation Time is	65	mins.	Control	10	m.	
	Normal Horse Serum 5cc.daily by mouth.						
26·2·10.	Coagulation Time	60	mins.	Control	10	mins.	
5·3·10.	" "	63	"	"	11	"	
12·3·10.	" "	62	"	"	10	"	
25·6·10.	" "	68	"	"	10	"	
9·7·10.	" "	43	"	"	9	"	

Witte's /

Case VIII


Minutes.
12.2.10
26.2.10
5.3.10
12.3.10
25.6.10
9.7.10
Patients' Coagulation Time.
Normal Coagulation Time.

Witte's Peptone has been recently tried in cases of haemophilia. It is not without its dangers, however, as it has the effect of momentarily increasing haemorrhage before it takes action. It is said to be well borne, and does not produce anaphylaxis on repeated use. It contains more thrombozyme than does serum, and may be given subcutaneously in 10 cc. doses of a 5% solution in 5% NaCl on every alternate day.

Direct Transfusion of human blood is said to be beneficial in cases of collapse from severe bleeding in haemophilia. Immediate results are obtained, and all further bleeding stopped.

Finally, after a severe haemorrhage, the resulting anaemia may be treated along ordinary lines, by complete rest, the use of iron, and later cod liver oil; careful diet and general hygienic treatment.

CASE I.

OCCUPATION. Watchmaker.

AGE. 24 years (1909).

Under observation from 12th February, 1909, to March, 1912.

HISTORY.

Patient has had usual children's diseases, and was especially ill with scarlet fever.

When 6 years old, patient had an attack of "inflammation of the stomach", and the doctor applied three leeches locally. Patient was then taken to the Infirmary, and his mother imagines that he may have had an internal haemorrhage, for he was passing blood by the bowels.

When 8 years old, patient fell while on his way to school and hurt his left knee, which became suddenly swollen; the swelling went away in about three or four weeks.

When 10 years old, patient had a tooth extracted at Marshall Street Dispensary, and bled for two or three days afterwards, when the bleeding seemed to stop spontaneously.

From this time onwards, till he was 17 years/

years old, he had several attacks of haematuria, with great pain , and his left knee troubled him from time to time; only once was he free for a whole year on end.

When 17 years old, he was admitted to the Deaconess' Hospital, and remained there for six months with a swelling on his leg (just below the knee and over the site of an old burn), which burst while he was in Hospital.

When 23 years old (last year), patient had a tooth drawn, after which there was no bleeding for an hour or two; then it started, and continued to bleed for more than a week off and on, in spite of treatment. Plugging with cotton-wool was tried, but the bleeding always started again after each meal, when the plug fell out.

From time to time during his life, patient has had swellings of his ankles (always one at a time), left elbow, and middle and small fingers of right hand. Patient has had numerous cuts in the fingers and head, and has had teeth pulled, on all of which occasions he bled profusely and always took long to heal. His gums bleed from time to time, apparently without cause, and also if he scrubs his teeth with any vigour while cleaning them./

them. After the knee begins to swell, he feels flushed and nervous, but never before the onset of the swelling, so does not have true prodromal symptoms.

A week before admission to Hospital, patient's left knee suddenly got swollen. On the Monday, 8th February, 1909, he returned to work, the swelling having disappeared, till Wednesday, 10th February, 1909, when he was wakened up from sleep by the knee having become swollen again, and he had to take off the bandage to relieve the pain. Patient's attacks of swelling seem to vary in intensity. Sometimes the swelling is quite soft, whilst at other times it is very tense.

FAMILY HISTORY.

(For Family History of Haemophilia see separate chart.)

Father	dead	Mason's Disease.
Mother	alive and healthy.	
Brother	alive	Slight Bronchitis and Haemophilia.
Brother	dead	In Infancy, cause unknown.
Brother	dead	In Infancy, cause unknown.
Sister	alive and healthy.	
Sister	dead	In Infancy, cause unknown.

Mother's/

Mother's cousin died of haemorrhage, and was a haemophilic. A grand uncle, a brother, and three male cousins (two dead) are bleeders.

The following is a note of a cousin of this patient.

He is one of six brothers, and has seven sisters, all healthy. All his brothers died when he was young, and he was told that they had died from the same complaint as the one he suffers from, namely haemophilia. He has also a step-brother - from the same mother, but a different father - and this step-brother has never ailed anything.

Patient is 25 years of age. He was found to be a haemophilic when 8 years old, when he cut his gum and it bled a good deal for several days. He has suffered from swellings of joints and bursae for some years. Thus the left olecranon bursa began to swell 8 years ago, following a slight injury. His left knee first swelled 6 years ago. At other times, the right knee and right olecranon bursae have received slight injuries and have become swollen. If he does a hard day's work for several days, his knees become swollen. Seven years ago, patient had a tooth drawn, and the bleeding was so severe

that/

that he had to be admitted to hospital for two weeks. In May, 1910, he had a fluid swelling in his left knee, but apparently confined to the inner side. It felt to be in the joint, but may actually have been in the tendon sheaths on the inner side of the knee. His right knee was normal. The left olecranon bursa was distended with fluid. There was some slight heat, but no discolouration in either knee or elbow. On May 27th, 1910, while kicking a football, he caught his foot against another person's heel and received a contusion of the foot, with resulting pain, heat, redness and swelling of the tissues around, and possibly some fluid in the ankle joint. There was no subcutaneous haemorrhage.

ON ADMISSION.

Patient is intelligent-looking and bright, apparently otherwise healthy. Skin is soft.

RESPIRATORY SYSTEM)
CIRCULATORY SYSTEM) Nothing to note.
ALIMENTARY SYSTEM)
NERVOUS SYSTEM)

HAEMOPOIETIC/

HAEMOPOIETIC SYSTEM:-

Blood Examination shows. 13·2·09.

R.B.C.	4,280,000.
Hb.	105%.
C.I.	1·2.
W.B.C.	6,875.

GENITO-URINARY SYSTEM

Nothing special to note.

Urine Sp. Gr. 1030.
Reaction Neutral.
Deposit Urates.
Albumin None.
Sugar None.

LOCAL CONDITION.

The left knee is swollen, tense, and kept in a semi-flexed position, and very painful, the patient being unable to straighten it. Its measurements are:-

Above Knee Joint $11\frac{3}{4}$".
Over Knee Joint $14\frac{1}{4}$".
Below Knee Joint $11\frac{1}{2}$".

TREATMENT

TREATMENT and PROGRESS.

13·2·09. Knee wrapped up in cotton-wool, and a pillow placed under it for support and rest.

Given Trional grs. XX. at night.

14·2·09. Knee still painful and keeps patient from sleeping.

Measures Above knee 11".

At knee 14¼".

Below knee 10¾".

Pressure applied and Trional grs. XX. given at night.

15·2·09. Knee very sore, applied Lead and Opium fomentation and given Trional grs. XX. at night.

16·2·09. Knee easier to-day. Lead and Opium fomentations still applied.

Measures Above knee 11".

At knee 14¼".

Below knee 11".

17·2·09. Right knee painful to-day and somewhat swollen. The left knee is better. Rise of temperature to 103° F., and pulse of 134 in evening. Given paraldehyde Dr.1½. at night.

19·2·09/

19·2·09. Weight, 8 st. 2 lbs.

Height, 5 ft. 9 ins.

Feeling much better. Temperature down again.

25·2·09. Left knee measures, Above knee $10\frac{1}{2}$".

At knee 13".

Below knee $10\frac{1}{2}$".

Coagulation Time of Blood tested by McGowan's Method in morning -

found to be 42 minutes)

Control (self) 16 minutes) McGowan's Method.

Temperature 54°F. or 11°C.)

Given 10cc. Normal Horse Serum intravenously. Very gentle massage started to left knee.

26·2·09. Local ecchymosis at site of intravenous injection and very slight pain on palpation only.

Coagulation Time was 32 minutes in Forenoon.

Control 10 minutes)

Temperature 52°F. or 10°C.) McGowan's Method.

28·2·09. Allowed up for first time.

4·3·09. Discharged to-day, apparently well, after an uninterrupted recovery since being allowed up.

8·3·09/

8·3·09. Patient started his usual work again, and remained at it for two weeks.

14·3·09. Coagulation Time was 70 minutes.)

Control	20 minutes	McGowan's Method.
Temperature	54°F. or 11°C.	
Time	1 p.m.	

Started on 10cc. of Normal Horse Serum daily, given in three doses by the mouth. (3cc. t.i.d.)

17·3·09. Finger which had been punctured to estimate the coagulation Time started to go septic from the local blood-clot, but patient says he got dirt into it while at his work. Poultices were applied. The patient jagged it himself, thinking it was only blood clot, then it started to "fester".

18·3·09. Coagulation Time was 40 minutes.

Control	16 minutes	McGowan's Method.
Temperature	58°F. or 15°C.	
Time	3.30 p.m.	

20·3·09. Patient laid up in bed. He thinks he took too long a walk and tired himself. The right knee (not the left, which is the one usually affected), became swollen and caused him great pain for three days.

26·3·09/

26·3·09. Patient re-admitted to Hospital to-day. His finger this morning is worse. The inflammation has spread down the finger, which is now quite red. A lump can be felt at the elbow - epitrochlear gland swollen - and the axillary glands are swollen and tender. The finger was opened and pus let out - no extensive haemorrhage ensued - boracic poultices were applied and the condition got better in a few days.

1·4·09. Stopped Horse Serum and put on 10 grs. calcium lactate for three days - upset his stomach, so was not persisted in.

3·4·09. Blood Examination shows.

R.B.C.	6,000,000
Hb.	130%
C.I.	1·08
W.B.C.	14,062

Coagulation Time, 58 minutes at 4 p.m., with Temperature 52°F. or 10°C., while Control was 14 minutes (McGowan's Method).

14·4·09. Soft swelling in left knee, went away with two days rest.

22·5·09/

22·5·09. Started 10cc. daily Normal Horse Serum.

23·5·09. Coagulation Time 40 minutes Control 9 mins.

30·5·09. " " 44 " " 10 "

13·6·09. " " 38 " " 11 "

27·6·09. " " 35 " " 15 "

18·7·09. " " 31 " " 12 "

25·7·09. Developed a bruise below the left elbow, without any apparent cause, which spread up the arm 4 days later and disappeared in three days.

1·8·09. Coagulation Time 24 minutes Control 12 mins.

8.8.09. " " 19 " " 6 "

28·8·09. Stopped the Normal Horse Serum.

29·8·09. Coagulation Time 13 minutes) Control 9 mins.
(McGowan's
Temperature 64°F. 18°C.) Method.
(
Time 1.30 p.m.)

13·9·09. Started to bleed into left elbow and right big toe, which became discoloured. Patient could not put on his boots for the swelling of his toe, and though he cannot quite straighten his elbow, yet he feels he could have worked with it after three days when the swelling had subsided considerably.

19·9·09/

19· 9·09. Blood Pressure 124.

30·9· 09. Swelling of right knee - off work for three weeks (21·9·09 to 11·10·09).

1·11·09. Swelling of left knee - for five nights the pain gave patient no sleep, and he was off work for two weeks.

14·11·09. Started work again to-day. Started Normal Horse Serum again, 10cc. by mouth daily. Patient's left knee cannot be fully extended yet, and he finds walking very tiring.

Blood Examination shows.

R.B.C.	5,500,000
Hb.	90%.
C.I.	·9
W.B.C.	13,125

Blood Film shows nothing special of note. The red cells appear normal in every respect. Out of 300 white cells counted, the Polymorphs show 74%, Lymphocytes, 25% and Eosinophiles 1%. Coagulation Time taken with Addis' Coagulometer (all subsequent estimations done with this method). Serum one inch.

No./

No. 1. Start 3.43 p.m. Finish 4.30 p.m. Coagulation Time, 52 minutes. Serum one inch. Temperature being 20°C. and Control, 10 minutes 4 p.m. to 4.10 p.m. No serum.

The tubes showed one inch of serum separated at upper end.

21·11·09. Patient feels better, knee is a little straighter and walking is less tiring.

Blood Examination shows.

R.B.C.	5,550,000
Hb.	90%
C.I.	·9
W.B.C.	8,125

Coagulation Time is 41 minutes - the average of two estimations - with Temperature of 20°C.

No.1. Start 3.36 p.m. Finish 4.21 p.m.) = 45 m.(
No. 2 " 3.41 p.m. " 4.18 p.m.) = 37 m.(=41m.
Control " 3.52 p.m. " 4 p.m. = 8m.

28·11·09. Patient feels quite well again.

Blood Coagulation is 32 minutes - the average of two estimations - with Temperature of 20°C.

No./

No.1. St. 3.36 p.m. F. 4.17 p.m.=41m.

No.2. " 3.47 p.m. " 4.15 p.m.=28m.) (32m.

No.3. " 3.52 p.m. " 4.18 p.m.=26m.)

Cont. " 4.2 p.m. " 4.14 p.m.=12m.

The tubes show no serum at top now.

12·12·09. Patient feels his left hip slightly swollen and painful on pressure.

Blood Examination shows.

R.B.C.	5,720,000
Hb.	70%
C.I.	·69
W.B.C.	7,167

Coagulation Time is 27 minutes - the average of three estimates - with temperature 20°C.

No.1 St. 3.9 p.m. F. 3.41 p.m.=32 m.

No.2. " 3.15 p.m. " 3.42 p.m.=27 m.) (27m.

No.3. " 3.26 p.m. " 3.49 p.m.=23 m.)

Cont. " 3.30 p.m. " 3.40 p.m.=10m. =10m.

Reduced dose of Horse Serum to 5cc. daily by mouth.

19·12·09. Patient has a slight feeling of malaise, with slight cold, his knees are now quite better.

Blood/

Blood Examination shows.

R.B.C.	6,500,000
Hb.	90%.
C.I.	·7
W.B.C.	8,125

Coagulation Time is 33 minutes - the average of two readings - with temperature of 20°C.

No.1. St. 3.1 p.m. F. 3.27 p.m.=26m.
No.2. " 3.3 p.m. " 3.39 p.m=36m.) (33m
No.3. " 3.6 p.m. " 3.43 p.m.=37m.)
Cont. " 3.9 p.m. " 3.18 p.m.= 9m. =9m.

21·12·09. Patient has developed a soft swelling in his knee (left). He was laid up in bed for 3 days and off work (till 27·12·09).

24·12·09. Patient rose from bed to-day. Knee better and swelling practically gone.

26·12·09. Patient is practically well again and has merely a tired feeling now, though last night he was able to dance two slow waltzes.

Blood Coagulation is 25 minutes - the average of three estimations - with temperature of 20°C.

No./

No.1.	St. 3.22 p.m.	F. 3.45 p.m.	=23m.	
No.2.	" 3.27 p.m.	" 3.54 p.m.	=27m.	25m.
No.3.	" 3.30 p.m.	" 3.55 p.m.	=25m.	
Cont.	" 3.35 p.m.	" 3.45 p.m.	= 10m.	

27·12·09. Started again on 10cc. daily of Normal Horse Serum.

9 ·1·10. Patient has felt exceptionally well for the last two weeks.

The Blood Examination shows.

R.B.C.	6,530,000
Hb.	104%
C.I.	·8
W.B.C.	10,200

The Viscosity of the Blood is 6·10

The Blood Coagulation Time is 26 minutes - the average of three estimations - with temperature of 20°C.

No.1.	St. 3.16 p.m.	F. 3.43 p.m.	=27m.	
No.2.	" 3.19 p.m.	" 3.44 p.m.	=25m.	26m.
No.3.	" 3.24 p.m.	" 3.50 p.m.	=26m.	
Cont.	" 3.30 p.m.	" 3.39 p.m.	= 9m.	

23·1·10/

23·1·10. The Blood Coagulation Time is 25 minutes - the average of three estimations - with Temperature of 20°.

No.1.	St. 3.17 p.m.	F. 3.43 p.m.	=26m.	
No.2.	" 3.22 p.m.	" 3.45 p.m.	=23m.	25m.
No.3.	" 3.27 p.m.	" 3.53 p.m.	=26m.	
Cont.	" 3.30 p.m.	" 3.40 p.m.		= 10m.

The Hb. was 98% and the Viscosity of the blood, 6·06.

6·2·10. The Blood Coagulation Time is 28 minutes - the average of three estimations - with Temperature of 20°C.

No.1.	St. 2.56 p.m.	F. 3.25 p.m.	=29M.	
No.2.	" 2.58 p.m.	" 3.26 p.m.	=28m.	28m.
No.3.	" 3·1 p.m.	" 3.28 p.m.	=27m.	
Cont.	" 3.5 p.m.	" 3.13 p.m.		= 8m.

10·2·10. In the evening patient noticed his left knee a little swollen.

11·2·10. Patient was off work for the day and had to lie up in bed.

12·2·10. Patient went back to work again.

13·2·10. Patient feels his neck stiff and swollen. The left arm is a little stiff and he cannot quite straighten it out, though he can almost do so.

The/

The Blood Coagulation Time is 29 minutes - the average of three estimations - with temperature of 20°C.

No.1.	St. 4·8 p.m.	F. 4·33 p.m. = 25m.	
No.2.	" 4·9 p.m.	" 4·34 p.m. = 25m.	29m.
No.3.	" 4·11 p.m.	" 5·47 p.m. = 36m.	
Cont.	" 4·13 p.m.	" 4·20 p.m.	= 7m.

About 60cc. of blood was drawn from the median basilic vein for experimental purposes by Dr. Addis - who found that he got as much thrombokinase from this as could be got from normal white blood corpuscles.

Stop the Horse Serum for one week.

20·2·10. No ill effects from intravenous puncture.

The Blood Coagulation Time is 36 minutes - the average of three estimations - with temperature of 20°C.

No.1.	St. 3·34·30	F.4·9·30 p.m. = 35m.	
No.2.	" 3·36· 0	" 4·11·0 " = 35m.	36m.
No.3.	" 3·38· 0	" 4·16·0 " = 38m.	
Cont.	" 3·40· 0	" 3·50·0	= 10m.

The Viscosity of the Blood is 6·25 and of the plasma 2·2.

Blood/

Blood Examination shows.

R.B.C.	6,300,000
Hb.	105%.
C.I.	·83
W.B.C.	11,000

54cc. of blood was taken from the left median basilic vein for Dr. Addis, who found that this haemophilic fibrinogen coagulated just as quickly as normal fibrinogen.

10cc. of Normal Horse Serum was injected intravenously into the right median basilic vein.

21·2·10. Patient felt his right arm itchy about seat of puncture, with formation of white blobs.

22·2·10. Discolouration of right arm around seat of puncture.

23·2·10. Patient showed me his right arm, which was very itchy - greatly discoloured - owing to ecchymosis all over front of elbow.

27·2·10. The Coagulation time of blood is 28 minutes/

minutes - the average of six estimations with Temperaure 20°C.

No.1. 31 minutes.

No.2. 28 minutes.

No.3. 27 minutes.

No.4. 26 minutes.

No.5. 29 minutes.

No.6. 28 minutes.

Cont. 10 minutes.

The Viscosity of the blood is 6·108.

" " " " plasma is 2·06.

" " " " serum is 1·902.

Blood Examination shows.

R.B.C.	5,910,000
Hb.	104%.
C.I.	·88
W.B.C.	9,000

6·3·10. The Coagulation Time is 32 minutes - the average of four estimations with Temperature 20°C.

No.1. 23 minutes)
No.2. 40 minutes) 32 minutes.
No.3. 34 minutes)
No.4. 31 minutes)

Cont. 12 minutes.

The/

The Viscosity of the blood is 5·86.

Blood Examination shows.

R.B.C.	6,200,000
Hb.	103%.
C.I.	·83
W.B.C.	10,800

13·3·10. The Coagulation Time is 37 minutes - the average of three estimations taken with Temperature 20°C.

No.1.	3·13·30	3·48·30 = 35 m.)	
No.2.	3·15· 0	3·50· 0 = 35 m.)	37 m.
No.3.	3·16·30	3·57·30 =41 m.)	
Cont.	3·18· 0	3·26· 0	= 8 m.

Blood Examination shows.

R.B.C.	6,040,000
Hb.	102%.
C.I.	·85
W.B.C.	9,687

20·3·10. Two sets of estimations made - one set done with tubes through which normal Horse/

Horse Serum had been run and another set through which no serum had been run.

10cc. Normal Horse Serum was injected intravenously in basilic vein after these estimations were made.

1st series - with serum previously passed through the coagulation tubes.

Start.	Finish.	Coagulation Time.
9. 2. 0	9. 53.0	51 m.
9. 4. 0	9.52. 0	48 m.
9. 6. 0	10. 0. 0	54 m.
9. 8. 0	10. 0. 0	52 m.
9. 9. 0	9.55. 0	46 m.
9.10. 0	.0. 5. 0	55 m.

Average Coagulation Time 51 minutes.

2nd Series - without serum being previously passed through the coagulation tubes.

Start.	Finish.	Coagulation Time.
9.59. 0	10.30. 0	31 m.
10. 0. 0	10.30. 0	30 m.
10. 3. 0	10.35. 0	33 m.
10. 4. 0	10.40. 0	36 m.
10. 7. 0	10.40. 0	33 m.
10.12. 0	10.45. 0	33 m.
Control		
10.15. 0	10.25. 0	.0m.

Average Coagulation Time 32 minutes.

24·3·10. Complaining of slight pain in lower part of abdomen, which passed off in 3 or 4 days.

27·3·10./

27.3.10. Coagulation Time 31 minutes.

No. 1. 3.13.0 3.45.0 = 32 m.)
No. 2. 3.14.0 3.45.0 = 31 m.) 31 m.
No. 3. 3.15.0 3.45.0 = 30 m.)

Cont. 3.17.00 3.27.00=10 m.

28·3·10. Complained of sore wrist and was off work only one day, though the wrist remained swollen and painful for four days.

31·3·10. Felt a little pain over bladder about 5 p.m., but was able to go out to the theatre. At 11 p.m., however, he took a sudden and severe pain in right side and passed urine soon after this, which was clear, but pain lasted till 3 a.m., when he passed blood in his urine, after which his acute pain seemed to disappear and left him with only a dull sort of pain, which lasted for two days and he was subsequently noticed by his friends to be paler.

3·4·10. Coagulation Time 31 minutes.

No. 1 42 minutes)
No. 2. 20 minutes) 31 minutes
No. 3. 30 minutes)

Control 10 minutes.

18·4·10/

18·4·10. Coagulation Time 48 minutes.

No.1.	3. 8. 0	3.53. 0	= 45 m.	
No.2.	3.11. 0	3.53. 0	= 42 m.	
No.3.	3.13. 0	4. 2. 0	= 49 m.	48 m.
No.4.	3.16. 0	4.13. 0	= 57 m.	
Cont.	3.20. 0	3.29. 0		= 9 m.

Puncture wounds bled rather freely, and continued to be troublesome all next day.

20·4·10. Patient knocked his left elbow, which became swollen and was very sore for six hours, though he was never off work with it. It kept him from sleep that night, but cleared up completely in two days.

Coagulation Time 37 minutes.

No.1.	4. 1. 0	4.54. 0	= 53m.	
No.2.	4. 2. 0	4.38. 0	= 36m.	
No.3.	4. 3. 0	4.38. 0	= 35 m.	
No.4.	4.28. 0	4.57. 0	= 29m.	37 m.
No.5.	4.31. 0	5.11. 0	= 40m.	
No.6.	4.34. 0	5. 7. 0	= 33m.	
Cont.	4.36. 0	4.46. 0		= 10 m.

25.4.10. Left knee swollen, laid up in bed for two days and off work for three days.

1.5..0/

1·5·10. Coagulation Time 39 minutes.

No.1.	4. 1. 0	4.35. 0	= 34 m.	
No.2.	4. 4. 0	4.50. 0	= 46 m.	
No.3.	4. 6. 0	4.40. 0	= 34 m.	39 m.
No.4.	4. 7. 0	4.46. 0	= 39 m.	
No. 5.	4. 9. 0	4.54. 0	= 45 m.	
Cont.	4.12. 0	4.20. 0	= 8 m.	

3.5.10. Left wrist slightly swollen and stiff.

Upper first left molar has been bleeding slightly all week.

Coagulation Time 32 minutes.

No.1.	3. 4. 0	3.41. 0	= 37 m.	
No.2.	3. 6. 0	3.40. 0	= 36 m.	
No.3.	3. 8. 0	3.35. 0	= 27 m.	32 m.
No.4.	3.11. 0	3.38. 0	= 27 m.	
Cont.	3.14. 0	3.24. 0	= 10 m.	

15·5.10. Coagulation Time 37 minutes.

No.1.	3.53. 0	4.34. 0	= 43 m.	
No.2.	3.56. 0	4.29. 0	= 34 m.	37 m.
No.3.	4.24. 0	5. 0. 0	= 36 m.	
Cont.	4.26. 0	4.35. 0	= 9 m.	

22·5·10./

22·5·10. Coagulation Time 61 minutes.

No.1.	4.16. 0 5. 8. 0 = 52 m.	
No.2.	4.18. 0 5.25. 0 = 67 m.	61 m.
No.3.	4.23.30 5.27.30 = 64 m.	
No.4.	4.25. 0 5.29. 0 = 64 m.	
Cont.	4.29. 0 4.39. 0 = 10 m.	

29.5.10 Coagulation Time 52 minutes

No.1.	3.19. 0 4. 9. 0 = 50 m.	
No.2.	3.21. 0 4.11. 0 = 50 m.	52 m.
No.3.	3.23. 0 4.19. 0 = 56 m.	
Cont.	3.25. 0 3.25. 0 = 10 m.	

31·5·10. Left ankle sore, with bruising, but no swelling, from no apparent cause. The left elbow is stiff and cannot be fully extended, which patient thinks has been induced by his trying to ride a bicycle.

5.6.10. Coagulation Time 61 minutes.

No.1.	4. 2. 0 5. 3. 0 = 61 m.	
No.2.	4. 3. 0 5. 4. 0 = 61 m.	61 m.
No.3.	4. 5. 0 5. 5. 0 = 60 m.	
Cont.	4. 9. 0 4.18. 0 = 9 m.	

7·6·10. Off work for one day owing to left elbow becoming swollen, which patient still thinks was due to the strain of holding the handlebars when trying to cycle.

12·6·10/

12·6·10. Coagulation Time 60 minutes.

No.1.	3.33.0	4.33. 0	= 60 m.	
No.2.	3.35.30	4.34.30	= 59 m.	
No.3.	3.37. 0	4.36. 0	= 59 m.	60 m.
No.4.	3.39.30	4.41.30	= 62 m.	
No.5.	3.41. 0	4.43. 0	= 62 m.	
Cont.	3.46. 0	3.55. 0	= 9 m.	

19·6·10. Coagulation Time 61 minutes.

No.1.	3.41. 0	4.45. 0	= 64 m.	
No.2.	3.43. 0	4.39. 0	= 56 m.	
No.3.	3.45. 0	4.44. 0	= 59 m.	61m.
No.4.	3.47. 0	4.55. 0	= 68 m.	
Cont.	3.50. 0	3.57. 0	= 7 m.	

26·6·10. Coagulation Time 58 minutes.

No.1.	3.44. 0	4.40. 0	= 56 m.	
No.2.	3.47. 0	4.45. 0	= 58 m.	58 m.
No.3.	3.48. 0	4.48. 0	= 60 m.	
Cont.	3.50. 0	3.59. 0	= 9 m.	

10·7·10. Coagulation Time 66 minutes.

No.1.	3. 8. 0	4.19. 0	= 71 m.	
No.2.	3.11. 0	4.12. 0	= 61 m.	
No.3.	3.13. 0	4.21. 0	= 68 m.	66 m.
No.4.	3.15. 0	4.20. 0	= 65 m.	
Cont.	3.20. 0	3.31. 0	= 11 m.	

Blood/

Blood Examination shows.

W.B.C.	15,937
R.B.C.	6,810,000
Hb.	80%
C.I.	·5

19·7·10. Coagulation Time 53 minutes.

No.1.	10.40. 0	11.32. 0	= 52 m.	
No.2.	10.41. 0	11.40. 0	= 59 m.	53 m.
No.3.	10.43. 0	11.34. 0	= 51 m.	
No.4.	10.46. 0	11.35. 0	= 51 m.	
Cont.	10.48. 0	10.56. 0	= 8 m.	

24·7·10. Coagulation Time 54 minutes.

No.1.	7.59. 0	8.53. 0	= 52 m.	
No.2.	8. 1. 0	8.59. 0	= 58 m.	
No.3.	8. 3. 0	8.56. 0	= 53 m.	54 m.
No.4.	8. 4. 0	9. 2. 0	= 58 m.	
No.5.	8. 6. 0	8.58. 0	= 52 m.	
Cont.	8.10. 0	8.22. 0	= 12 m.	

30·7·10. Twisted his left knee.

31·7·10. Noticed a lump at outer side of left knee, which did not prevent patient from walking and which was painful even when at rest, in fact he felt it less when he was moving the knee joint.

1·8·10./

1·8·10. Coagulation Time 40 minutes.

No.1.	3.30. 0	4. 5. 0 = 35 m.	
No.2.	3.33. 0	4.15. 0 = 42 m.	
No.3.	3.34.30	4.15.30 = 40 m.	40 m.
No.4.	3.36. 0	4.17. 0 = 42 m.	
No.5.	3.39. 0	4.23. 0 = 44 m.	
Cont.	3.40. 0	3.50. 0	= 10 m.

7·8·10. Coagulation Time 56 minutes.

No.1.	3.12. 0	3.52. 0 = 40 m.	
No.2.	3.17. 0	4.28. 0 = 71 m.	
No.3.	3.19. 0	4.23. 0 = 64 m.	56 m.
No.4.	3.21. 0	4.13. 0 = 52 m.	
Cont.	3.24. 0	3.33. 0	= 9 m.

Blood Count. W.B.C. 7,812.

.14·8·10. Coagulation Time 56 minutes.

No.1.	2. 1. 0	3. 3. 0 = 62 m.	
No.2.	2. 3.30	2.47.30 = 44 m.	
No.3.	2. 6. 0	3. 6. 0 = 60 m.	56 m.
No.4.	2. 8. 0	3. 7. 0 = 59 m.	
Cont.	2.10. 0	2.20. 0	= 10 m.

Blood Count. S.B.C. 8,750.

18·8·10/

18·8·10. Coagulation Time 42 minutes.

No. 1.	9.16. 0	9.52. 0	= 36 m.	
No. 2.	9.17. 0	10.10. 0	= 53 m.	
No. 3.	9.18. 0	9.54. 0	= 36 m.	42 m.
No. 4.	9.22. 0	10.15. 0	=53 m.	
No. 5.	9.23. 0	9.57. 0	= 34 m.	
Cont.	9.26. 0	9.34. 0	= 8 m.	

23·8·10. Coagulation Time 57 minutes.

No. 1.	9. 3. 0	10.10. 0	= 67 m.	
No. 2.	9. 6. 0	10.10. 0	= 64 m.	
No. 3.	9. 7. 0	10.13. 0	= 63 m.	57 m.
No. 4.	9.10. 0	9.56. 0	= 46 m.	
No. 5.	9.12. 0	9.58. 0	= 46 m.	
Cont.	9.15. 0	9.24. 0	= 9 m.	

2·9·10. Patient felt a little pain over the region of Scarpa's triangle in the right thigh, with area of anaesthesia over a small area just above the patella in front. He attributes these symptoms to over exertion while on holiday during the last week, when he was golfing every day over a rather hilly golf course. He had been playing two rounds a day, for the first two days, but the third day/

day he felt his elbow sore (but no swelling) and was unable to play for the rest of the week.

3.9.10. The anaesthesia is a little increased in extent, and patient feels a little lame.

4.9.10. Coagulation Time is 52 minutes.

No.1.	3.13. 0	4.15. 0	= 62 m.	
No.2.	3.14. 0	4. 5. 0	= 51 m.	
No.3.	3.16. 0	4. 9. 0	= 53 m.	52 m.
No.4.	3.18. 0	4.11. 0	= 53 m.	
No.5.	3.19. 0	4. 0. 0	= 41 m.	
Cont.	3.22. 0	3.31. 0	= 11 m.	

5·9·10. Patient laid up in bed. There is very little swelling over Scarpa's triangle, but the part is painful.

6·9·10. The thigh is now extremely painful, and patient cannot sleep at night with it.

10·9·10. No restful sleep since the 6th September. On careful examination, there is anaesthesia down the front of the right thigh, as far as the knee, and patient cannot move his leg for pain, the most painful area being over the head of the trochanter and in towards the pubis. It was most severe about 3 p.m. He has/

has not slept all night and looks tired out, so given grs. ½ morphia hypodermically. On measurement the circumference of the right thigh at level of Scarpa's triangle is two inches more than that of the left thigh - being respectively 19" and 17" in circumference.

11·9·10. Area of skin anaesthesia has increased to half way down the leg, but the thigh is still very painful. The patient has slept well all last night after the morphia.

12·9·10. Area of skin anaesthesia now reaches down to the toes and there is a hot shooting pain right down the centre of the leg. There is hyperaesthesia of the sole of the foot. He is not able to move his leg. Last night did not sleep at all. His mother had to sit up all night with him and applied lead and opium fomentations, which were of no use. A hypodermic gr. ½ of morphia relieved the pain and he slept a little in the afternoon, but not at night.

13·9·10./

13·9·10. Pain very severe still - given morphia grs.½ hypodermically, which relieved pain but did not induce sleep.

14·9·10. Pain appears to be getting easier.

15·9·10. Pain gone, but anaesthesia just the same. The areas affected were those supplied by (1) The anterior branch of External Cutaneous;(2) Both divisions of the Middle Cutaneous; (3) Both divisions of the Internal Cutaneous; (4) The long saphenous. The last three are apparently all affected at or close to their origin from the Anterior Crural Nerve. The first named has evidently been caught just after its division into an anterior and posterior branch, the clot not having extended sufficiently round the thigh to catch the latter.

17·9·10. Developed haematuria this morning. Has been up for a few hours in an armchair, and felt the benefit of this. He can straighten his leg out now, but there is still no diminution of the anaesthesia.

23·9·10/

23·9·10. Haematuria has gone on for last six days, but is now stopped. He has been up every day since the 17th September, and been exercising his leg a little more each day and thinks the exercise has done him some good.

26·9·10. Went down one stair for first time, with no bad results. To be massaged every day till the 1st October, 1910, at first for 10 minutes and gradually increasing in time and vigour each day.

2·10·10. Was out for first time, he feels his right knee giving way under him occasionally.

Coagulation Time 61 minutes.

No.1.	3.36. 0	4.42. 0	= 66 m.	
No.2.	3.38. 0	4.43. 0	= 65 m.	
No.3.	3.42. 0	4.41. 0	= 59 m.	61 m.
No.4.	3.44. 0	4.45. 0	= 61 m.	
No.5.	3.47. 0	4.43. 0	= 56 m.	
Cont.	3.50. 0	3.59. 0	= 9 m.	

Given 10cc. Normal Horse Serum intravenously into Median Basilic Vein.

2·10·10./

2·10·10. Six hours later.

No.1.	9·30· 0	10·39· 0 = 69 m.		
No.2.	9·32· 0	10·45· 0 = 73 m.		
No.3.	9·34· 0	10·44· 0 = 70 m.	70 m.	
No.4.	9·37· 0	10·41· 0 = 64 m.		
No.5.	9·40· 0	10·55· 0 = 75 m.		
Cont.	9·45· 0	9·55· 0 = 10 m.		

3·10·10. Twelve and a half hours later.

No.1.	10· 0· 0	11· 7· 0 = 67 m.		
No.2.	10· 2· 0	11·14· 0 = 72 m.		
No.3.	10· 4· 0	11· 3· 0 = 59 m.	68 m.	
No.4.	10· 6· 0	11·15· 0 = 69 m.		
No.5.	10·10· 0	11·25· 0 = 75 m.		
Cont.	10·15· 0	10·25· 0 = 10 m.		

4·10·10. Thirty-six hours later.

No.1.	9·30· 0	10·32· 0 = 62 m.		
No.2.	9·32· 0	10·26· 0 = 54 m.		
No.3.	9·35· 0	10·43· 0 = 68 m.	65 m.	
No.4.	9·38· 0	10·56· 0 = 78 m.		
No.5.	9·41· 0	10·46· 0 = 65 m.		
Cont.	9·44· 0	9·53· 0 = 9 m.		

Forty-eight hours later.

No.1.	9·32· 0	10·39· 0 = 67 m.		
No.2.	9·36· 0	10·24· 0 = 48 m.		
No.3.	9·38· 0	10·32· 0 = 54 m.	60 m.	
No.4.	9·40· 0	10·50· 0 = 70 m.		
No.5.	9·41· 0	10·43· 0 = 62 m.		
Cont.	9·43· 0	9·53· 0 = 10 m.		

4·10·10./

4.10.10 Left knee a little swollen and painful.

9·10·10. Coagulation Time 50 minutes.

No.1.	3.47. 0	4.34. 0 = 47 m.	
No.2.	3.49. 0	4.49. 0 = 60 m.	
No.3.	3.51. 0	4.30. 0 = 39 m.	50 m.
No.4.	3.54. 0	4.46. 0 = 52 m.	
No.5.	3.56. 0	4.48. 0 = 52 m.	
Cont.	4. 0. 0	4.10. 0	= 10 m.

23· 1·11. The numbness of his right leg is still present to some extent, though not so complete as it was at first, still owing to it he slipped off a stool he was sitting on about 9 a.m., and twisted his right knee, without actually striking it. The knee became at once swollen and painful and patient could not rise from the floor. As the day went on the knee became steadily more painful and tight, and the skin over it harder. He was in great pain all day, and was unable to eat. He felt sick in the evening, and vomited once at 6 p.m. There was no feeling of faintness, however. His pulse/

pulse was 92, temperature 99·4° and respirations 18 per minute. On examining the affected knee, it was seen to be considerably swollen, the hollows at the side of the patella were filled up, and there was a crescentic bulging above the patella in the situation of the sub-crural bursa. The skin is not shiny, and there is no reddening. The joint does not feel hot, it is extremely tender, and the swelling feels firm, but fluctuation can be made out.

Lead and Opium fomentations applied locally and morphia gr. $\frac{1}{4}$ was given hypodermically at 10·30 p.m., but had to get another gr.$\frac{1}{6}$ at 2 a·m. before any relief was felt.

25·1·11. Morphia gr. $\frac{1}{4}$ at 9.30 p.m. was found necessary.

26·1·11. The knee is still very swollen and painful. The swelling is now more marked, being in lower part of thigh, and there is a little redness. The horse-shoe-shaped outline of the subcrural swelling is in consequence less distinct. Given Morphia grs. $\frac{1}{4}$ at 10 p.m.

Also/

Also opening medicine (Pil. Colocynth and Hyoscyamus grs. V.) was given.

27·1·11. Morphia grs. $\frac{1}{4}$ at 10 p.m. Condition much the same, but temperature tends to run above normal (see chart), being 100° to-night.

28·1·11. Morphia grs. $\frac{1}{4}$ at 10 p.m.

29·1·11. Heroin hypodermic grs. $\frac{1}{12}$ given at 10 p.m. Swelling beginning to show signs of abating, but is still painful, and necessitates a gr. $\frac{1}{12}$ hypodermic of Heroin every night.

1·2·11. The swelling is steadily growing less. The temperature is still raised a little.

2·2·11. Normal Horse Serum given night and morning, 5cc.

3·2·11. Knee blistered, but no beneficial result ensued. The pain is gradually getting less and so is the swelling.

7·2·11. Hypodermic nightly injections of Heroin stopped.

15·2·11. Haemorrhage into left elbow, no cause, immobilised in a splint. Hypo. Heroin gr. $\frac{1}{12}$ at night.

18·2·11. Temperature has now practically settled. The knee swelling is becoming absorbed and/

and lessened nicely. Having massage gently every day.

22·2·11. Swelling in elbow has now subsided, without discolouration. The knee is gradually returning to its normal contour.

28·2·11. Patient can now walk with the aid of a stick.

15·3·11. Patient quite well again, and going about his work as usual.

19·4·11. Patient put on 10cc. Fresh Horse Serum by the mouth daily.

Coagulation Time 57 minutes.

No.1	10. 7. 0	11. 5. 0	= 58 m.	57 m.
No.2	10. 8. 0	11. 6. 0	= 58 m.	
No.3.	10. 9. 0	11. 8. 0	= 59 m.	
No.4	10.11. 0	11. 9. 0	= 58 m.	
No.5	10.13. 0	11.10. 0	= 58 m.	
No.6	10.15. 0	11.11. 0	= 56 m.	
Cont.	10.20. 0	10.31. 0	= 11 m.	

Blood Count. W.B.C. 8,432

R.B.C. 5,810,000

20·4·11./

20. 4.11 Coagulation Time 61 minutes.

No.1. 9.40. 0 10.39. 0 = 59 m.)
No.2. 9.41. 0 10.41. 0 = 60 m.)
No.3. 9.42. 0 10.42. 0 = 60 m.) 61 m.
No.4. 9.44. 0 11. 1. 0 = 77 m.)
No.5. 9.46. 0 10.39. 0 = 53 m.)

Cont. 9.50. 0 9.59. 0 = 9 m.

Blood Count W.B.C. 10,312.
R.B.C. 5,450,000.

21·4·11. Coagulation Time 51 minutes.

No.1. 9.55. 0 10.38. 0 = 43 m.)
No.2. 9.56. 0 10.59. 0 = 63 m.)
No.3. 9.57. 0 10.40. 0 = 43 m.) 51 m.
No.4. 9.59. 0 10.41. 0 = 42 m.)
No.5.10. 0. 0 11. 8. 0 = 68 m.)

Cont.10.5. 0 10.14. 0 = 9 m.

Blood Count W.B.C. 8,437.
R.B.C. 4,710,000.

22·4·11. Blood Count. W.B.C. 8,125.
R.B.C. 4,590,000.

Coagulation/

Coagulation Time 48 minutes.

No.1.	9.19. 0	10.11. 0 = 52 m.		
No.2.	9.21. 0	10.15. 0 = 54 m.		
No.3.	9.22. 0	10. 7. 0 = 45 m.	48 m.	
No.4.	9.23. 0	10. 9. 0 = 46 m.		
No.5.	9.25. 0	10.10. 0 = 45 m.		
Cont.	9.30. 0	9.40. 0	= 10 m.	

23·4·11. Coagulation Time 49 minutes.

No.1.	9.13. 0	10. 4. 0 = 51 m.		
No.2.	9.14. 0	10. 5. 0 = 51 m.		
No.3.	9.15. 0	10. 9. 0 = 54 m.	49 m.	
No.4.	9.17. 0	10. 7. 0 = 50 m.		
No.5.	9.20. 0	10. 0. 0 = 40 m.		
Cont.	9.25. 0	9.37. 0	= 12 m.	

26·4·11. Coagulation Time 47 minutes.

No.1.	10.10. 0	11. 1. 0 = 51 m.		
No.2.	10.12. 0	11. 2. 0 = 50 m.		
No.3.	10.13. 0	11. 3. 0 = 50 m.	47 m.	
No.4.	10.15. 0	11. 4. 0 = 49 m.		
No.5.	10.17. 0	10.56. 0 = 39 m.		
Cont.	10.20. 0	10.31. 0	= 11 m.	

12·6·11./

12·6·11. Coagulation Time 55 minutes.

No.1.	9.53. 0	10.46. 0 = 53 m.	
No.2.	9.55. 0	10.53. 0 = 58 m.	
No.3.	9.58. 0	10.56. 0 = 58 m.	55 m.
No.4.	10. 0. 0	10.49. 0 = 49 m.	
No.5.	10. 2. 0	10.58. 0 = 56 m.	
Cont.	10. 5. 0	10.15. 0	= 10 m.

8·2·12. Has developed an eczematous eruption all over back and upper part of front of chest. Given Unguentum Hydrarg. Ammoniata to apply locally.

17·2·12. Eruption disappeared completely from front of chest, where ointment was applied, but still present on back where ointment has not been applied.

22·2·12. Eruption now all gone from the back as well, the ointment having been carefully applied.

4.3.12. Has developed a haemorrhage into his left elbow, from no apparent cause, very painful and tense - cannot straighten or move arm without extreme pain. Given hypodermic of morphia gr. $\frac{1}{2}$.

5·3·12/

5·3·12. Slept well and is much better this morning, can now move elbow fairly well without pain.

8·3·12. Developed a haemorrhage over the outer malleolus of left ankle - extremely painful, but not swollen or discoloured. Confined to bed.

9·3·12. Had a sleepless night from pain in his ankle. Given morphia gr. $\frac{1}{4}$ hypodermically.

10·3·12. Much easier to-day, still in bed. Some redness and swelling over outer part of left ankle joint.

12·3·12. Got up to-day and able to walk with a stick.

15·3·12. Going about and resumed work as usual.

CASE II.

Male, age $6\frac{7}{12}$, was under observation from the 16th May 1910 to the 15th June 1910.

FAMILY HISTORY. (See Family Chart).

Father healthy. no Rheumatism, Phthisis, etc. Mother " " " " etc., but comes from a haemophilic stock.

FAMILY. 7 children alive, 2 miscarriages and 1 still born child.

Child 1 = boy, healthy - "Not a bleeder", Age 26.
" 2 = boy, "bleeder" (Case III.) " 25.
" 3 = girl, healthy " 23.
" 4 = miscarriage at six weeks.
" 5 = " " " "
" 6 = girl, healthy " 18.
" 7 = girl, " " 16.
" 8 = girl, stillborn.
" 9 = boy, "Bleeder", (Case IV.), " 11.
" 10 = boy, "Bleeder", (Case II.) mentally deficient.
" 11 = miscarriage at six weeks.

Mother/

Mother in good health during all her pregnancies, except the second last (child 10), when she was much troubled with giddiness. Labours have all been quick, easy and natural. This is the fourth generation of "bleeders" in the family.

SWELLING of JOINTS.

Never commenced in any member of this family till the age of five years; in no case later than the eighth year. In Child 9, (Case IV.), the condition appeared at 4 years of age. The swelling (knee, generally), occurred after haemorrhages; 1st, from a cut on the forehead, 2nd, from a crushed finger. The swelling generally comes on after the bleeding has stopped, and especially on occasions when the patient is run down. The affected joint is always painful, (Two of the patient's uncles, who were haemophilics, were in the habit of injecting morphia into each other for relief of the pain), and appears white and swollen, but usually there is no skin discolouration, except sometimes as the joint is beginning to recover.

The joint symptoms are very sudden in onset, and these may occur without any apparent antecedent injury.

The/

The knee joints are most frequently affected, then the ankles, elbows, wrists, and sometimes the finger joints.

All the bleeder descendants in this family were troubled with joint swellings and bruises.

HOME SURROUNDINGS.

Very satisfactory, and every care and attention is bestowed upon patient.

INFECTIOUS DISEASES.

Measles)
(2 years of age.
Whooping Cough)

Scarlet Fever at 6½ years of age.

GENERAL HISTORY of PATIENT.

Instrumental birth. Child healthy at birth, the marks of the forceps rapidly disappeared and caused no bruising.

Teeth appeared at 10 months, and no bleeding occurred while they were being cut.

He began to speak at 2 years.

He was two years old before he could sit up by himself, and even yet cannot walk by himself.

MENTAL/

MENTAL CONDITION.

He is a mentally deficient child, very irritable at times and very emotional.

In September 1907, (when $3\frac{11}{12}$ years of age), he started to take fits, and has had twelve in all at various intervals up to the present time. No injury was sustained which might have accounted for their appearance. Their duration varied from half an hour to three hours. In two of these fits there were noticed convulsions of the left arm, leg and face, and in one, of the right arm, leg and face. His eyes remained open wide, fixed and turned up. He generally vomited on coming out, and then slept for about two hours after. There was never any warning of onset, and the child was often in unusually good health before it. He did not scream on taking the fit. Convulsive movements began gradually, and became more and more violent, breathing became laboured. Face did not become dusky, but he passed urine during the fit.

Within the last two years the fits have tended to become less severe and prolonged. There has been no twitching, and they usually come on when awakening from sleep. He turns blue, and has/

has convulsive movements of his throat, which last about one minute or so, then he comes to with a sigh and gives a smile as if nothing had happened.

HAEMORRHAGIC HISTORY.

Bruising was first noticed when patient was 3 months old, the bruising always being of the nature of a small discoloured lump, which took weeks to go away.

In February 1906, (when 3 years old), his tongue bled a lot, and continued to do so for eight days. On the 25th October, 1906, he had a similar haemorrhage from the tongue from a small bleeding point at the left edge near the tip, which started at dinner time, while taking his food. Next day he was admitted to the Royal Hospital for Sick Children, where his pulse was said to be rapid, and scarcely perceptible. The mouth was cleaned out, and adrenal chloride applied locally to the mucous surface, and calcium chloride grs. iii t.i.d. given for nine days, after which he was given Ferri Redactum grs. vii. t.i.d. Bleeding persisted till the early hours of the next day, and that same evening he became very blanched and "heady". The pulse became very rapid, the temperature rose, and his skin was hot and dry and he was very thirsty.

The/

The following day he had melaena, but the bleeding from the tongue never recurred. He is very easily bruised. From time to time his left elbowjoint became swollen and painful; discolouration of the skin appeared when the swelling was disappearing and the pain gone.

On the 29th May 1908, this left elbow joint was noticed to be swollen, and he was in great pain and not able to sleep for it. This same day he took a fit, which lasted for about half an hour, the convulsions being confined to his face. The extreme pain in his elbow, which was bandaged up and kept in a semi-flexed position, lasted till the next day, and for several more days was tender to the touch. He could not move it himself without suffering pain. Three days later the pain had gone, and he could almost fully extend his elbow; no discolouration of the skin developed over the joint.

From time to time after this, the patient suffered more or less severely from "bleedings" into his other joints. There are bruise marks all over his legs, and rigidity of the right knee joint, which/

which he does not appear to be able to fully extend.

In May 1910, he was brought voluntarily to the Royal Hospital for Sick Children, where the effect of Normal Horse Serum upon the coagulation time of his blood was noted.

CONDITION upon EXAMINATION.

Healthy-looking child, though obviously mentally deficient. Rather pale, no cyanosis - no skin eruptions. There are evidences of old bruising on all his limbs. He has an internal strabismus. No evidence of rickets, tubercle or syphilis.

RESPIRATORY)
CIRCULATORY)
ALIMENTARY) SYSTEMS, Nothing special to note.
GENITO-URINARY)

NERVOUS SYSTEM.

Irritable and mentally deficient.

Knee jerks are active. Plantar reflex is flexor. Abdominal reflexes are normal.

There is rigidity of the right knee joint, which cannot be fully extended.

TREATMENT/

TREATMENT and PROGRESS.

20·5·10. Coagulation Time is 70 minutes.

No.1.	5·30· 0	6·40· 0	= 70 m.	
No.2.	5·32· 0	6·31· 0	= 59 m.	
No.3.	5·36· 0	6·38· 0	= 62 m.	70 m.
No.4.	5·38· 0	6·58· 0	= 80 m.	
No.5.	5·41· 0	7· 0· 0	= 79 m.	
Cont.	5·45· 0	5·56· 0	= 11 m.	

23·5·10. Coagulation Time is 65 minutes.

No.1.	3·20· 0	4·40· 0	= 80 m.	
No.2.	3·22· 0	4·11· 0	= 49 m.	65 m.
No.3.	3·25· 0	4·32· 0	= 67 m.	
Cont.	3·30· 0	3·40· 0	= 10 m.	

Child became restless and resented being pricked with a needle, so that only three estimations could be made.

25·5·10. Coagulation Time is 85 minutes.

No.1.	8·45· 0	10·19· 0	= 94 m.	
No.2.	8·43· 0	10·20· 0	= 92 m.	
No.3.	8·50· 0	10· 8· 0	= 78 m.	85 m.
No.4.	8·52· 0	10· 7· 0	= 75 m.	
No.5.	8·54· 0	10·20· 0	= 86 m.	
Cont.	8·56· 0	9· 7· 0	= 11 m.	

29·5·10. 10cc. of Normal Horse Serum injected sub-cutaneously/

subcutaneously into the back near angle of scapula on right side; no bleeding nor bruising resulted from the needle puncture.

30·5·10. Patient was given chloroform (which he took well) in order to get X ray photographs taken of his joints.

1·6·10. Coagulation Time is 60 minutes.

No.1.	3·20· 0	4·20· 0	= 60 m.	
No.2.	3·23· 0	4· 5· 0	= 42 m.	
No.3.	3·25· 0	4·24· 0	= 59 m.	60 m.
No.4.	3·26· 0	4·40· 0	= 74 m.	
No.5.	3·28· 0	4·35· 0	= 67 m.	
Cont.	3·32· 0	3·42· 0	= 10 m.	

3·6·10. Coagulation Time is 73 minutes.

No.1.	4· 0· 0	5·22· 0	= 82 m.	
No.2.	4· 2·30	5· 7·30	= 65 m.	
No.3.	4· 4· 0	5·23· 0	= 79 m.	73 m.
No.4.	4·7·30	5·24·30	= 77 m.	
No.5.	4·10· 0	5·14· 0	= 64 m.	
Cont.	4·15· 0	4·25· 0	= 10 m.	

5·6·10. Developed a "serum rash", which appeared chiefly in the neck and chest - not at the site of injection, as usually is the case - and having an urticarial appearance, but no "wheals". There was no sickness/

sickness, no enlarged glands in neck, no sore throat and no albuminuria. In the evening complained of sore limbs, and during the night was very restless. This is the eleventh day since the injection of horse serum.

6.6.10. Patient very uncomfortable and sore all over, especially his joints, which show no swelling, but are too painful to move - no temperature however. The rash has completely gone and did not re-appear again, as is sometimes the case.

7·6·10. Patient much better. Can move his limbs now without great pain.

8·6·10. Condition quite cleared up and patient appears normal again.

10·6·10. Coagulation Time is 80 minutes.

No.1.	3· 0· 0	4·30· 0	= 90 m.	
No.2.	3· 2· 0	4·27· 0	= 85 m.	
No.3.	3· 4· 0	4· 9· 0	= 65 m.	80 m.
No.4.	3· 6· 0	4·33· 0	= 87 m.	
No.5.	3·10· 0	4·23· 0	= 73 m.	
Cont.	3·15· 0	3·26· 0	= 11 m.	

14·6·10. Patient looking unwell, has not taken his food well to-day, is more irritable and "wants/

"wants to be left alone".

15·6·10. Has sore throat - tonsils large and inflamed - glands palpable in the neck - and a suspicious-looking rash over the neck and front of chest. Tongue furred and papillae prominent. In the afternoon the rash was well out all over the body. Circumoral pallor well-marked. Patient undoubtedly has developed scarlet fever, and was soon removed to the Fever Hospital, where he was further observed.

17·6·10. Rash very faded, and almost gone. Patient scratched his skin the whole time the rash was present.

18·6·10. Developed a bruise on left elbow. The tongue is clean, very red, and papillae markedly enlarged.

21·6·10. Bruise on back of right hand.

22·6·10. Slight"powdering"of skin started in neck.

23.6.10. Right ear started to bleed and continued to do so for some days.

24·6·10. Bruise over left ankle.

28·6·10. Desquamation general over whole trunk.

NOTE/

NOTE to CASE II.

Sister of Case II. Age 15; "non-bleeder" The Coagulation Time of her blood was taken for comparison with that of her brother, a "bleeder", and found to be 10 minutes.

14·6·10.	No.1.	4·13· 0	4·23· 0 = 10 m.	
	No.2.	4·15· 0	4·25· 0 = 10 m.	10 m.
	No.3.	4·17· 0	4·27· 0 = 10 m.	
	Cont.	4·20· 0	4·30· 0 = 10 m.	

CASE/

CASE III.

Elder Brother of Case II. For Family History see Case II. and Family Chart .

Male, age 25 years. Under observation from the 15th May 1910 to the 31st July 1910.

Golf club maker.

1890. Condition manifested itself at 5 years of age, when patient first suffered from swollen ankles, for which he had occasionally to go to bed.

1891. When 6 years old, he developed a swollen knee, which appeared just as he was getting better from a severe haemorrhage from a tooth. The doctor said it was a "white swelling", and treated him with extension apparatus. The knee would not get better, so his father removed the apparatus, and the swelling soon subsided.

Once or twice has got a small tag of mucous membrane between the upper lip and gums cut by accident, and bled freely for two or three days after.

Both his wrists became swollen and painful from/

from time to time during his school days, and he had a serious haemorrhage when one of his first teeth was extracted.

1902. When 17 years old, a bruising appeared over his left knee joint. He tried to make it disappear by rubbing in paraffin, which caused extreme itchiness and led to his scratching it and inducing ulceration and bleeding, for which he was admitted to Leith Hospital.

1907. This year he fell into a hole on the floor, and bent his knee suddenly. It became swollen and painful, and he remained 10 days laid up with it. Later on he started cycling, since when his leg joints and wrists have never troubled him, being occasionally only slightly swollen, but never bad enough to keep him off his work.

1908. On August 29th, patient fell off his bicycle, and knocked out his left upper incisor tooth, which bled profusely. He was treated at the Royal Infirmary Out Patient Department for the next two days, during/

during both of which the bleeding continued. He was admitted for a week to the wards, where he was treated by plugging with cottonwool soaked in turpentine.

1910. In February, on waking up in the morning, his tongue started to bleed for no obvious reason, and was bad enough for him to get treated as an out patient at Hospital.

When his joints get swollen, he is in the habit of locally applying a liniment, consisting of menthol ($\frac{1}{6}$ oz.) and methylated spirits (1 gill).

15·5·10. The Coagulation Time is 68 minutes.

No.1.	4· 4· 0	5·51· 0 = 48 m.	
No.2.	4· 7· 0	5·10· 0 = 63 m.	68 m.
No.3.	4·11· 0	5·45· 0 = 94 m.	
Cont.	4·14· 0	4·24· 0	= 10 m.

20·5·10. Given 10cc. Normal Horse Serum by mouth daily.

22·5·10. The Coagulation Time is 64 minutes.

No.1.	2·57· 0	4· 6· 0 = 69 m.	
No.2.	2·53· 0	4·11· 0 = 73 m.	64 m.
No.3.	3· 0· 0	3·50· 0 = 50 m.	
Cont.	3· 5· 0	3·15· 0	= 10 m.

29·5·10./

29·5·10. The Coagulation Time is 63 minutes.

No.1.	2·23· 0	3·34· 0	= 71 m.	
No.2.	2·25· 0	3·52· 0	= 87 m.	63 m.
No.3.	2·27· 0	3· 0· 0	= 33 m.	
Cont.	2·30· 0	2·40· 0	= 10 m.	

The White Blood Count was 7,187.

5·6·10. The Coagulation Time is 106 minutes.

No.1.	3· 8· 0	4·59· 0	=111 m.	
No.2.	3· 9· 0	5· 1· 0	=112 m.	106 m.
No.3.	3·10· 0	4·46· 0	= 96 m.	
Cont.	3·12· 0	3·23· 0	= 11m.	

Stopped the Normal Horse Serum.

7·7·10. Cut his finger badly and bled from it for two days. Normal Horse Serum applied locally, but did not seem to be of any use.

31·7·10. Blood Count showed.

W.B.C. 8,437.

R.B.C. 5,280,000.

The Coagulation Time is 144 minutes.

No.1.	4· 8· 0	6·52· 0	= 164 m.	
No.2.	4·10· 0	6·53· 0	= 163 m.	
No.3.	4·12· 0	6·50· 0	= 158 m.	144 m.
No.4.	4·14· 0	6·16· 0	= 122 m.	
No.5.	4·16· 0	6·12· 0	= 116 m.	
Cont.	4·20· 0	4·30· 0	= 10 m.	

CASE IV.

Brother of Case VI.

For Family History, see Case VI.

Male, age 11 years.

Under observation from 15th May 1910.
to 14th June 1910.

1902. When 3 years old was in hospital with a cut in his thumb, which bled for four days before being arrested.

1903. Has a swollen ankle - the first appearance of joint manifestations in this patient, which showed itself on recovering from a cut on his forehead. Later in the year his left knee became swollen on recovering from a crushed finger, which bled profusely for a whole day.

1904. In February he fell on a chair and cut his head; he had to be taken to hospital before the bleeding could be stopped.

1909. In August, patient sprained his right ankle, and was laid up for a whole week.

15·5·10. On Examination patient looks fairly healthy, not pale in the least, but rather high-coloured. He has a fair skin and dark/

dark hair. his left knee is slightly bigger than the the right knee joint.

Measurements of Knees.

Right:-		Left:-	
Just above Joint	9½"	Just above Joint	10"
At Knee Joint	11¼"	At Knee Joint	11½"
Just below Joint	11¼"	Just below Joint	10¾"

15·5·10. The Coagulation Time is 52 minutes.

No.1.	4·44· 0	5·47· 0	= 63 m.	
No.2.	4·55· 0	5·29· 0	= 34 m.	52 m.
No.3.	4·58· 0	5·58· 0	= 60m.	
Cont.	4·26· 0	4·35· 0	= 9 m.	

Put on Normal Horse Serum by mouth daily (5cc. morning and evening).

17·5·10. The Coagulation Time is 50 minutes.

No.1.	3· 0· 0	3·36· 0	= 36 m.	
No.2.	3· 2· 0	4· 6· 0	= 64 m.	50 m.
No.3.	3· 4· 0	3·54· 0	= 50 m.	
Cont.	3·10· 0	3·20· 0	= 10 m.	

20·5·10. Coagulation Time is 58 minutes.

No.1.	3· 0· 0	4· 9· 0	= 69 m.	
No.2.	3· 3· 0	4· 8· 0	= 65 m.	58 m.
No.3.	3· 5·30	3·47·30	= 42 m.	
Cont.	3· 8· 0	3·18· 0	= 10 m.	

23·5·10/

23·5·10. Coagulation Time is 27 minutes.

No.1.	3· 7· 0	3·44· 0 = 37 m.)	
No.2.	3·14· 0	3·40· 0 = 26 m.)	27 m.
No.3.	3·17· 0	3·36· 0 = 19 m.)	
Cont.	3·30· 0	3·40· 0 = 10 m.	

28·5·10. Coagulation Time is 25 minutes.

No.1.	2·33· 0	3· 3· 0 = 30 m.)	
No.2.	2·37· 0	3· 8· 0 = 30 m.)	25 m.
No.3.	2·38· 0	2·55· 0 = 17 m.)	
Cont.	2·40· 0	2·50· 0 = 10 m.	

11·6·10. Patient says he feels very "fit" and has had a sense of "well-being" since taking the serum. He has just returned from a holiday in the country, during which time he has not had any haemophilic symptoms or discomfort.

Stopped Normal Horse Serum.

14·6·10. Coagulation Time is 36 minutes.

No.1.	4· 4· 0	4·44· 0 = 40 m.)	
No. 2.	4· 6· 0	4·42· 0 = 36 m.)	36 m.
No.3.	4· 9· 0	4·41· 0 = 32 m.)	
Cont.	4·20· 0	4·30· 0 = 10 m.	

Patient has not been seen since.

CASE V.

Male, age 25. Haemophilic.

Cousin of Cases II. III. and IV.

Examined only on two occasions.

As a young boy he suffered from bruises when he received any hard knock. He has had epistaxis, no haematemesis or haemoptysis. His joint troubles began when he was 5 years old, when he fell off a chair and hurt his left knee, which became swollen and painful. Since then most of his joints have been affected at various times, but never very badly. Since he became 18 years old, he says he has suffered much less and is seldom off work owing to his trouble. He does not look a robust person, but he says that, apart from the usual children's diseases and his haemophilia, he has never been ill, except when he had influenza on two occasions.

22·5·10. Coagulation Time is 29 minutes.

No.1.	4· 3· 0	4·20· 0 = 17 m.	29 m.
No.2.	4· 5· 0	4·51· 0 = 46 m.	
No.3.	4· 9· 0	4·33· 0 = 24 m.	
Cont.	4·29· 0	4·39· 0 = 10 m.	

Put on Normal Horse Serum 10cc. daily by mouth.

24·5·10./

24·5·10. Right elbow has become rather stiff and swollen.

28·5·10. Right knee has become swollen and painful.

30·5·10. Right knee better, can almost walk straight with it.

5·6·10. Coagulation Time is 33 minutes.

No.1.	2·58· 0	3·23· 0	= 25 m.)	
No.2.	3· 0· 0	3·37· 0	= 37 m.)	33 m.
No.3.	3· 2· 0	3·40· 0	= 38 m.)	
Cont.	4· 9· 0	4·18· 0	= 9 m.	

Patient not seen again.

NOTE to CASE V.

Brother of Case V. Age 17. Has never been troubled with any haemophilic symptoms.

5·6·10. Coagulation Time is 8 minutes.

No.1.	3·45· 0	3·53· 0	= 8 m.)	
No.2.	3·47· 0	3·55· 0	= 8 m.)	8 m.
No.3.	3·48· 0	3·56· 0	= 8 m.)	
Cont.	4· 9· 0	4·18· 0	= 9 m.	

CASE/

CASE VI.

Male, age 9 years. Was under observation from the 21st June 1910 to the 15th October 1910.

Cousin of Cases VII. and VIII.

FAMILY HISTORY.

Mother comes from a haemophilic stock (vid. Family Chart). She has had no miscarriages, and has had thirteen children, eight of whom are alive - the other five having died young of ordinary children's troubles - none of them being bleeders as far as she can say. Out of the eight children, this patient is the only "bleeder". Mother is not a "bleeder". The second child - a girl - was dead born - full time. Before her last confinement she had three uterine haemorrhages, at intervals of about two weeks each, losing over a pint of blood each time. At the second haemorrhage (fearing placenta praevia), her doctor examined her carefully, getting a finger quite easily well up inside the os, and felt what he took to be placental margin, but pretty high up. The labour, however, was quite natural, and twins were born, with no remarkable bleeding./

bleeding.

The Grandmother (mother's mother) was a bleeder, having many attacks of severe epistaxis. Two of the mother's brothers were also bleeders, one dying of uncontrollable epistaxis and one from loss of blood, caused by an incised wound on the lip. Information further back is not reliable.

Parents have lived for eleven years in a two-roomed ground floor house, which is damp. There is no family history of tubercle or insanity. Both parents are rheumatic.

PATIENT'S HISTORY.

Pregnancy normal, labour normal, full time, no after haemorrhage. Mother made a good recovery, and rose the fifth day after delivery. Patient normal at birth, no jaundice - no trouble with the cord, the "scab" coming off on the fifth day, and no bleeding resulted. Breast fed for nine months. Cut first tooth at eleven months, with no bleeding from gums. Started walking at fourteen months, and began to speak at eighteen months. He was said to be weak in the back, which was consequently bathed with salt water, and to this weakness was attributed the/

the delay in starting to walk.

No congenital syphilis; no rickets; digestion, sleep, bowels satisfactory. No attacks of vomiting, but suffered from attacks of diarrhoea while teething.

There was never any discharge from nose, ears or eyes. No history of enlarged glands, bronchitis, or sore throats, but tonsils sometimes became swollen and then disappeared again without treatment. No haematemesis or haemoptysis; there was always melaena next day after an attack of epistaxis - but never at any other time. Epistaxis was the first symptom of haemophilia noticed, and this first occurred when he was three and a half years old; it always started when he got a knock, no matter on what part of the body the violence occurred, and only when the knock was severe, usually when he fell down and hurt himself.

There seems to be no periodicity in his haemorrhages, and they have never been noticed to come without some definite assignable cause. The epistaxis was frequently checked by applying cold water locally, also a cold key down the back of the neck. When he reached about 3 years of age, and was getting stronger, the attacks of epistaxis became/

became less frequent, and for the last eighteen months he has only had one attack, i.e., February 1910, which lasted for one day. There have been occasional bleedings from the gums, lasting for a day or two at a time.

The first joint to be affected was the left ankle joint, which was injured when he was aged five years. It became swollen, blue and discoloured, and he was laid up with it for about two weeks; he has never been affected in this joint since. The left hand and wrist were next attacked - when he was about six years old - but have never troubled him since then.

Two days before being examined he fell and bruised his right thigh; it became swollen and discoloured. During attacks of haemorrhage the appetite is lost, patient becomes very thirsty, and the bowels are usually constipated. Frequently the pain prevents sleep; as a rule he takes cold and has a cough for a day or two, when he goes out for the first time after an attack. The only infectious disease he has had was whooping-cough at two years of age. The liver and spleen are not enlarged. Glands in neck and groins are palpable, but/

but very small. Heart sounds closed in all areas. The lungs are both clear, and reveal no abnormal condition.

HISTORY of PRESENT ATTACK.

On Friday, 17th June 1910, patient received a knock, and his right thigh became very swollen, being $2\frac{1}{2}$ inches greater in circumference than the left one. It showed well-marked bruising right down the front of the thigh, and was very painful. A few days previous to this, his left wrist was injured by a fall, and there developed on the dorsum of the wrist a localized round swelling, fluctuating in character and bluish in appearance, evidently in the synovial sheath.

23·6·10. Slight epistaxis, which continued for two days.

26·6·10. Only two coagulation estimations could be made, owing to patient's nervousness.

Coagulation Time is 59 minutes.

No.1.	3·55· 0 4·55· 0 = 60 m.)	(59 m.
No.2.	3·57· 0 4·55· 0 = 58 m)	
Cont.	4· 0· 0 4·11· 0 =	11 m.

28·6·10. Put on 10cc. Normal Horse Serum daily by mouth.

30·6·10./

30·6·10. Coagulation Time is 57 minutes.

No.1.	3· 5· 0	4· 3· 0 = 58 m.		
No.2.	3· 7· 0	4· 6· 0 = 59 m.		
No.3.	3· 9· 0	4· 8· 0 = 59 m.	57 m.	
No.4.	3·12· 0	4· 9· 0 = 57 m.		
No.5.	3·15· 0	4·10· 0 = 55 m.		
Cont.	3·20· 0	3·29· 0 =		9 m.

1·7·10. Coagulation Time is 53 minutes.

No.1.	4· 0· 0	4·59· 0 = 59 m.		
No.2.	4· 2· 0	4·50· 0 = 48 m.		
No.3.	4· 4· 0	5· 1· 0 = 57 m.	53 m.	
No.4.	4· 6· 0	5· 0· 0 = 54 m.		
No.5.	4· 8· 0	4·57· 0 = 49 m.		
Cont.	4·12· 0	4·21· 0	=	9 m.

2·7·10. Coagulation Time is 60 minutes.

No.1.	3· 0· 0	3·48· 0 = 48 m.		
No.2.	3· 3· 0	4·12· 0 = 69 m.		
No.3.	3· 5· 0	4· 5· 0 = 60 m.	60 m.	
No.4.	3· 8· 0	4· 7· 0 = 59 m.		
No.5.	3· 9· 0	4·16· 0 = 67 m.		
Cont.	3·12· 0	3·22· 0	=	10 m.

3·7·10. Coagulation Time is 55 minutes.

No.1.	3·30· 0	4·29· 0 = 59 m.		
No.2.	3·33· 0	4·11· 0 = 38 m.		
No.3.	3·35· 0	4·41· 0 = 66 m.	55 m.	
No.4.	3·37· 0	4·46· 0 = 69 m.		
No.5.	3·40· 0	4·25· 0 = 45 m.		
Cont.	3·45· 0	3·55· 0	=	10 m.

4·7·10/

4·7·10. Thigh very much better and swelling almost gone. The knee region, however is still rather swollen, and patient cannot bend his leg yet without pain.

8·7·10. The left ankle was noticed to be swollen about 4 a.m., without obvious cause, and patient says he did not knock it. There was no bruising. It soon became very tense and painful. Lead and opium fomentations had to be applied locally to alleviate suffering, but were not of much use. The temperature was a little raised for the two days during which the symptoms were acute.

11·7·10. Ankle still swollen, but no longer painful.

24·7·10. Coagulation time is 44 minutes.

No.1.	3·32· 0	4·17· 0	= 45 m.	
No.2.	3·35· 0	4·18· 0	= 43 m.	
No.3.	3·38· 0	4·10· 0	= 32 m.	44 m.
No.4.	3·40· 0	4·28· 0	= 48 m.	
No.5.	3·42· 0	4·34· 0	= 52 m.	
Cont.	3·46· 0	3·56· 0	= 10 m.	

Blood Count.

		Differential Count.	
R.B.C.	4,200,000		
Hb.	72%	P.	68%.
C.I.	·85	L.	30%.
W.B.C.	5,600	E.	2%.

Viscosity 4·24.

27·7·10/

27·7·10. Haemorrhage into tendon sheath of right hand. No injury was received as far as patient knows. The hand has become very swollen and extremely painful.

29·7·10., Normal Horse Serum was stopped to-day, 10cc. of which was being given by the mouth daily since the 29th June last (one month ago).

30·7·10. Wrist is so painful that $\frac{1}{20}$ gr. hypodermic injection of morphia at night was found necessary, and this had to be repeated again once at 2·30 a.m. before the pain subsided. Lead and opium was applied locally as well. The knee is still swollen, but no longer painful. Massage started very gently to-day for first time.

5·8·10. Wrist now practically better, no pain felt and only a little swollen now. Swelling of knee now gone, and patient can bend leg fairly well without discomfort; he cannot, however, completely straighten out his knee joint.

15·8·10. Epistaxis, slight, and lasting two days before stopping.

18·8·10/

18·8·10. Slight melaena for last two days, obviously the result of the epistaxis.

24·8·10. Coagulation Time is 50 minutes.

No.1.	5· 0· 0	5·50· 0	= 50 m.	
No.2.	5· 3· 0	5·39· 0	= 36 m.	
No.3.	5· 5· 0	6· 4· 0	= 59 m.	50 m.
No.4.	5· 8· 0	6· 8· 0	= 60 m.	
No.5.	5·12· 0	5·59· 0	= 47 m.	
Cont.	5·16· 0	5·28· 0	= 12 m.	

4·9·10. The gums bled slightly the whole day, but stopped about 9 p.m.

15·9·10. Sudden swelling of right wrist on its dorsal surface noticed in the morning, patient not conscious of knocking it during the night. The pain is bad, but not severe. Lead and opium fomentations applied locally.

24·9·10. Coagulation Time is 48 minutes.

No.1.	4·30· 0	5·15· 0	= 45 m.	
No.2.	4·33· 0	5·13· 0	= 40 m.	
No.3.	4·36· 0	5·35· 0	= 59 m.	48 m.
No.4.	4·38· 0	5·30· 0	= 52 m.	
No.5.	4·40· 0	5·28· 0	= 48 m.	
Cont.	4·45· 0	4·55· 0	= 10 m.	

14·10·10/

14·10·10. Has not had any further haemorrhages all month. Has gained 3 lbs. 8 ozs. in weight since the 23rd of June last, being 44 lbs. 12 ozs., as against 41 lbs. 4 oz.

NOTE to CASE VI.

9·7·10. The infant brother of this case was examined, with a view of determining the coagulation time of the blood. His age is 10 months. There is no history of umbilical haemorrhage at birth or of any other haemophilic symptom since, but the child looks very pale and anaemic. Only two estimations were made, as it was found difficult to bleed the child, and the Coagulation Time was found to be 12½ minutes.

No.1.	3·40· 0	3·54· 0 = 14 m.)	(12·30 m.	
No.2.	3·44· 0	3·55· 0 = 11 m.)		
Cont.	3·50· 0	4· 0· 0	= 10 m.	

The/

The Blood Count was found to be as follows:-

R.B.C.	4,525,000	Differential Count.	
Hb.	65%.	P.	60·5%.
C.I.	·72	L.	39%.
W.B.C.	14,375	E.	·5%.

CASE/

CASE VII.

Male. Age 9 years. Cousin of Case VI and brother of Case VIII.

Under observation from 9th August 1909 to 28th October 1911.

FAMILY HISTORY.

For family chart see separate chart.

Mother comes from a haemophilic stock and is a sister of the mother of Case VI. She never lost much blood at her confinements, but usually had some bleeding each time after getting up. She has had one miscarriage at about 2½ months, between the births of Cases VII and VIII. She was very ill and lost a lot of blood. She is usually very ill at her monthly times and is now reaching the menopause - last week she was ill five days instead of the usual three days and lost a great deal more blood than normally.

She has had eight children.

Child/

Child 1 = Girl, healthy.

Child 2 = Girl, healthy.

Child 3)
(= Girls - both healthy.
Child 4)

Child 5 = Girl, healthy.

Child 6 = Boy, bleeder. (Case VII).

Child 7 = Boy, bleeder. (Case VIII).

Child 8 = Boy - non-bleeder, so far - but is just an infant in arms still.

HOME SURROUNDINGS.

Quite satisfactory.

PATIENT'S GENERAL HISTORY.

Pregnancy normal, labour normal - with no severe bleeding - full time - no post partum haemorrhage. Mother made a good recovery, rising on the 4th day, when she commenced to bleed a little. Child normal at birth, "fine, healthy baby," no bleeding when cord was cut, it came away on the 5th day with no subsequent bleeding. No jaundice - breast fed for 14 months. Cut first tooth at four months - no bleeding from gums.

No evidence of congenital syphilis or rickets/

rickets. No history of syphilis, tubercle, or rheumatism. Never had haematemesis, except subsequent to an attack of epistaxis. No haemoptysis, no melaena. The first sign of the condition showing itself was when he was 2 years old, when he was injured by some china ornaments. There was a cut between the first and second fingers, which bled very severely and had to be stitched. Next, between the ages of 3 and 4 years, he developed his first attack of epistaxis, without obvious cause. The bleeding is always from the left nostril, and still comes on from time to time, though there has been no recurrence for a whole year now.

At 6 years of age, the first joint troubles appeared, when he injured his left ankle, which became swollen and painful for some days. Since then he has had frequent recurrences. During the acute stage, patient feels most comfortable when hanging his leg over the edge of the bed, and cannot bear keeping it under the bedclothes, owing to the pain, which also keeps him from sleeping.

No other joints seem to have become affected. Patient frequently has bruises over various parts of his body, usually due to slight knocks. During/

During haemorrhages he does not lose his appetite, and does not become very thirsty.

Liver and spleen normal. Heart sounds closed in all areas, Lungs clear.

He had whooping cough at 2 years, measles at $2\frac{1}{2}$ years.

TREATMENT and PROGRESS.

Patient lives in the country.

9·8·09. Patient has recently been suffering from a severe gastric haemorrhage; he looks very bloodless and weak.

The Blood Count shows.

R.B.C.	2,550,000
Hb.	30%.
C.I.	·6
W.B.C.	14,062

The Coagulation Time was taken by McGowan's method at Temperature 80° F., and found to be 40 minutes.

7·55· 0 8·35· 0 = 40 m.
Cont. 7·58· 0 8·10· 0 = 12 m.

Patient put on Normal Horse Serum 10cc. daily by the mouth.

16·8·09./

16·8·09. Patient looks a little better, but still appears very blanched.

The Blood Count shows.

R.B.C.	3,100,000
Hb.	45%.
C.I.	·7
W.B.C.	10,312

The Coagulation Time (McGowan's method) with Temperature 70° F.)is 63 minutes.

No.1. 6· 5· 0 7·13· 0 = 68 m.)
(63 m.
No.2. 6· 7· 0 7· 6· 0 = 59 m.)

Cont. 6·10· 0 6·21· 0 = 11 m.

31·8·09. Blood Count shows.

R.B.C.	4,520,000
Hb.	65%
C.I.	·7
W.B.C.	9,000

The Coagulation time taken by McGowan's method, with temperature 64°F. is 104 minutes.

6·32· 0 8·16· 0 = 104 m.

Cont. 6·36· 0 6·49· 0 = 13 m.

Normal Horse Serum stopped.

9·9·09./

9·9·09. The Coagulation Time taken by McGowan's method, with temperature 70° F. is 95 minutes.

No.1.	7·30· 0	9· 0· 0	= 90 m.)	95 m.
No.2.	7·32· 0	9·12· 0	=100 m.)	
Cont.	7·35· 0	7·48· 0	= 13 m.	

16·9·09. The Coagulation Time by McGowan's Method, with Temperature 68° F. is 95 minutes.

No.1.	6·15· 0	7·55· 0	= 100 m.)	95 m.
No.2.	6·18· 0	8· 3· 0	= 105 m.)	
No.3.	6·21· 0	7·43· 0	= 82 m.)	
Cont.	6·25· 0	6·36· 0	= 11 m.	

Nov.1909. Patient has severe epistaxis, which has lasted for about two days on and off. Haematemesis followed, due to the swallowing of blood. Shortly after this, his right ankle became swollen and painful and he had to lie up for a week with it.

Dec.1909. The right ankle is now quite better.

12·2·10. Patient not seen since December last. Coagulation Time taken by Addis' method (all subsequent estimations done by this method)/

method) was found to be 62 minutes.

No.1. 3·25· 0 4·11· 0 = 46 m.)
No.2. 3·28·30 4·47·30 = 79 m.) 62 m.
No.3. 3·30· 0 4·32· 0 = 62 m.)

Cont. 3·36· 0 3·46· 0 = 10 m.

Blood was again taken from the first puncture 9½ minutes later, and the Coagulation was found to be markedly diminished, being as low as 18 minutes.

No.1. 3·34·15 3·52·15 = 18 m.

The Blood Count shows.

R.B.C.	6,280,000
Hb.	65%.
C.I.	·5
W.B.C.	10.000

17·2·10. Started 5cc. Normal Horse Serum by mouth daily.

26·2·10. Complains of pain in his right knee, which got bruised some time ago, otherwise feels quite well - still very pale.

The Blood Count shows(average of two complete estimations).

R.B.C.	6,310,000
Hb.	80%.
C.I.	·63
W.B.C.	10,625

Viscosity/

Viscosity 34·5.

The Coagulation Time is 64 minutes.

No.1.	4· 0· 0	5·16· 0 = 76 m.		
No.2.	4· 2· 0	4·50· 0 = 48 m.	64 m.	
No.3.	4· 4· 0	5·12· 0 = 68 m.		
Cont.	4· 8· 0	4·18· 0	= 10 m.	

5·3·10. The Coagulation Time is 70 minutes.

No.1.	4· 5· 0	4·37· 0 = 32 m.		
No.2.	4· 7· 0	5·41· 0 = 94 m.	70 m.	
No.3.	4· 9· 0	5·33· 0 = 84 m.		
Cont.	4·12· 0	4·23· 0 =	11 m.	

12·3·10. Coagulation Time is 65 minutes.

No.1.	5· 0· 0	6· 4· 0 = 64 m.		
No.2.	5· 2· 0	5·54· 0 = 52 m.	65 m.	
No.3.	5· 4· 0	6·24· 0 = 80 m.		
Cont.	5·10· 0	5·20· 0	= 10 m.	

Blood taken from first puncture 12 minutes later shows,

5·12· 0 5·28· 0 = 16 m.

Taken 15 minutes later,

5·15· 0 5·21· 0 = 6 m.

No more blood could be expressed from same puncture wound.

19·3·10./

19·3·10. The Coagulation Time is 60 minutes.

No.1. 4·30· 0 5·30· 0 = 60 m.)
No.2. 4·32· 0 5·51· 0 = 79 m.) 60 m.
No.3. 4·34· 0 5·17· 0 = 41 m.)

Cont. 4·40· 0 4·49· 0 = 9 m.

Blood taken from second puncture five minutes later showed,

No.2. 4·37· 0 4·57· 0 = 20 m.

Taken 10 minutes later,

4·42· 0 4·54· 0 = 12 m.

Taken 15 minutes later, had to be squeezed out from puncture wound.

4·47· 0 4·53· 0 = 6 m.

No more blood could be expressed.

Normal Horse Serum stopped.

26·3·10. Coagulation Time is 50 minutes.

No.1. 3· 0· 0 4· 1· 0 = 61 m.)
No.2. 3· 2· 0 3·44· 0 = 42 m.) 50 m.
No.3. 3· 4· 0 3·52· 0 = 48 m.)

Cont. 3· 8· 0 3·18· 0 = 10 m.

Blood taken from third puncture six minutes later showed.

3·10· 0 3·35· 0 = 25 m.

Taken twelve minutes later,

3·16· 0 3·26· 0 = 10 m.

No/

No more blood could be expressed from same puncture wound.

25·6·10. Coagulation Time is 88 minutes.

One and a half inches of clear serum separated out at top of each capillary coagulation tube, while estimations were being carried out.

No.1.	3·24· 0	4·57· 0 =	93 m.)	
No.2.	3·26· 0	4·34· 0 =	72 m.)	88 m.
No.3.	3·29· 0	5·10· 0 =	101 m.)	
Cont.	3·32· 0	3·42· 0 =	10 m.	

Blood taken from second puncture wound four minutes later.

No.2. 3·30· 0 3·50· 0 = 20 m.

Taken eight minutes later,

No.2. 3·34· 0 3·40· 0 = 6 m.

No more blood could be got.

Patient looking very pale and anaemic. He has never been able to attend school since last seen in August, being frequently troubled with his right ankle, and also with severe attacks of epistaxis.

Put on 5cc. Normal Horse Serum by mouth daily.

9·7·10./

9·7·10. Coagulation Time is 83 minutes.

No.1. 4·15· 0 5·39· 0 = 84 m.)
No.2. 4·18· 0 5·40· 0 = 82 m.) 83 m.
No.3. 4·21· 0 5·41· 0 = 80m.)

Cont. 4·35· 0 4·44· 0 = 9 m.

About one inch of serum separated out at top of capillary coagulation tubes No.1 and No.2.

Blood taken from first puncture wound. five minutes later, showed.

No.1. 4·20· 0 4·50· 0 = 30 m.

Taken ten minutes later.

No.1. 4·25· 0 4·42· 0 = 17 m.

Taken fifteen minutes later, had to be expressed.

No.1. 4·30· 0 4·43· 0 = 13 m.

1·9·10. Started bleeding from his gums at upper left hand side of mouth, which went on for about 6 days before stopping. He has no toothache with it.

6·9·10. Left ankle swollen and painful, noticed in the morning, when about to rise, and seems to have come on without any obvious cause.

He has a croupy cough at times; this has only recently come on, since he had bronchitis/

bronchitis six months ago. When this cough starts, it usually starts an attack of epistaxis.

On the whole, however, since first seen in August 1909, his general condition seems to be better, and his bleeding attacks less frequent and less severe.

Coagulation Time is 40 minutes.

No.1. 3·20·0 4·5·0 = 45 m.)
No.2. 3·22·0 3·57·0 = 35 m.) 40 m.
No.3. 3·24·0 4·6·0 = 42 m.)

Cont. 3·30·0 3·40·0 = 10 m.

Blood taken from third puncture wound four minutes later.

No.3. 3·28·0 3·53·0 = 30 m.

Taken eight minutes later.

No.3. 3·32·0 3·48·0 = 16 m.

Taken twelve minutes later, had to be expressed.

No.3. 3·36·0 3·45·0 = 9m.

No more blood could be got for accurate testing.

20·9·10. Coagulation Time is 30 minutes.

No.1. 3·0·0 3·24·0 = 24 m.)
No.2. 3·2·0 3·38·0 = 36 m.) 30 m.
No.3. 3·4·0 3·36·0 = 32 m.)

Cont. 3·8·0 3·18·0 = 10 m.

Blood/

Blood taken from third puncture, six minutes later.

No.3. 3·10· 0 3·30· 0 = 20 m.

Blood taken twelve minutes later.

No.3. 3·16· 0 3·28· 0 = 12 m.

No more blood could be got.

Blood Count shows.

R.B.C. 3,210,000

W.B.C. 8,125

23·8·11. Patient has been comparatively free from any "bleedings" since last September. On this date, however, he fell and his head struck a stone, causing a cut about 1½ inches long. A running suture was put in by the local doctor. It bled a great deal, but the day following, it stopped.

2·9·11. At night the wound started to bleed again, wet compresses were applied, which practically stopped the bleeding, except for some slight oozing.

4·9·11. The bleeding started once more, and then a swelling developed underneath the skin at the site of the injury.

5·9·11./

5·9·11. Stitches were removed, and bleeding became worse.

6·9·11. Bleeding still going on, and patient has now lost a lot of blood. Adrenalin chloride in gauze applied to the cut and firmly bandaged on. The oozing still continuous. Human blood was applied to the cut, but the clot which formed was washed away. Oozing continued, and by midnight the bleeding had soaked through the bandage. Human blood again applied to wound, but had not much effect, for oozing still went on. Has been very sick all day.

7·9·11. Dressed in morning - still oozing away, and bandage was soaked with blood. In the evening the dressing was again removed, and it was found that part of the slough of cut had come away; the oozing was now very slight. Thermo-cautery applied to edges of wound and small opening through which blood was coming, and this seemed to arrest the haemorrhage. Very sick still, and pulse very poor.

The/

The Blood Count shows:

R.B.C.	3,510,000
Hb.	45%.
C.I.	·6
W.B.C.	15,000

The film shows poikilocytosis and a few nucleated red cells.

8·9·11. Started giving Horse Serum, 10cc. per rectum daily. Coagulation Estimations suspended, owing to anaemic condition of patient. Blood oozed through bandage. Dressed at 5·30 a.m., Liq. Ferri Perchlor. put in gauze and applied to the wound. In forenoon the dressing was taken off and gauze soaked in Tinct. Benzoini Co. applied. Not bleeding much now. Has been very sick all day, and is very thirsty and continually wants water to drink.

9·9·11. Slept a little during night for the first time since two days. He retains his salines well and his pulse is rather better. Bleeding has practically stopped now, only occasionally starts to ooze for a few hours and then stops entirely for/

for a time. Put on rectal salines oz.iv. 4 hourly.

10·9·11. Slept well last night and is not so thirsty to-day. Slept a lot during day too. Sickness is also better, and he was able to retain some milk without any vomiting afterwards. He has developed a well-marked "bruit de Diable".

11·9·11. Pulse is stronger - patient is still rather thirsty and looks blanched. The vessels in the neck are throbbing markedly.

12·9·11. Put on Normal Horse Serum 10cc. daily by mouth, instead of per rectum. No bleeding now, except an occasional slight oozing. The gauze over his wound is kept soaked in Friar's Balsam.

14·9·11. Has been sick during the night, and also this morning after getting his milk. Is still extremely anaemic-looking, but sleeps very well on the whole.

16·9·11. No more sickness, and is beginning to "pick up" again. The pulse is much stronger and he takes his food well.

18·9·11. Well-marked haemic murmurs at base of heart, and also "Bruit de Diable". Was sick/

sick once this morning.

22·9·11. Wound in head looks cleaner, and is being sprayed with Hydrogen Peroxide.

Stopped the Horse Serum and put on Ferri Redact. grs. ii. t.i.d.

25·9·11. Able to sit up in bed now. Haemic murmurs still very marked all over.

29·9·11. Blood Count shows:

R.B.C.	2,300,000
Hb.	40%.
C.I.	·7
W.B.C.	11,200

4:10:11. Looks very much better, and is anxious to be allowed up. His appetite is now excellent.

8·10·11. Right ankle found to be rather swollen and painful, mostly round the external malleolus.

9·10·11. Second phalangeal joint of right middle finger rather swollen and painful.

13·10·11. Swelling in both joints now subsiding. Haemic bruits much less marked, and have almost disappeared.

15·10·11./

15·10·11. Coagulation Time is 30 minutes.

No.1.	6· 2· 0	6·32· 0	= 30 m.	
No.2.	6· 5·30	6·35·30	= 30 m.	30 m.
No.3.	6· 9· 0	6·39· 0	= 30 m.	
No.4.	6·11· 0	6·41· 0	= 30 m.	
Cont.	6·15· 0	6·25· 0	= 10 m.	

The Blood Count shows.

R.B.C.	3,710,000
Hb.	45%.
C.I.	·6
W.B.C.	5,625

10 grs. of Calcium lactate injected intramuscularly into right gluteal region.

20·10·11. Swelling of both joints still subsiding; otherwise general condition very satisfactory.

22·10·11. Coagulation Time is 21 minutes.

No.1.	4·33· 0	4·50· 0	= 17 m.	
No.2.	4·35·30	4·52·30	= 17 m.	
No.3.	4·38·30	5·12·30	= 34 m.	21 m.
No.4.	4·40· 0	5· 4· 0	= 24 m.	
No.5.	4·42· 0	4·56· 0	= 14 m.	
Cont.	4·48· 0	4·59· 0	= 11 m.	

Blood/

CASE VIII.

Male, age 7 years. Haemophilic.

Younger brother of Case VII., and cousin of Case VI.

For Family History see Case VII. and Family Chart 3.

Under observation from 12th February 1910 to 9th July 1910.

This patient is rather thin, and does not look robust. He has a "fine" skin, and is of a fair complexion. He has suffered from infancy from the usual haemophilic symptoms at various times, but not so severely as his brother, Case VII.

He has had attacks of epistaxis occasionally and frequent bruising on the least injury. No haematemesis or haemoptysis - melaena always after attacks of epistaxis. The first joint symptoms appeared when he was five years old, when he injured his left elbow, which became swollen and painful for fully five days before subsiding completely.

31·3·09. His gums started to bleed at 8 a.m., and continued to do so for 4 hours, when they/

they stopped naturally without treatment, but three days later they started again, and did not stop till the mouth had been washed out with weak Liq. Ferri Perchlor. and the gums plugged with Normal Horse Serum.

7·9·09. Left knee became swollen and painful, but there was no discolouration of the skin. It lasted for over a week, during which time he was in bed.

12·2·10. First seen to-day. Coagulation Time is 65 minutes. (Addis Method).

No.1.	3·40·30	4·51·30 = 71 m.)	
No.2.	3·47·15	4·50·15 = 63 m.)	65 m.
No.3.	3·51· 0	4·52· 0 = 61 m.)	
Cont.	3·36· 0	3·46· 0	= 10 m.

The Blood Count shows.

R.B.C.	5,200,000
Hb.	60%.
C.I.	·57
W.B.C.	10,200

17·2·10./

17·2·10. Put on 5 cc. Normal Horse Serum daily by mouth.

18·2·10. Struck by a car conductor's book on the top of his head, which caused his nose to start bleeding at once (11 a.m.). It continued to do so till evening, except for one hour, from 3 p.m. to 4 p.m., when he fell asleep, but it started again when he woke and did not stop till 7 p.m., when his nose was plugged with cotton wool soaked in normal Horse Serum.

26·2·10. Is looking much better again.

Viscosity 52.

The Blood Count shows (average of two estimations)

R.B.C.	4,400,000
Hb.	55%.
C.I.	·6
W.B.C.	9,194

Coagulation Time is 60 minutes.

No.1. 4·12· 0 5· 6· 0 = 54 m.)
No.2. 4·14· 0 5·23· 0 = 69 m.) 60 m.
No.3. 4·16· 0 5·15· 0 = 59 m.)

Cont. 4· 8· 0 4·18· 0 = 10 m.

5·3·10./

5·3·10. Coagulation Time is 63 minutes.

No.1.	4·16· 0	5·28· 0	= 72 m.	
No.2.	4·18· 0	5· 6· 0	= 48 m.	63 m.
No.3.	4·20· 0	5·29· 0	= 69 m.	
Cont.	4·12· 0	4·23· 0	= 11 m.	

Stopped the Normal Horse Serum.

12·3·10. Coagulation Time is 62 minutes.

No.1.	5·14· 0	6·23· 0	= 69 m.	
No.2.	5·16· 0	6·15· 0	= 59 m.	62 m.
No.3.	5·19· 0	6·19· 0	= 60 m.	
Cont.	5·10· 0	5·20· 0	= 10 m.	

25·6·10. Coagulation Time is 68 minutes.

No.1.	3·12· 0	4·20· 0	= 68 m.	
No.2.	3·17· 0	3·57· 0	= 40 m.	68 m.
No.3.	3·20· 0	4·56· 0	= 96 m.	
Cont.	3·32· 0	3·42· 0	= 10 m.	

9·7·10. Coagulation Time is 43 minutes.

No.1.	4·27· 0	5·23· 0	= 56 m.	
No.2.	4·29· 0	4·59· 0	= 30 m.	43 m.
No.3.	4·31· 0	5·14· 0	= 43 m.	
Cont.	4·35· 0	4·44· 0	= 9 m.	

No further haemorrhages.

Not seen again.

CONCLUSIONS./

CONCLUSIONS.

The conclusions arrived at by the study of these cases have already been discussed at length in the foregoing pages, and need only be briefly summarized in a few words.

1. The transmission of the disease in all the cases is according to the usual rule - through the female line.

2. The Prolific tendency of the disease is well marked in all the family pedigree charts.

3. There is an absence of symptoms in early infancy.

4. No prodromal symptoms were ever complained of.

5. The frequent nocturnal onset of symptoms is well seen in these cases.

6. The joint symptoms are shown to occur at an earlier age than is generally stated - five years instead of twelve to fourteen years - they are very rapidly recovered from. In the foregoing cases the knee joints were most frequently affected, and next the elbow joints/

joints. X ray photographs may be useful in diagnosis.

Facts noted about the Blood.

7. Blood Counts were done on fully 40 occasions. The Red Counts and Haemoglobin showed nothing special to note. The White Counts, however, in no case showed a leucopaenia, as stated by Wright, but were found to be all normal or slightly raised.

8. The differential Counts (300 cells being counted in each film) likewise show no departure from the normal, and no evidence was seen, in either the blood of the patients themselves, or that of their non-haemophilic relatives, of a polymorphonuclear leucopaenia, stated by Wright to be a constant feature of the disease.

9. The Blood Pressure was normal.

10. The Viscosity of the Blood in the majority of the cases was below normal, and in only one case was it above normal; as held to be the usual rule by Weil.

11./

11. The local applications to bleeding surfaces are shown to be of little use. Local applitions of normal horse serum are equally disappointing

12. The Coagulation of haemophilic blood shows no material difference from that of normal blood, except that it takes place in a relatively much longer time. Experiments showed that each successive specimen of blood taken from the same puncture wound increased in rate of coagulation, till it became instantaneous, and this delay is supposed to be due more to a qualitative than to a quantitative change in the blood.

13. The series of blood coagulation estimations, (of which about 500 were done), taken at each sitting, were found to vary considerably in time, and to a greater extent than could be accounted for by experimental error. Those taken from the control and from the "non-bleeder" relations of the patients were not found to vary to an appreciable extent.

14./

14. In so-called "Spontaneous Haemophilia", normal serum has been found to give excellent results, but in true hereditary haemophilia, it never brought about a sudden fall in coagulation time. In the severe cases, it had some slight effect, but in the milder cases appeared to be inert. On the whole, therefore, normal serum, as a therapeutic agent in haemophilia, was found to be disappointing, and its action on the blood coagulation uncertain, slight and transient.

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