An Address

ON

SYMPTOMS AND PATHOGENESIS OF THE
HAEMORRHAGIC DIATHESIS.*

BY

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THE term "haemorrhagic diathesis" is applied to a condition in which, without cause, extravasation of blood tends to take place into the skin and from the mucous membranes. The group in the past has been usually known by the name of "primary purpura," but numerous other terms have been employed. Purpura is the most striking feature of the group, since its occurrence as a primary symptom is confined to this entity, but it is not invariably or necessarily present. The essential characteristic of the disease is the tendency to spontaneous haemorrhages, and the nature of these may be very varied. In secondary purpura the symptomatology may be identical, but some recognizable primary disease is present. Haemophilia, however, is a syndrome of a different nature.

PATHOGENESIS.

The cause of these haemorrhages is still in doubt. Various organs and tissues have been held to be initially at fault, and the influence and action of these will be considered below.

Increased Capillary Permeability.—The small size of many of the cutaneous haemorrhages leaves no doubt that the blood has escaped from the capillaries. It is well known that the blood cells are able, in certain circumstances, to traverse the walls of these vessels. An increase in the permeability of the endothelium of the capillaries, on reaching a certain stage, would permit the blood cells to escape through the vessel walls in such a degree as to result in the appearance of cutaneous and other haemorrhages, depending on the site and extent of the change. Is there any evidence for the occurrence of such undue permeability in the haemorrhagic diathesis? As the permeability increases from its normal grade it will reach a point at which it permits the passage of an increased amount of plasma, but not of cells. Accumulations of such plasma must manifest themselves as wheals, local oedema of the tissues, and urticaria. Lewis,¹⁴ in his study of the blood vessels of the skin, came to the conclusion that skin stimulation produces wheals by causing active dilatation and increased permeability of the minute endothelial vessels. The fluid present was proved to be blood plasma. Therefore, if increased permeability is the cause of primary haemorrhages, we would expect in the haemorrhagic diathesis to find the occurrence of local oedemas and urticaria. It is well recognized that this is so.

Clinically, in certain types of the haemorrhagic diathesis, there is close relationship between the occurrence of wheals and urticaria, and the occurrence of purpura and ecchymoses. For example, in a given individual attacks of urticaria and of haemorrhages may alternate, or both may be present simultaneously. This is referred to further under "Symptomatology." Obviously it may be accepted that in such cases the formation of wheals and of urticaria, and the occurrence of haemorrhages, are due to the same factors. A striking phenomenon to which Lewis called attention is the occurrence of "refractoriness" in the minute vessels. If a wheal is produced by skin stimulation, the site affected will not produce another wheal until after the lapse of some days. For that period it is refractory to the same or similar stimuli. In refractoriness the minute vessels are dilated, and do not respond either to vaso-constrictor substance or, on the other hand, to histamine or causes of increased permeability. Lewis decided that this is a direct property of the blood vessels. Apparently the same phenomenon occurs in the haemorrhagic diathesis. Osler,¹⁶ in 1911, recorded a case in which a mustard leaf was placed on the epigastrium of a man on account of a sudden pain. In fact, this pain was the first

symptom of the onset of acute purpura haemorrhagica, and on the next day the purpura appeared, and eventually haemorrhages extended over the entire body, except the site which had been covered and stimulated by the mustard leaf. In a case of mine, a man had a pain in the knee, which he thought was due to a strain, and for which he put on an elastic knee-cap. Purpura subsequently developed. When I saw him both lower extremities were covered with spots, except the area which had been compressed by the knee-cap, which was entirely free. It may be suggested that the refractoriness in these purpuric cases is similar to that observed by Lewis, and exhibits the relationship between haemorrhage and wheal formation. Bedson,¹ in experimental purpura, watched the mesenteric vessels under a microscope, and observed the haemorrhages forming by an "exaggerated type of diapedesis"—that is to say, an increased permeability. He noted that the current of blood was not slowed, which agrees with Lewis's conclusion that there is active dilatation of the minute vessels during wheal formation. Thus there are several lines of evidence suggesting that primary haemorrhages on the one hand, and urticaria and wheal formation on the other, are allied manifestations due to undue permeability of the capillary endothelium. It may be noted here that in urticaria there is, as far as is known, no marked variation in the number of platelets,¹⁵ nor does the spleen enlarge. Observations, however, are scanty.

The Influence of the Blood Platelets.—In cases of the haemorrhagic diathesis, when haemorrhages are occurring, and especially if they are severe, the blood platelets are usually reduced in number, and may be entirely absent. This has given rise to the theory that the diminution of platelets is the essential cause, especially in the grave form known as purpura haemorrhagica. Frank⁶ believed that thrombopenia only occurred in purpura haemorrhagica, and not in other types or lesser grades of primary haemorrhage. He held the view that the thrombopenia was due to a primary defective action of the bone-marrow, and was the direct cause of the haemorrhage. For this reason he introduced the term "essential thrombocytopenic purpura haemorrhagica." Frank now agrees that another factor besides thrombopenia is necessary, and this he finds in "microtrauma," such as pressure of bed clothes. It is now recognized that the platelets may be greatly reduced or even entirely absent, and yet no haemorrhages take place: this may be so in known cases of the haemorrhagic diathesis, and also in other conditions in which reduction of platelets develops. Further, in a case of the haemorrhagic diathesis, the platelets may be normal in number, even at a time when haemorrhages are definitely occurring—that is to say, when the disease is active. This is often found in the type known as Henoch's purpura. Bedson¹ was able to prepare an anti-platelet serum, injection of which resulted in complete absence of platelets in the blood of an animal, yet no purpura or haemorrhages appeared. But if subsequently a second serum was injected, designed to act on the endothelium of the vessels, then haemorrhages developed. No ordinary serum had such a result. Thus the absence of platelets does not result, by itself, in the occurrence of haemorrhages.

It has been argued that the absence of haemorrhage in complete thrombopenia is due to the presence of protective substances set free by the destruction of platelets. This argument is contradicted by the fact that haemorrhages result in experimental thrombopenia if an anti-blood-vessel serum is injected. On the other hand, this serum does not produce haemorrhages in a normal animal—that is, with normal platelets. The conclusion appears to be that platelets have a protective action against the occurrence of capillary haemorrhages, but their absence is not a direct cause of such bleeding. The primary cause of the haemorrhage must be another factor. When this factor is absent haemorrhages will not occur, whether platelets are present or not. When this factor is present the function of the platelets is to act as a protection, and this may be achieved partly or completely. Increased permeability of the capillary endothelium will fulfil this factor. With regard to the mode of the protective action of the platelets, the platelets possess two

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principal functions which are related to each other.^{5 3} First, they tend to adhere in numbers, or even in masses, to injured endothelium. This has been observed taking place in injuries of capillary endothelium. In larger vessels it is now known that the white thrombi, which often cover or start from a patch of atheroma or other pathological site, are composed of platelets. The composition of these white thrombi long puzzled our predecessors. Secondly, platelets or their products are concerned in promoting the coagulation of blood. How far the coagulation time varies with the number of platelets will be discussed later. Both these functions tend to protect a site of capillary endothelium which is either injured by trauma or weakened in other manners. But if the demand is excessive, and frequently repeated, platelets will be consumed and thrombopenia result. Such thrombopenia is a secondary occurrence, and is the result, and not the cause, of the haemorrhagic diathesis. But it establishes a vicious circle, owing to the protective powers of the platelets being diminished.

The Influence of the Spleen.—A difficult question is the reason why the spleen sometimes enlarges in the haemorrhagic diathesis, and the nature of its activity. Kaznelson¹¹ discovered that cases of the haemorrhagic diathesis with thrombocytopenia benefited from splenectomy. He argued that the spleen produces a toxin which acts on the marrow, resulting in thrombopenia, and that the haemorrhages are due to this thrombopenia. As stated above, thrombopenia by itself is insufficient to account for haemorrhage. Kaznelson's theory might be modified to suppose the existence of a splenic toxin acting on the capillary endothelium and causing increased permeability. Such a toxin might be a histamine-like body. On this theory the spleen is the primary cause of the haemorrhagic state. There is no doubt that splenectomy generally has this beneficial effect in the haemorrhagic diathesis. The strongest evidence for the existence of a primary splenic action on the vessels is the frequent occurrence of cases in which haemorrhages cease after splenectomy although thrombopenia persists. But, on the other hand, haemorrhages will sometimes recur, or continue, after operation. In explanation of these recurrences it has been suggested that the reticulo-endothelial tissues elsewhere take up the activities of the spleen and produce an identical toxin. It is difficult to prove or disprove such a suggestion. Since time must elapse before the reticulo-endothelial tissues could develop such functions fully, this theory would not explain the cases occasionally met with in which the haemorrhages continue unaffected by splenectomy. Another theory is that the activity of the spleen is originally secondary to the haemorrhagic state, but results in a vicious circle. From this point of view the action of the spleen in acholuric jaundice is worth consideration. It is generally accepted that the primary fault in acholuric jaundice is the production by the marrow of a proportion of red cells of excessive fragility. The spleen treats these as effete, destroys them in large numbers, and enlarges spodogenously. The symptoms of acholuric jaundice are mainly due to the anaemia and other results of the excessive activity of the spleen, and are relieved by splenectomy, although the fragility remains. The operation removes a link in a vicious circle which has come into being but does not deal with the essential factor. There is no evidence subsequently that this excessive activity is taken over to any appreciable degree by the reticulo-endothelial tissues elsewhere.

It is possible that the spleen holds a similar and secondary position in relation to the haemorrhagic diathesis. Its increased action is thus explained as being destruction of defective platelets produced under stress by the marrow, or the disposal of debris of capillary haemorrhages. Splenectomy will permit these platelets, which are somewhat defective but still valuable, to remain in the circulation. The spleen is not always enlarged. In severe acute cases the spleen is rarely more than just palpable, and frequently is not enlarged at all. This is consistent with the mode of action suggested. But, on the other hand, in chronic cases the larger the spleen the less marked in general are the haemorrhages. As we follow the increasing grade of splenomegaly we come to cases with

definitely enlarged spleen, severe anaemia, a tendency to ecchymoses, and occasionally a few purpuric spots, and finally to cases of "splenic anaemia," often with no haemorrhages at all. All these latter grades usually benefit from splenectomy; but it is difficult to account for them on either of the two theories mentioned. In favour of a primary splenic action on the permeability of the blood vessels is the frequent cessation of haemorrhage after splenectomy. Against this view is the recurrence or persistence of haemorrhage in certain cases, the absence of any relation between the size of the spleen and the severity of the haemorrhages, and the absence of any obvious connexion between the spleen and the allied phenomena of urticaria. Cases of "splenic anaemia" are difficult to fit into either view.

The Influence of the Bone-marrow.—In fatal cases of the haemorrhagic diathesis there are no constant changes in the bone-marrow, and this is confirmed in the few instances in which biopsy has been performed. The marrow may be hyperplastic, aplastic, or apparently normal. It is known from other conditions that neither hyperplasia nor aplasia of marrow, even when extreme, is necessarily associated with the occurrence of haemorrhage. In agreement with these varying states of the marrow, there is no characteristic blood picture, either in acute or in chronic forms. The red cells, of course, are usually diminished in number, but may be normal or even above normal. Any of these changes in the red cells may be combined with increase or decrease of the white cells, probably depending on whether the bone-marrow is, on the one hand, hyperplastic, or, on the other hand, either aplastic or temporarily exhausted. Diminution of red or white cells of itself does not result in capillary haemorrhage; such haemorrhages do not occur in persons bleeding to death or in many forms of advanced anaemia. The influence of the marrow in the haemorrhagic diathesis is therefore not primary, but secondary. Owing to exhaustion, temporary or permanent, it becomes unable to respond to the increased demand for platelets. The exhaustion may also apply to blood cells, and the degree can be measured by the resulting leucopenia.

The general conclusion may be drawn that the essential cause of the haemorrhages is an increase in the permeability of the capillary endothelium. The platelets attempt to protect the weak spots, and are thus removed from the circulation. Increased demands for platelets consequently fall on the bone-marrow, which may or may not respond successfully. The normal action of the spleen in destroying defective constituents of the blood increases, and the spleen tends to enlarge spodogenously. So far the position is fairly clear, though, of course, open to alternative views. The doubtful points are why the capillary permeability varies, and whether there is a primary action of the spleen causing this permeability.

SYMPTOMS OF THE HAEMORRHAGIC DIATHESIS.

The cardinal feature naturally is the tendency to the occurrence of haemorrhages. The most characteristic forms of haemorrhage are purpura, ecchymoses, and bleeding from the mucous membranes. The haemorrhages may be of any of these types, separately or together, and of any grade of severity and chronicity. The occurrence of the haemorrhages may be intermittent or continuous. Cases are met with in which fresh purpuric spots have apparently occurred daily for many years. On the other hand, there may be complete freedom from haemorrhages for long periods. It is by no means invariable for haemorrhages to occur into the skin or into the subcutaneous tissues. Certainly the occurrence of these capillary haemorrhages into the skin often determines the diagnosis. Unfortunately in the past purpura has been considered the essential phenomenon, and cases with other features of the haemorrhagic diathesis but without purpura have consequently been regarded as curiosities. A single mucous membrane may be repeatedly involved, such as the nose, kidney, or uterus, or even the stomach; subsequently haemorrhages may develop at other sites, or a family history may reveal the nature of the bleeding. Most of these variations have received independent and elaborate names, especially in the absence of purpura. It may be noted that haemorrhage

into the joints or the pleural cavity is very rare, but meningeal haemorrhage is not so uncommon.

Although haemorrhages are the outstanding manifestation of the haemorrhagic diathesis, there is another factor to be considered in the production of symptoms. As mentioned under "Pathogenesis," the capillary endothelium may permit the passage of increased amounts of blood plasma without permitting the passage of blood cells. This increased passage of plasma is the cause of ordinary wheal formation. In different grades of severity it produces urticaria, and occurring in other sites it results in localized oedema of the subcutaneous and other tissues. Such oedematous areas are rarely absent in cases of the haemorrhagic diathesis of more than slight severity, and are usually recognized without any difficulty when looked for. They are often tender, and are usually ascribed to "deep haemorrhages," but it will be found that such areas frequently subside rapidly and without any ecchymoses or bruising. When the tissues of the face are affected the appearance may closely resemble acute nephritis. It is consequently of importance to consider what symptoms may occur in urticaria (including angioneurotic oedema or giant urticaria) uncomplicated by any haemorrhage. There are two special groups. First, abdominal pain, often colicky in nature, is a frequent symptom, and may be accompanied by diarrhoea and occasionally by vomiting. With the diarrhoea there may be bleeding from the intestinal mucous membrane. Secondly, the joints are often painful and sometimes swollen, and these swellings may subside with great rapidity. There can be no doubt that these symptoms are due to effusions into the deeper tissues. It will be observed that identical symptoms are prominent in certain forms of the haemorrhagic diathesis, and are rarely absent to some degree in any acute case.

The symptomatology of the haemorrhagic diathesis consequently falls into three groups: (1) the occurrence of haemorrhages; (2) anaemia due to loss of blood and the drain on the blood-forming tissues; (3) the results of escape of plasma into the tissues—namely, oedematous areas, abdominal colic, and pain and swelling of the joints. The swelling may be considerable, but does not lead to the after-effects seen in the haemorrhages of haemophilia. Splenic enlargement is variable. In severe acute cases the spleen is rarely palpable at the onset, though it may become so after a few days. In more chronic cases it may be noted that in general the larger the spleen the less severe are the haemorrhages, though anaemia is usually marked. Unlike Banti's disease, the haemorrhagic diathesis never terminates in cirrhosis of the liver and ascites. Females are generally believed to be affected more frequently than males. In a consecutive series of twenty cases seen in private practice, nine were males and eleven females, which may be regarded as equal. Most cases are sporadic, but there is abundant evidence from the literature that the condition may be hereditary or familial, or both, and that inheritance may be through either sex. Of these twenty cases, one male had a sister affected and one female had a mother affected. There was no familial history in any of the others.

CLASSIFICATION.

The haemorrhagic diathesis has in the past usually been classified into the following groups: (1) purpura simplex; (2) purpura rheumatica or Schönlein's purpura; (3) Henoch's purpura; and (4) purpura haemorrhagica.

For a long time it was considered that these groups were only slightly connected with each other. Even recently it has been strongly held that purpura haemorrhagica is an entirely separate entity, on the erroneous view that in this group alone are the platelets diminished and that any benefit follows splenectomy. But in general the more correct view has been gaining ground that these groups possess common factors, and to some extent represent degrees of severity. Considering Henoch's purpura, the attacks of abdominal pain are the outstanding complaint. With these attacks there is frequently diarrhoea, often with passage of blood. Joint pains and swelling may also occur. Not uncommonly the onset of these symptoms precedes any superficial haemorrhage. On examination of a case of Henoch's purpura, areas of oedema are usually easily recognized and are often extensive. It will also be

found in many cases that the superficial haemorrhages are mainly ecchymoses and that true purpuric spots are scanty. These ecchymoses tend to be on swollen oedematous areas, the sites often being more urticarial than haemorrhagic. The area of an ecchymosis is thus consistent with a small amount of blood cells and a large amount of plasma, the swelling being out of proportion to the staining. The appearance can be produced by the injection of 1 or 2 c.cm. of saline subcutaneously in a haemorrhagic subject, the haemorrhage in such circumstances being probably due to the distension injuring capillaries which are already of less than normal resistance, the escaping blood cells being diluted by the excess of fluid present.

In accordance with these observations, the degree of anaemia in Henoch's purpura may be comparatively slight, and the platelets may be normal or increased; the spleen is rarely palpable, or not more than the tip can be felt. Thus the subject of Henoch's purpura is more ill than the severity of the haemorrhages and the condition of the blood would suggest. He may be said to be more sick than purpuric, and the symptoms are those attributable to the urticarial factor—that is to say, to the escape of plasma rather than of blood cells. In general the anaemia appears to vary with the amount of purpura. The oedema of the face may be sufficiently severe to produce a facies suggestive of acute nephritis. Cerebral oedema may cause convulsions, and this is probably the origin of the statement that these cases often die of uraemia. As might be expected the margin between Henoch's purpura and a state with severe haemorrhage is comparatively small. The condition of Henoch's purpura may "change to purpura haemorrhagica." Indeed, cases have been described as commencing with urticaria, developing Henoch's purpura, and terminating as purpura haemorrhagica. Experimental anaphylaxis may exhibit the same sequence; in severe cases haemorrhage may occur and thrombopenia develop. Clinically Weil¹⁹ has recorded a case of a boy in whom urticaria followed the eating of eggs; the areas would sometimes become ecchymotic, or on other occasions purpuric spots would be present. In Henoch's purpura, therefore, the severity of the symptoms and of the constitutional disturbances is due to urticaria rather than to haemorrhage. Consequently the severity of symptoms cannot correctly be considered to place Henoch's purpura as a step between purpura simplex and purpura haemorrhagica in degrees of severity of haemorrhage. Henoch's purpura belongs to a subgroup in which urticaria and haemorrhages are both prominent. Purpura rheumatica is clearly of the same type as Henoch's purpura, but of less severity.

Excluding these two groups from the old classification, there remain purpura simplex and purpura haemorrhagica. These groups may be considered as the limits of mildness and severity, and the terms may be regarded as indicating these states. The grading must not be pressed too far, for the importance of haemorrhage depends not only on the extent, but on the duration. Thus individuals with only a few purpuric spots may exhibit any degree of anaemia. Unfortunately, also, this nomenclature leaves no title for the common cases in which the severity of the haemorrhages lies between these extremes, since, for reasons given above, Henoch's purpura cannot be placed correctly in this position.

The complete entity which we are considering thus has three principal groups:

1. *Pure Primary Haemorrhagia*.—All grades from "purpura simplex" to "purpura haemorrhagica." Symptoms attributable to anaemia are most prominent.

2. *Pure Primary Urticaria*.—Characteristic symptoms are abdominal colic and joint pains.

3. *Combined Haemorrhagia and Urticaria*.—This includes the forms Henoch's purpura and purpura rheumatica. The most prominent symptoms are due mainly to the urticarial factor, but this factor does not cause any drain on the blood-forming organs or the necessity for the removal of debris from the tissues, and the spleen does not enlarge from its activity.

CHANGES IN THE BLOOD.

Coagulation Time.—The coagulation time in the haemorrhagic diathesis is of considerable interest. It is unfortunate that most records of coagulation time in the literature are of little value for comparison owing to failure to recognize or to report certain factors which

influence both normal and abnormal coagulation. First, the method employed is of importance. Dale and Laidlaw's method is satisfactory for clinical purposes. Secondly, the temperature is of obvious importance, though often not mentioned. The temperatures most often employed are 36° to 38° C. and 25° C. The blood temperature should always be used for one set of observations, though in certain circumstances the blood clots so rapidly as to make the experimental error disproportionately large. At 25° C. the clotting in pathological conditions may be so long as to make observations on consecutive drops a practical difficulty. Probably 28° or 30° C. would be the best alternative temperature, though these have been little used, and there are few observations for comparison. A third factor of very great importance is the normal rapid variation in the coagulation time in successive drops from a prick. Though dimly recognized previously, this was first clearly stated by Christie.² For the first, second, third, and for the fourth and subsequent drops at 37° C., the following average times may be given: 2 min. 10 sec., 1 min. 5 sec., 45 sec., 40 sec. Christie found that the same curve was given in cases of purpura, though with some prolongation—namely, 2 min. 35 sec., 1 min. 30 sec., 1 min. 10 sec., 1 min. 5 sec. Other observers confirm the result that the coagulation time in the haemorrhagic diathesis tends to lengthen about 50 per cent. with a fall in platelets, but not more. According to Howel Evans,⁹ the coagulation time rose about this degree as the number of platelets fell to 100,000 per c.mm., but no increase follows any further fall. Roskam,¹⁸ in experimental thrombopenia in dogs, obtained a closely similar increase. In my experience, in cases of the haemorrhagic diathesis with normal numbers of platelets, the coagulation time has been, if anything, shorter than normal.

The following cases illustrate this point:

1. J. M., male, aged 53 years. Symptoms of Henoch's purpura for six months. Red cells, 5,900,000; haemoglobin, 90 per cent.; white cells, 4,200; platelets, 340,000. Bleeding time, 1 min. 40 sec. Coagulation time at 37° C.: first drop, 90 sec.; second drop, 50 sec.; third drop, 35 sec.; fourth drop, 30 sec.

2. R. W., female, aged 30 years. Spontaneous bruises for ten years. Family history of "bleeders." Red cells, 5,700,000; haemoglobin, 80 per cent.; white cells, 6,200; platelets, 370,000. Bleeding time, 2 min. 45 sec. Coagulation time at 37° C.: first drop, 75 sec.; second drop, 35 sec.; third drop, 35 sec.

3. A. B. H., male, aged 60 years. Purpura and epistaxis for fifteen years. Blood pressure, 160 mm. systolic. No splenomegaly. Red cells, 7,100,000; haemoglobin, 105 per cent.; white cells, 11,200; platelets, 285,000. Bleeding time, more than 20 min. Coagulation time at 37° C.: less than 30 sec. in first drop.

It would appear that in the haemorrhagic diathesis the basal coagulation time is as short as, or shorter than, normal. The time lengthens with the fall in platelets, just as it does with experimental thrombopenia in otherwise normal animals, but this increase does not exceed about 50 to 70 per cent. It is probable that this increase, together with some experimental error, has accounted for cases of the haemorrhagic diathesis occasionally being confused with haemophilia. The great lengthening characteristic of haemophilia never occurs in the haemorrhagic diathesis. In haemophilia, further, the coagulation time does not diminish in successive drops from a prick, but tends to lengthen.

Failure of Clot Retraction.—If blood is collected in a small test tube from a case of the haemorrhagic diathesis, it is frequently found that the clot, after forming, fails to retract and to express serum. This failure appears to run parallel with the diminution in platelets. It is difficult to say what effect this would have on haemorrhage occurring from a small vessel. A similar failure of retractability is frequently observed in many conditions in which there is no tendency to haemorrhages, or, so far as is known, any reduction in platelets.

Bleeding Time.—This test, was introduced by Duke⁴ in order to obtain some direct measure of the haemorrhagic tendency. The blood from a sharp prick is soaked off with filter paper without pressure every quarter to half a minute, and the length of time until bleeding has entirely ceased is noted. The normal bleeding time is one to two and a half minutes. The method has a suggestion of vagueness and may be tedious, and this no doubt accounts for its unpopularity. In fact, it is a valuable test of the

haemorrhagic state at the moment of examination; it is easy to perform, and the variations are often sufficiently great to leave no question of experimental error. The lobe of the ear is the best site, and it is essential that no pressure should be employed. The bleeding time may be greatly increased, even to an hour or more, in haemophilia and in the haemorrhagic diathesis. In haemophilia it runs parallel with, and is undoubtedly associated with, the difficulty in coagulation. But in the haemorrhagic diathesis the coagulation time cannot be an important factor in the bleeding time. Roskam¹⁸ found that enormous differences in the bleeding time existed in various cases with the same coagulation time. Roskam also observed that in experimental thrombopenia the bleeding time increased about three times as the platelets fell to zero, the coagulation time having lengthened about 50 per cent. Such an increase of the bleeding time is comparatively small in relation to the long duration often recorded in the haemorrhagic diathesis. In the haemorrhagic diathesis the bleeding time does not correspond either to the number of platelets or to the length of the coagulation time. Thus the great increase in the bleeding time cannot be principally due to variation in the number of platelets or in the coagulation time, though these are contributory factors. It is found, however, that the bleeding time varies closely with the actual occurrence of active haemorrhage. When the haemorrhages cease in an active case, the bleeding time will be found to have fallen almost to normal. When they recur, the bleeding time will have lengthened again. The platelets during these changes may have remained constant. This is well illustrated by the following case of Leschke and Wittkower.¹³

Woman, aged 40. Purpura and Bleeding from Mucous Membranes for Eight Years.

Date.	Platelets.	Bleeding Time.	Haemorrhages.
1924.			
March 29	10,000	60 min.	Extensive
April 2 ...	10,000	6 min.	Bleedings ceased
" 3 ...	10,000	4 min.	Skin clearing
" 7 ...	Splenectomy		
" 25 ...	13,000	2 hrs.	Petechiae and mucous membranes bleeding again
" 27 ...	30,000	3 min.	Bleedings ceased
" 29 ...	36,000	2 min. 50 sec.	Petechiae disappeared

Clearly the increase in the bleeding time depends essentially on the activity of the factor which results in the haemorrhage, and this is consistent with the view that the primary factor is the permeability of the capillaries.

Capillary Resistance Test.—This test is also known as Rumpel-Leede's or Hess's test. A tourniquet is placed round the upper arm and the pressure raised as in estimating blood pressure. In active states of the haemorrhagic diathesis, purpuric spots will appear on the lower arm. The test needs standardization both for the height of the pressure and for its duration, as Lewis¹⁵ has shown. Probably two minutes is the best duration. The pressure should be just sufficient to obliterate the pulse at the wrist. With these standards the production of purpura is evidence of an active haemorrhagic state. The results run parallel with the bleeding test. The crop of spots is sometimes very extensive, and the patient may be alarmed at their appearance. It must be noted that in a case of the haemorrhagic diathesis, an increased bleeding time and a positive capillary resistance test are evidence of activity at the moment, and also form a measure of the degree of the activity. But their absence does not necessarily prove that the patient is not a subject of the diathesis.

CHANGES IN THE BLOOD CELLS AND PLATELETS.

As stated above, there is no characteristic blood count. Since there is direct loss of blood, the blood-forming tissues must be called upon to supply more blood cells, and to an even greater extent more platelets in view of their action described above. The leucocytes, for example, may be consequently produced in sufficient numbers as the marrow reacts, or in excessive numbers, as also occurs

after severe haemorrhage, or in defective numbers, as the bone-marrow fails temporarily or permanently. Such is the probable explanation of the changes observed. Certainly the leucocytes may be increased or decreased, and the differential count may show wide variations. With extreme leucopenia, high percentages of lymphocytes may occur. With regard to the red cells and haemoglobin, diminution naturally is usual, but erythrocytosis is not unknown.

Blood Platelets.—Great differences in the number of platelets are found in different cases, and the number may also vary with great rapidity in a given instance. With severe acute haemorrhages, justifying the term "purpura haemorrhagica," the platelets are very scanty or absent. In such conditions the platelets may increase very rapidly with the cessation of active bleeding, and may reach normal in a few days. The active bleeding has been observed to cease before the increase of platelets commences, as in the following case recorded by Foerster⁵:

Woman, aged 48. Severe Purpura and Haemorrhages for Three Days.

Date.	R. B. C.	Hb.	W. B. C.	Platelets.	Haemorrhages.
June 5	5	80	11,600	Nil	Extensive
" 8	3.5	60	9,200	"	Extensive
" 10	2.8	35	11,100	"	Less; no haematuria
" 11	2.2	35	10,000	"	Almost ceased
" 12	1.8	30	11,200	"	Completely ceased
" 13	1.7	35	9,900	6,900	
" 14	1.8	35	11,400	340,000	
" 20	2	35	7,000	200,000	

Diminution of platelets may be present with haemorrhages of lesser severity. In chronic cases of moderate or even slight severity the number is often between 80,000 to 150,000 per c.mm., and variations do not occur very rapidly. In conditions of moderate severity of short duration the count may be within normal limits. In Henoch's purpura, even with considerable pain and constitutional disturbances, the number is frequently normal, or may show an increase. Hayem,⁸ in an early article, noted that diminution might occur in secondary purpura, but the observation apparently was overlooked.

RELATION OF THE HAEMORRHAGIC DIATHESIS TO CERTAIN CLINICAL CONDITIONS.

It is impossible to decide exactly what clinical groups are manifestations of the haemorrhagic diathesis. The difficulty, as usual, is mainly on the borderline where this and other entities merge together. Certain conditions may be referred to:

1. *Haemophilia.*—The lengthened coagulation time and the normal number of platelets need no further reference. It is noteworthy that purpura does not occur in haemophilia. It is now widely accepted that women are never haemophilic. There can be no doubt that nearly all alleged female haemophilics of the past (and some of the sporadic males) were cases of the haemorrhagic diathesis. Nevertheless, there is an impression among many females of haemophilic stock that they bleed more profusely and readily than ordinary individuals, though never to the degree of a male haemophilic. There are no modern studies of this possibility. The moderate lengthening of the coagulation time in the haemorrhagic diathesis may cause difficulties in diagnosis. Certainly there is no direct connexion between the two entities.

2. *Secondary or Symptomatic Purpura.*—The groups of "secondary purpura" recorded in textbooks need revision. Thus, purpura is not a feature of chronic leukaemia; indeed, the occurrence of any haemorrhage, even a few purpuric spots, heralds the termination of life in leukaemia. It may be doubted whether purpura can ever be justly attributed to jaundice. I do not recollect ever having seen purpura in the jaundice of gall-stones. Some at least of the "cachectic" purpuras are mythical. I have known a man with the haemorrhagic diathesis finally die from carcinoma of the stomach; in spite of extreme wasting and

an advanced chronic anaemia he had no purpura in the last six months of his life. There is no proof that purpura occurs in acute rheumatic fever: personally, I have never seen an example. Scurvy, of course, produces haemorrhages, but this is a vitamin deficiency and not cachexia. Nor does scurvy produce purpura. The influence of vitamin deficiency in the production of haemorrhages needs further investigation.

3. *Banti's Disease and Splenic Anaemia.*—These terms are often used as synonyms, and even as synonyms for the haemorrhagic diathesis. There is no doubt that several different entities are thus confused. Banti's disease is distinct from splenic anaemia and has no relation to the haemorrhagic diathesis; neither of these latter conditions ever terminates in hepatic cirrhosis and ascites. Since Banti's disease was first described several entities have been separated from it, such as the Egyptian form due to schistosomiasis. Banti's disease affects children and young adolescents. It does not occur in true adult life. The subjects are anaemic and icteroid, with palpable but not greatly enlarged spleens, and later the characteristic hepatic cirrhosis develops. The duration covers a few years. There is no purpura or ecchymoses. The entity has been confused by the pathology ascribed to it by Banti, which needs reconsideration. Splenic anaemia usually occurs in adults, but may be found in childhood. The spleen is markedly enlarged, and commonly reaches to the umbilicus. Anaemia is severe. The facies is usually extremely pale, but without the muddy icteroid complexion of Banti's disease. The duration is often very long and may be twenty or thirty years, but cirrhosis of the liver and ascites never develop.

It is difficult to know where to draw the line between splenic anaemia and the haemorrhagic diathesis. Cases of splenic anaemia are common with markedly enlarged spleens, advanced anaemia, and no record of any haemorrhage. If this group be considered alone, there is no reason for including it in the haemorrhagic diathesis, and on any of the theories in dispute it is difficult to account for the combination of splenic enlargement and absence of haemorrhage. But on the other hand, gross haemorrhage, especially haematemesis, is a recognized feature of many cases of splenic anaemia. Formerly the gross haematemesis was usually ascribed to the large spleen kinking the gastric vessels, but haematemesis may occur in undoubted cases of the haemorrhagic diathesis, even in the absence of splenic enlargement, and may be safely attributed to oozing into the stomach. Possibly in splenic anaemia both causes are acting. A definite sequence can be traced between splenic anaemia without haemorrhage and cases of the fully developed haemorrhagic diathesis. Thus in the first step there are cases with recurrent haematemesis, then cases with occasional haematuria or rectal haemorrhage in addition to haematemesis, and then a further group with a few purpuric spots. It is noticeable that the size of the spleen tends to diminish as we pass from "splenic anaemia" to the definite haemorrhagic diathesis. The question is still unsettled, but it may prove that some of the cases of typical splenic anaemia without obvious haemorrhage belong to the haemorrhagic diathesis. Others may be separate entities. Banti's disease may be regarded as distinct.

4. *Aplastic Anaemia.*—In this syndrome there is severe anaemia, leucopenia, thrombopenia, and aplasia of the bone-marrow. The condition may be either primary, without obvious cause, or secondary. A simple secondary group is that produced by the action of certain coal-tar products—for example, T.N.T. The spleen may be palpable, but is not greatly enlarged. Haemorrhages may or may not occur in this group. The development of haemorrhages is partly explained by the thrombopenia, but the nature of the additional factor necessary is doubtful. There may be no evidence of sepsis. It must be remembered that the aplastic state is not confined to the bone-marrow, and the blood vessels may share in the dyscrasia. In the haemorrhagic diathesis the marrow may become aplastic from exhaustion. But many cases of aplastic anaemia have no connexion with the haemorrhagic diathesis, and the haemorrhages are a secondary phenomenon; indeed, the patient may die of anaemia without their occurrence.

5. *Haemorrhages from a Single Site*.—An individual may have recurrent haemorrhages from the same site over a course of years. The occurrence of these in splenic anaemia has already been mentioned, but there is a group without splenic enlargement and with variable degrees of anaemia. The most common forms are epistaxis, haematuria, and metrorrhagia; but no mucous membrane is immune, and recurrent haemorrhages from the rectum and elsewhere may occur. These cases often cause much anxiety. At one time it was commonly believed that a surgical cause existed in every instance. It is now becoming recognized that these may be manifestations of the haemorrhagic diathesis. Kidd¹² was the first to observe purpura of the bladder in cases of haematuria of this origin. Probably these cases are rare, and every care must be taken to ensure that other organic causes are not overlooked. In several instances frequent severe haemorrhages have ceased after splenectomy.

TREATMENT.

Splenectomy.—Many successful results have been recorded from splenectomy in cases of the haemorrhagic diathesis. It is consequently important to consider in what instances it is indicated or advisable. The results which follow splenectomy in other conditions have now been studied in many cases. It is found that there is a temporary rise in leucocytes and in the blood platelets. This occurs very rapidly, and suggests the flooding of the circulating blood from the reserves. The leucocytes are mainly polymorphonuclears, the rise being of the same type as occurs after severe haemorrhages. Howel Evans¹⁰ has shown that a similar rise in platelets may follow other operations. This rise reaches its maximum about the twelfth day, that is to say at the time when it is known that post-operative thrombosis most commonly occurs. In these conditions the platelets have usually returned to normal about the twentieth day, although leucocytosis may persist much longer. In the haemorrhagic diathesis a similar rise in platelets is frequently observed to occur after splenectomy. Previous to operation the marrow will be producing platelets as rapidly as is possible for its state at the moment. In accordance with this the rise in platelets may reach a very high number. Rosenthal¹⁷ found that in such cases there was a considerable incidence of fatal thrombosis. In other cases, however, the marrow is either unable to produce so great a number, or possibly the demands consume all which are produced, consequently the rise in platelets is small or transient and in such conditions the risk of thrombosis is slight. In the haemorrhagic diathesis, consequently, there are two risks to be taken into account in splenectomy. First, the general risk of the operation; secondly, the special risk of excessive thrombocytosis with resulting thrombosis.

Usually we have to consider:

1. Is the patient ill enough to justify the general risk, or alternatively, too ill for any reasonable chance of recovery?
2. Is there a special grave risk of thrombosis?

With regard to the first point, the mortality from splenectomy in the very acute severe cases is very high. But on the other hand these cases practically all die, and unless rapid improvement follows blood transfusion, splenectomy gives the best chance of life. There is a large group of cases showing a chronic moderate grade of the haemorrhagic diathesis. Over many years there may be a tendency to bruising, some purpura, and occasional haemorrhages from mucous membranes. Many of these cases show no evidence of progressing, and the disability is not severe enough to justify an operation. The decision as to splenectomy in an individual case will largely rest on whether or not the degree of chronic anaemia is such as to prevent the following of a normal routine. From the point of view of the subsequent prognosis, the number of the leucocytes is also a useful guide. If leucopenia is definite and persistent, this points to exhaustion of the marrow. Such exhaustion may be a permanent aplasia, but the improvement which may occur shows that it is sometimes transient. Severe chronic anaemia and leucopenia are both indications for the performance of splenectomy. Many cases

of this chronic moderate group show a definite leucocytosis. It is evident that the marrow is not exhausted and is reacting, and in general it is safe to wait if the number of leucocytes is normal or above normal. With regard to the special risk of thrombosis, this undoubtedly exists in those cases in which the number of platelets is within or above normal limits. Probably the bone-marrow is producing an increased number, and after splenectomy the count may rise to very high figures, and thrombosis occur. In some instances the haemorrhages may form a prominent feature while the platelets are still normal, as often happens in Henoch's purpura. If, however, the haemorrhages are becoming dangerous, the platelets will usually fall, and splenectomy then becomes safer. In such cases the risk is greater if operation is done too early, and the decision as to when to operate is sometimes difficult. Experience shows that an excessive rise of platelets will not occur subsequently if the number is appreciably below normal at the time of operation. A considerable number of cases of the haemorrhagic diathesis will fall into this group. The haemorrhages may be moderate and chronic, or of a severer grade. Splenectomy will be specially indicated if anaemia is advancing and leucopenia is present in addition to the low platelet count. In this group the risk from operation is not high in the hands of experienced operators.

The haemorrhages have sometimes been observed to cease with great rapidity after operation. It is even claimed that oozing may be seen to cease directly the spleen has been removed, but this may be doubted. In many cases no haemorrhages are observed after the operation is completed. This rapid result is probably due to the flooding with platelets described above. It is not uncommon for a few haemorrhages to occur subsequently in the course of the next few weeks and then cease; occasionally they occur later over prolonged periods. In general, the operation in the conditions described is very successful. The platelets frequently fall to their previous level, and may even be completely absent without obvious haemorrhages occurring.

Blood Transfusion.—This is a very important method of treatment. In cases of severe haemorrhages blood transfusion should always be performed. This may of itself check the haemorrhages, and may be followed by complete cessation, at least temporarily. Blood transfusion should in all cases be performed before operation for splenectomy.

Haemostatics.—Many attempts have been made to check the haemorrhages with haemostatics. Injections of whole blood have been repeatedly successful in the haemorrhages of newly born infants, but do not appear to have the same effect in children and adults. Numerous patent haemostatic preparations are in existence. No definite results can be ascribed to these. Possibly the usual dosage is too small, as the value of some preparations is supported by experiment.

Calcium Salts.—The only object of injecting calcium salts must be to increase the coagulability of the blood. Observations show that the coagulation time is little altered, and any lengthening is due to deficiency of platelets, and not of calcium. As might be expected, there is no obvious benefit from the use of calcium.

Other Forms of Treatment.—Intravenous injections of adrenaline 1 in 1,000 have been known to check the haemorrhages in children.⁷ Injections of T.A.B. vaccine have also been used with a view to obtaining an anaphylactic effect. This is not an irrational procedure, and successful results have been reported in children. In adults, and in many children, no benefit has been observed.

SUMMARY.

1. The haemorrhages in the haemorrhagic diathesis are primarily due to increased permeability of the capillary endothelium.
2. Blood platelets normally protect the capillary endothelium, and the diminution in number observed in the haemorrhagic diathesis is secondary to this action.
3. Escape of plasma from the vessels accounts for certain of the symptoms, especially abdominal colic.
4. Haemorrhages from a single site—for example, haematuria—may occur.
5. There is no constant characteristic change in the blood cells.

6. No sharp dividing line separates the haemorrhagic diathesis from splenic anaemia, but Banti's disease and haemophilia are separate entities.

7. Splenectomy is indicated and successful in severe cases, but is contraindicated unless the platelets are diminished in numbers.

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NON-FILARIAL ELEPHANTIASIS.

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A CASE of non-filarial elephantiasis recently treated at the Cardiff Royal Infirmary illustrates the value of a modified Kondoleon operation. The patient had suffered for twenty-three years from a complaint which she had come to regard as incurable, and which not only caused her considerable discomfort, but, as she put it, entirely did away with any chances she might otherwise have had of finding a husband.

History.

The patient, A. B., was 40 years of age. At the age of 12 she suffered from a curvature of the spine, tuberculous in origin, and a tuberculous abscess on a rib. When aged 15 she was stung on the left thigh by a wasp; this soon got well. At 17 the left ankle began to swell, but the swelling disappeared overnight. It then reappeared and gradually increased, and a doctor was consulted. He recommended a tight bandage from the knee to the ankle; in the patient's opinion, this drove the swelling from the leg into the thigh.

In 1913, at the age of 23, she was admitted into Guy's Hospital, where lymphangioplasty was performed without result. She was again admitted to Guy's in 1920, and was operated upon by Mr. Davies Colley. The hospital notes were copied by the patient when the nurses were not looking. These notes are so concise that they are quoted in full.

The swelling extends from the ankle to Poupart's ligament anteriorly, and to the level of the iliac crest posteriorly. Patient has angular curvature of the spine.

X-ray Report.—Old caries of the fifth lumbar spine, probably tuberculous; hip-joint negative.

December 9th, 1920.—Operation by Mr. Davies Colley. Anaesthetic, C. and E., followed by ether. A U-shaped incision was made on the dorsum of the left thigh, the loop of the U being about a handbreadth above the knee-joint; the two limbs were carried up to the level of the lesser trochanter. The flap of skin with the adherent adipose tissue was reflected upwards and the deep fascia exposed. An elliptoidal flap of deep fascia was removed, exposing the muscles of the thigh and some fat deep to the fascia. This fat was not as translucent as that under the skin. The enlargement of the limb was thus found to be due to increase of adipose tissue between the skin and deep fascia. Some of the adipose tissue adherent to the skin reflected was excised. The skin flap was reduced in size and stitched back. The calf of the same leg was treated in the same way.

December 10th, 1920.—Wounds dressed, much serous discharge.

December 12th, 1920.—Wounds healing.

January 12th, 1921.—Wounds healed. Circumference of thigh on admission 29 inches; now 26 inches. The leg is diminished in size. There is loss of cutaneous sensibility in a patch of skin below both incisions, but deep sensibility is not impaired.

Figures 1 and 2, showing the condition of the leg in October, 1920, indicate the enormous increase in the size of the limb. Figure 3 shows the condition on September 1st, 1929.

Operation.

The patient was admitted into the Cardiff Royal Infirmary on September 11th, 1929—ten days after the third photograph was taken—and was operated upon on September 14th. One incision was made in the thigh, extending from the inner end of Poupart's ligament to the adductor tubercle of the femur; another was made in the leg from a point one inch below the knee to the level of the internal malleolus, and just posterior to the inner border of the tibia. The deep fascia was considerably thickened, and strips one inch wide were removed the whole length of the incisions. The incisions were sutured with S.W. gut, and healed in ten days.

The patient left hospital on October 21st, the limb showing very little improvement. In January, 1930, the oedema had almost completely disappeared from the lower half of the limb, but the thigh was still almost as oedematous as before the operation.

FIG. 1.

FIG. 2.

On May 7th I received a photograph (Fig. 4) from the patient, with a note stating:

"I think you will be interested to know that my leg has steadily improved since you saw it last January, and I am enclosing photograph taken on May 5th, 1930. I also desire to express my gratitude to you for such a successful operation. It makes me very happy to be freed from an encumbrance which I have carried for so many years."

The photographs speak for themselves. The actual measurements at present are: Right thigh, 20 inches; left thigh, 21 inches; right calf, 12½ inches; left calf, 13½ inches.

FIG. 3.

FIG. 4.

COMMENTS.

1. This case illustrates the value of Kondoleon's operation in elephantiasis.

2. Hardly any improvement was seen during the first five weeks following the operation while the patient was still in hospital.

3. The oedema gradually disappeared from below upwards, and the greater part of a year elapsed before the limb became normal.

4. The incisions were planned to follow roughly the course of the main superficial lymphatic trunks. It was considered that anastomoses between the superficial and deep lymphatics were more likely to form here than in any other area of the limb.

5. The operation is easy to carry out, and appears to be devoid of risk.