THE DIAGNOSIS AND TREATMENT OF PURPURA

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The term purpura is used to designate a heterogeneous group of maladies that has one sign in common, namely, bleeding into the skin, mucosae, internal organs, and other tissues. The aetiology and pathogenesis of the various conditions vary greatly: thus, in some forms, there are striking changes in the blood, whereas, in others, no haemic abnormalities can be detected. The clinical features are equally variable: thus, there are cases with haemorrhages and no other signs, while others are characterised by urticaria, arthropathy and colic, in addition to bleeding.

It is customary to divide the group of haemorrhagic diseases into those in which the number of platelets is reduced (thrombocytopenic purpura) and those with a normal number of platelets (non-thrombocytopenic purpura). This division is, unfortunately, not an absolute one, because some maladies that are accompanied by purpura may, or may not, show thrombocytopenia. For instance, in the haemorrhagic forms of the acute specific fevers, the platelets may be normal in number or may be greatly reduced. Then again, bleeding is by no means always closely related to the degree of thrombocytopenia.

In spite of these defects, this classification will be used here.

CLASSIFICATION OF PURPURA

I. *Thrombocytopenic purpura*:—

A. Essential purpura (Werlhof's disease).

B. Symptomatic purpura:—

(i) Blood Diseases:

(a) Leukaemia, especially acute forms. Bleeding due to thrombocytopenia and to leukaemic infiltrations.

(b) Various anaemias associated with general dysfunction of the marrow, e.g. aplastic (aplasia due to poisons, see II B below); replacement of marrow by neoplasms or osteosclerosis, i.e. myelophthisic anaemia: severe pernicious anaemia; severe chronic hypochromic anaemia.

(c) Spleen disorders:—Banti's disease (occasionally); Gaucher's disease; Felty's syndrome; splenic panhaematopenia, Hodgkin's disease (rarely).

(ii) Infections:

Septicaemia, subacute bacterial endocarditis, etc. Glandular fever (rarely).

(iii) Due to various agents:

(a) Chemical, e.g. benzol, sedormid, etc.

(b) Animal, e.g. snake venom, etc.

(c) Physical:—X-rays, radium, etc.

II. *Non-thrombocytopenic purpura*:—

A. Anaphylactoid purpura: Henoch-Schönlein purpura.

B. Symptomatic purpura:—

(i) Blood diseases:—leukaemia (bleeding due to infiltrations).

(ii) Infections, e.g. subacute bacterial endocarditis, meningococcal septicaemia, etc.

(iii) Drugs, e.g. iodides, copaiba, etc.

(iv) Avitaminosis, viz. scurvy.

C. Miscellaneous, including various skin diseases.

Obviously, discussion of all these maladies is impossible in a short paper, and in fact, the classification itself gives a good deal of information of practical significance. We may, therefore, deal with a few important diagnostic points, before describing some of the less well-known conditions that may give rise to purpura.

First, it is clear that blood will not exude through normal capillaries; in other words, purpura, whether thrombocytopenic or not, is always associated with increase of capillary permeability. This fact is the basis of the so-called tourniquet test, which is positive if petechiae develop below the armlet of the sphygomanometer when the pressure is kept at slightly above the diastolic pressure for five minutes.

There is some relationship between the number of petechiae and the number of platelets, although the correlation is not close. In non-thrombocytopenic cases, only few petechiae develop, presumably because there is an adequate supply of platelets for plugging the holes in the capillaries.

A rather more delicate test is performed by intradermal injection of 0.1 c.c. of 1 in 3,000 moccasin snake venom. The development of an haemorrhagic area 1 cm. or more in diameter within an hour is a positive result. This depends upon the action of the venom on unduly fragile capillaries. And therefore, unlike the tourniquet test, there is more bleeding in the non-thrombocytopenic cases, especially in the anaphylactoid ones.

Then again, in thrombocytopenic cases the bleeding time is prolonged, although the coagulation time is normal. And this apparently paradoxical finding needs some discussion.

The bleeding time is estimated by making a sharp cut on the finger or ear-lobe, sufficiently deep for blood to ooze out without pressure. Then, at intervals of thirty seconds, the drop of blood is removed by the edge of a piece of filter paper, of course, without touching the skin. Normally, bleeding will cease in under four minutes.

The apparent paradox of prolonged bleeding time, but normal clotting time in thrombocytopenic cases, depends upon the peculiarity of the clot in these cases. Although the time taken for clotting is not prolonged, the clot that is formed does not retract properly; this is well seen if blood is taken into a test-tube, because the time taken for serum to separate is very long; indeed, the serum may never be completely expressed. Obviously then, only few platelets are needed to initiate coagulation, but an approximately normal number is required to squeeze out serum and convert the soft non-retractile gel into a firm haemostatic plug.

Of course, none of these tests suffices to determine with certainty whether or not there is thrombocytopenia; only enumeration of the platelets can show this. And it is a great pity that most so-called "complete" blood counts do not include enumeration of these elements.

There is now no real doubt that the platelets are produced by the megakaryocytes in the bone-marrow, and a great deal of information can be elicited in cases of purpura by examination of marrow obtained by sternal puncture. For instance, in essential thrombocytopenia, some of the megakaryocytes present structural changes, such as deficiency of granules, vacuolation of the cytoplasm, and nuclear pyknosis. Obviously, the greater the proportion of such degenerated parent-cells the more severe is the morbid process; and conversely, the more numerous the young megakaryocytes the greater is the degree of regeneration, with a correspondingly improved outlook.

In symptomatic thrombocytopenia the marrow-picture varies greatly. Thus, extreme degrees of poisoning with, for example, benzol, lead to complete aplasia of all myeloid elements, including, of course, the megakaryocytes. Smaller doses of the same poison may affect only the megakaryocytes, which then present degenerative changes, which, at least in the early stages, are reversible.

The thrombocytopenic purpura that may follow administration of sedormid is peculiar, inasmuch as it develops only in persons who have become sensitised to the drug. In them, an ordinary medicinal dose may cause the platelets to disappear from the blood within an hour, obviously as a

result of destruction in the circulation. In addition, there is delay in the maturation of megakaryocytes in the marrow, so that sternal puncture reveals the presence of a number of senile cells, although, if the drug is not stopped, there is also proliferation of younger ones. Provided the drug is withdrawn, a steady and progressive increase in platelets starts on the third day, reaching normal or even higher levels by the end of a week.

Another form of thrombocytopenia deserves mention: that is the condition described in detail by Altschule. In this, thrombocytopenic purpura occurs as a result of loss of platelets by the formation of widespread platelet thrombi in the capillaries. Such withdrawal of enormous numbers of platelets from the circulation plays no part in the ordinary form of essential thrombocytopenia: it occurs, so far as is known, only in this peculiar malady, which has been observed only in women.

Oddly enough, little is known about the mechanism by which the number of platelets is kept almost constant, but the fact that splenectomy may cure essential thrombocytopenia is an old observation. And it will be useful to discuss briefly the relations between the spleen and the bone marrow, partly because a good deal more is known about the pathology of the spleen than about its normal activity.

In the normal spleen there is a functional balance between blood destruction and blood formation, and the significant point in the present connection is that destruction of blood cells is preceded by sequestration in the sinusoids, where they lie in stagnant bays in which the phagocytic reticulo-endothelium can ingest them.

This sequestrative power may be disordered in a variety of ways. Thus red corpuscles may be selectively sequestered and destroyed, as in acholuric family jaundice; or the neutrophils may be picked out (primary splenic neutropenia), or the platelets may be affected, as in essential thrombocytopenia. It is also known that all the elements of the blood may be sequestered and destroyed in excessive numbers, causing anaemia, leucopenia and thrombocytopenia, but despite the resemblance of the blood picture to that of aplastic anaemia, the marrow is hyperplastic.

There is no evidence for the old view that the spleen produces some substance inhibiting the activity of the marrow. For instance, it is noticeable that thrombocytopenia is usual in advanced Gaucher's disease, but the marrow is over-active, and this is again an example of selective sequestration and destruction by the splenic reticulo-endothelium.

We are quite ignorant of the means by which the haemopoietic balance is re-equilibrated after surgical removal of the spleen, but it is notorious

that it is restored. The normal spleen is apparently not essential to life or health at any age, whereas the disordered spleen may constitute a grave danger to health or even a threat to life.

Direct investigation of the spleen is not always possible. If the organ is much enlarged, it is easy and safe to puncture it, just as the sternal marrow may be punctured, but a spleen of normal size cannot be investigated in this way. There is, however, an important method, although a laborious one, of estimating the functional ability of the spleen. This is by the adrenalin test, first described by Benda.

Subcutaneous injection of 15 minims of 1/1,000 adrenalin into a normal person is followed by changes in the blood picture. The test is best performed under "basal" conditions; and, after a preliminary complete blood count, the injection is given; then blood counts are performed every ten minutes under the pulse-rate and blood-pressure reach their maximum (this is supposed to coincide with the greatest contraction of the spleen). Blood counts are now carried out every fifteen minutes until the conditions before the test are regained. Normally, there is an increase of red corpuscles, leucocytes and platelets, which starts within five minutes of the injection; this is followed by some increase of less mature neutrophiles (of course, from the bone marrow), and next the monocytes increase. If the marrow is aplastic, only monocytosis results; but, in spleen diseases, more complicated changes occur. First, there is an increase of every type of formed element, then a moderate fall, which is followed by a secondary rise prior to return to the pre-test conditions. This biphasic curve is very characteristic of disorder of the spleen's power of sequestration. As may be imagined, the information obtained is specially valuable in those cases that resemble aplastic anaemia in their blood picture, but are accompanied by hyperplasia of the marrow. But even in thrombocytopenia, the information is of considerable diagnostic and prognostic significance.

If, for example, the adrenalin test shows no increase in the number of platelets, the assumption is that there is hypoplasia of megakaryocytes in the marrow. This is not always the case, because no thrombocytosis occurs during the acute stage of sedormid purpura, simply because there are so few platelets in the body, although the marrow is not damaged. Of course, the result of the test becomes normal within a few days of withdrawing the drug.

In essential thrombocytopenia, injection of adrenalin is followed by a biphasic curve of platelet increase, fall, and secondary rise, even although the peaks are usually not high. As has already been mentioned, the megakaryocytes in this condition

show some degenerative changes, together with the presence of young, actively thrombocytopoietic ones; hence the rise that occurs during the test.

Symptomatic thrombocytopenia, due to damage to the marrow cells, does not show a positive adrenalin test; and this is a very important differential point.

There is, in fact, no reason to assume that the spleen secretes any substance that directly affects the marrow. The relationship of the two organs is a peculiar one; the marrow produces the platelets and in health, the spleen sequesters and destroys effete ones. In essential thrombocytopenia, this selective sequestration and destruction of platelets in the spleen becomes overactive, hence the paucity of thrombocytes in the blood, with a fairly normal, or even an increased, number of megakaryocytes in the marrow. The state of affairs in the cumbrously named condition, primary splenic haematopenia, is similar, except that the sequestrative and destructive activity of the spleen is not selective, it deals with all the types of formed elements in the blood, so that the haemogram is that of aplastic anaemia, while the marrow is hyperplastic.

Splenectomy as a method of treatment of essential thrombocytopenia thus receives a more or less rational basis, inasmuch as the removal of the diseased organ permits the platelets to live their normal life-span in the circulation. Unfortunately, we have no knowledge of the means by which the body adapts itself to the loss of the lytic organ and restores the proportions of the blood cells to normal. That it usually does so rapidly is notorious, but there are examples of excessive thrombocytosis following splenectomy, with the danger of widespread thromboses. Thus, removal of the spleen in cases of Banti's disease in which the platelets are not much reduced is dangerous for this reason; whereas, if the platelets are scanty, the number in the circulation rises to normal very rapidly after splenectomy. In fact, the speed with which the platelets increase after ablation of the spleen is a striking evidence of the truth of the view here put forward.

Within a few minutes of tying the pedicle of the spleen in a case of thrombocytopenic purpura of the "essential" type, the platelets rise to normal, or even a little higher. This cannot be due to a sudden increase in the formative activity of the megakaryocytes; it results from the injection of a normal number of platelets from the marrow into the circulation, whence they are not removed by the abnormal spleen. In fact, the contraction of the spleen that follows injection of adrenalin has little effect on the number of platelets in the circulation, at least, directly. That is to say, the spleen is not to be regarded as a reservoir of

platelets in health, and the thrombocytosis that occurs after adrenalin in pathological states of the spleen is due to the extrusion of platelets from the sinusoids before they can be engulfed by reticulo-endothelial cells, but there is no direct effect of splenic contraction on the marrow itself.

It is not, however, only in "primary" thrombocytopenia that splenectomy is useful. For instance, removal of the spleen in Gaucher's disease is followed by increase of platelets up to the normal level and, as there is no ill-effect on the course of the disease, the operation is indicated in all the cases in which spontaneous haemorrhages occur. This is usually in the advanced cases, but even the removal of an enormous spleen does not present great difficulty, while the danger of the operation is very small.

Occasionally, extensive deposits of lymphadenoma in the spleen are associated with thrombocytopenia and purpura, but obviously, splenectomy, while stopping the haemorrhages, does not retard the progress of the morbid process as a whole.

It is thus almost true to say that splenectomy is indicated in those cases of purpura in which there is extensive disorder of the spleen, but that it is worse than useless when the marrow is hypoplastic or, *a fortiori*, aplastic.

The differences between cases curable by splenectomy, and those that remain unimproved are brought out by a comparison between, for instance, essential thrombocytopenia and the reduction of platelets that is found in advanced leukaemia. In the latter condition, the whole function of the parent-cells in the marrow is disordered, whereas, in the former, there is "hypersplenism," and this is indisputable whether the "phagocytic" nature of spleen activity is accepted or whether the older view of an hormonal influence of spleen on marrow is preferred. Again, such a state as Felty's syndrome, which appears to be very closely related to Still's disease in children, is an example of reduction of all types of formed elements in the blood as a result of excessive activity on the part of the spleen. As is, then, to be expected, removal of the spleen cures the anaemia, leucopenia and thrombocytopenia and, for some unknown reason, results in considerable improvement of the arthritis. It is not known whether splenectomy has an equally beneficial effect in Still's disease as found in childhood; but careful blood, marrow, and spleen-function tests should determine whether the operation is likely to be successful.

The Henoch-Schönlein syndrome is even less clearly understood than the thrombocytopenia purpuras. The clinical picture is fairly distinctive although a typical case of the Henoch variety may be very difficult to diagnose. The occurrence of

severe colicky belly-ache with blood in the stool is almost certain to be diagnosed as intussusception if the patient is a small child. It is only if some other signs of allergy are detectable that a suspicion of Henoch's purpura will be aroused, and the skin of every child with the symptoms of intussusception should be examined for urticarial wheals and for purpuric spots.

Of course, an error in diagnosis may have grave consequences; to regard a case as Henoch's purpura when it is in fact an intussusception will have fatal results. It is, therefore, safer to operate if there is genuine doubt, especially because the swollen haemorrhagic patch that occurs in Henoch's purpura may excite intussusception. On the other hand, to operate in a case of the combined Henoch-Schönlein picture is inexcusable. A child with signs of intussusception, together with urticarial wheals, perhaps with superimposed petechiae, can safely be regarded as suffering from the rather vague condition, anaphylactoid purpura. Of course, most careful observation is required to detect the development of intussusception in such a case; then operation is urgently necessary, but premature surgical intervention has no prophylactic value.

Anaphylactoid purpura is not confined to childhood, although it is rarely seen above the age of 30. A suspicion of intussusception is less likely to be aroused in an adult; and concomitant urticaria and peri-articular swellings are commoner after puberty than in childhood.

In these conditions, the adrenalin test gives a normal response, but the tourniquet test is always positive, although the number of petechiae that develop distal to the cuff is less than in thrombocytopenic purpura. In this connection it must be recalled that a few petechiae may develop even in normal persons, especially in women just prior to the menstrual period.

The marrow in anaphylactoid purpura is essentially normal, although some rather senile megakaryocytes are often found.

Treatment is totally unsuccessful, but, fortunately, the disease is one that is usually "grown out" of. Occasionally injections of calcium seem to cause subsidence of the signs, but, in a disease so liable to remissions, it is difficult to be sure that this is not fortuitous, especially as the blood calcium level is normal.

Among the miscellaneous group of purpuras it is necessary to mention afibrinogenaemia. Total absence of fibrinogen from the plasma is a rare condition, which may be congenital or acquired. The former type, if in a male, is often diagnosed as haemophilia, even in the absence of the typical family history. In every apparently "first case" of haemophilia in a family, this possibility should

be borne in mind. As is to be expected, the prognosis is extremely bad, but, in some cases, there is only diminution of fibrinogen, without total absence, and then the prognosis is fairly good if the patient leads a careful life. Transfusion is a life-saving measure, but its effects are, of course, transient.

Differentiation from haemophilia is simple. The addition of a few drops of the thromboplastin solution used in the estimation of prothrombin-time causes prompt coagulation of haemophilic blood, but not of that in afibrinogenaemia.

Again, the family history is significant, especially as consanguinity of the parents is almost invariable in the cases of congenitally total absence of fibrinogen.

More striking and certainly commoner are cases of acquired absence or diminution of fibrinogen. In these there is a history of severe bleeding, perhaps after tooth extraction on one occasion, and medical advice is sought because of apprehension about subsequent operations. Often, at the time of examination, the fibrinogen content of the

plasma is found to be normal because, fortunately, acquired afibrinogenaemia is almost invariably a transient state, which can be detected only at the time of the initial bleeding or, by chance, if a very complete blood examination is performed for some other reason. Relapses occur but are by no means common.

Confusion between such an acquired condition and thrombocytopenic purpura is not possible if the platelets are enumerated; the only other abnormality in the blood in these cases is, possibly, anaemia due to haemorrhage. Nevertheless, the history in the two maladies may be confusing, because spontaneous remissions occur in both.

Among the confused chapters in haematology, purpura is the most confused, and although the present paper has presented some practical points it does not claim to have done anything to lighten the darkness that covers the more recondite aspects of the subject.

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A TECHNIQUE OF LOCAL ANAESTHESIA FOR ABDOMINAL OPERATIONS

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Preamble.—The purpose of this paper is to outline a method of local anaesthesia for operations on the abdomen. It has been used since June 1937, in over two thousand procedures. It was at first used as an alternative anaesthetic to general or spinal for abdominal operations, and in this way its qualities became well known. It is offered now as forming the principle partner of a combination of anaesthetics, i.e., local anaesthesia plus a sleep-producing agent. In 1942 one of my anaesthetic colleagues called the combination "Balanced Anaesthesia" and it has proved to be a singularly satisfactory method. One house-surgeon said, "Every partial gastrectomy got a chest of some sort after a general or spinal anaesthetic, but not with a local." Actually, whilst using local anaesthesia, I have lost one patient by death upon the table, but a considerable number in the same time when spinal and general anaesthesia was being used. Further, the post-operative morbidity and mortality is less. Patients, according to the opinion of experienced ward sisters, have a better post-operative convalescence.

Balanced Anaesthesia.—Balanced Anaesthesia for

abdominal operations enables a patient's needs to be fully met, whilst satisfying the anaesthetist, surgeon, and surgical team. The local consists of a simple readily-acquired technique (anaesthetists and house-surgeons quickly learn it) supplemented by omnopon and scopolamine, open ether or continuous pentothal to produce sleep. When carefully injected it gives complete relaxation for major procedures and easy closure of the wound. It permits successful major operations on the poor risk and elderly patient, especially on the upper abdomen, without heaving jerky, eviscerating respirations. The consistent quality of the anaesthesia with the quiet breathing and slow bleeding contrasts with general anaesthetics which are characterised by variability from perfection to exasperation for the surgeon and anaesthetist. In my practice Balanced Anaesthesia has abolished acrimonious incidents with the anaesthetist and has consolidated friendships. The local anaesthetic lasts for two or three hours, there is no need to hurry an operation because of the increasing dose of anaesthetic. The time needed for pain-taking craftsmanship can be given. The amount