TREATMENT IN GENERAL PRACTICE

This article is one of a series on the management of some diseases of the blood and blood-forming organs met with in general practice.

TREATMENT OF HAEMORRHAGIC DISEASES

BY

H. LETHEBY TIDY, M.D., F.R.C.P.

PART I

The haemorrhagic diseases include various conditions of which the pathology and treatment differ widely. The sole constant feature is a tendency to haemorrhage, though this differs in its nature and causation in the various groups. In discussing the treatment it will be assumed that an ordinary blood count is available, including the number of red cells and the percentage of haemoglobin, and the number of white cells, with a differential count. The following classification of the haemorrhagic diseases will be adopted.

A. PRIMARY NON-HEREDITARY HAEMORRHAGIC DIATHESIS

1. Purpura haemorrhagica: (a) acute; (b) chronic.
2. Anaphylactoid purpura (including Henoch's purpura and purpura rheumatica).

B. SYMPTOMATIC HAEMORRHAGIC STATES OR SECONDARY PURPURA

The important causal factors under this heading are: (i) infectious diseases; (ii) infections with pyogenic cocci; (iii) drugs, including benzol derivatives, gold preparations, salvarsan; and (iv) sensitivity to proteins.

C. HAEMORRHAGIC DEFICIENCY DISORDERS

1. Scurvy.
2. Melaena neonatorum.

D. HEREDITARY HAEMORRHAGIC DISORDERS

1. Haemophilia.
2. Hereditary haemorrhagic diathesis, including fibropenia and types which are intermediate with haemophilia.
3. Hereditary capillary telangiectasia.

Primary Non-hereditary Haemorrhagic Diathesis

It may be said, briefly, that the essential factor in the causation of the haemorrhages is undue permeability of the capillary endothelium, which may be chronic, sporadic, or intermittent. The cause of this increased permeability is uncertain, but it is not directly due to diminution of blood platelets. These may be completely absent without the development of haemorrhages; the term "essential thrombocytopenia" is thus a misnomer, and should not be used. The increased permeability may permit the passage either of plasma only, or of blood cells, or mainly of plasma with a small amount of blood. If plasma alone escapes the resulting condition is urticaria, which will not be further referred to. If blood escapes the resulting condition is purpura haemorrhagica. If plasma escapes, with some amount of blood, the resulting condition is anaphylactoid purpura.

The clinical and laboratory characteristics of the haemorrhagic diathesis during periods of activity are:

1. *Haemorrhage*.—Haemorrhage from the mucous membranes and into the superficial and deep tissues, constituting purpura, petechiae, ecchymoses, and haematomata, may be at any site; cerebral haemorrhage has often been the final cause of death. It is now known that certain cases of

repeated haemorrhage from a single site, such as repeated epistaxis, haematuria, and menorrhagia, belong to the haemorrhagic diathesis.

2. *Prolongation of the Bleeding Time (Duke's Test)*.—This test is the most important and sometimes the sole evidence that the haemorrhagic tendency is active at the moment of examination, and while the test is easily performed it is essential that it should be done properly. A deep, sharp prick is made in the ear with a cutting needle, and the blood is soaked off with filter paper or soft blotting-paper every twenty seconds. No pressure must be used. In normal persons the bleeding ceases in one to two and a half minutes. When the haemorrhagic diathesis is active it is prolonged to many minutes or even an hour. A normal bleeding time does not in itself prove that the individual is not a subject of the haemorrhagic diathesis, but only that there is no active tendency to haemorrhage at that moment.

3. *Capillary Resistance Test (Rumpel-Leede Test)*.—This is performed by constricting the arm with a sphygmomanometer band at a pressure of 70 mm. for two minutes. When the haemorrhagic diathesis is active a crop of petechiae appears below the band. This test may be difficult to estimate if there is already extensive purpura. It becomes negative when the active tendency has subsided, but usually persists longer than the prolongation of the bleeding time.

In addition to these features the blood platelets tend to be reduced in number, and in serious cases may be almost or completely absent. Even complete absence is not a proof, however, that the haemorrhagic tendency is active at the moment, but must be regarded as evidence that if haemorrhages do arise they are likely to be severe. There are no constant or characteristic changes in the blood cells. Anaemia will inevitably be present if the haemorrhages are severe or chronic. Leucopenia is evidence of exhaustion of the bone marrow, which may be temporary or permanent.

Acute Purpura Haemorrhagica

This may be seen at any age, though it is commonest in childhood. The onset is sudden and progress rapid, but rarely attains the severity of the "purpura fulminans" of the symptomatic purpuras, for which there is an obvious predisposing cause.

Treatment is local and general. It is important to remember that the majority of cases recover even in the absence of any specific treatment, since the acute haemorrhagic tendency may cease as suddenly as it began. After recovery the patient may remain free from all symptoms for many years, or even throughout life.

Local treatment is only of use for checking gross haemorrhage from a mucous membrane, and should be carried out in accordance with ordinary procedures and the special methods described under haemophilia. General treatment aims at aborting the general haemorrhagic tendency, temporarily or permanently. The measures which need careful consideration are blood transfusion and splenectomy.

BLOOD TRANSFUSION

Transfusion may end temporarily the active haemorrhagic tendency, apart from the benefit which the anaemic patient will derive from the volume of normal blood. It is better to transfuse moderate quantities, repeated if necessary, than to give a large amount and risk a severe reaction.

Blood transfusion is indicated in all cases of acute purpura haemorrhagica and should be performed as soon as the diagnosis has been made, as the future course cannot be predicted. The blood must be carefully grouped and cross-grouped with the prospective donor's blood. Serious reactions are not common, though more frequent than in normal individuals, but it is proper to run the risk of their occurrence. Occasionally in severe cases the transfused blood is haemolysed rapidly and the haemoglobin excreted even after careful grouping. The amount injected should be about 300 c.cm. for an adult, and there is no objection to using citrated blood. The bleeding time must be watched subsequently, and if there is no evidence of a definite reduction in twelve hours the transfusion should be repeated. If a skin incision has to be made in order to find a vein it is advisable not to put stitches into it as a troublesome haematoma usually forms.

Auto-agglutination in the patient's blood is occasionally a difficulty, though it is more common in the symptomatic group. In these circumstances the patient's serum usually agglutinates all other bloods when tested in the usual manner, and the group cannot be ascertained. Auto-agglutination, however, is confined almost entirely to reactions at room temperature, and does not take place at blood temperatures. If there is difficulty in estimating the reaction at a temperature of 37° C. a Group IV donor should be employed; this has been done safely on several occasions, although the patient's blood may contain haemolysins which rapidly haemolyse the donor's blood.

SPLENECTOMY

There can be no doubt that a successful splenectomy brings to an end the haemorrhagic tendencies in a high proportion of cases, but nevertheless the decision to operate must not be made lightly.

Splenectomy in otherwise normal individuals, as, for example, following trauma, is followed by a rapid rise of the blood platelets and the leucocytes. The platelets rise to their maximum in a few days and return to normal in about three weeks. It is worthy of mention that a rise of platelets follows any major operation, but is less rapid than that which follows splenectomy. After splenectomy for purpura haemorrhagica the rise in platelets may be very rapid and marked, and if the number has been within normal limits at the time of operation may reach a level at which there is a serious danger of thrombosis, which has been observed in several cases. In acute purpura haemorrhagica of great severity it may be said that the platelets are always definitely diminished in number, and the risk of thrombosis does not arise. If the platelets are found to be within normal limits with the clinical manifestations described it is more probable that the case belongs to the symptomatic or hereditary group.

In deciding if splenectomy should be performed in a case of primary acute purpura haemorrhagica several factors must be taken into consideration.

1. Many patients recover without specific treatment, since the active haemorrhagic tendency may stop at any moment, and these patients may subsequently remain free of any symptoms for many years or throughout life.
2. The operation has a high mortality, and it must be decided whether or not the patient is so ill that the chance of surviving such an operation is almost hopeless.
3. The previous history must be carefully considered in order to make certain, if possible, that the patient really belongs to the group of primary non-hereditary haemorrhagic diathesis.
4. Blood transfusion must always be tried first, but if at the end of twenty-four hours, after two transfusions, the bleeding time is still excessive and shows no sign of returning to normal then, but not before, the question of splenectomy

must be seriously thought of. The wait of twenty-four hours is fully justified, for it will undoubtedly save some patients from an operation which they would be unlikely to survive.

When this position has been arrived at and the factors already mentioned reviewed splenectomy is justified only if the haemorrhages are continuing, the haemoglobin percentage is falling, and the general condition is deteriorating. There are some further subsidiary points which are to be taken into consideration. Leucopenia suggests that the bone marrow is exhausted temporarily, and this would weigh in favour of operation. A high platelet count would be a distinct indication against splenectomy. It is best to come to a decision on the conditions existing at the moment, and not to be swayed by the history of previous attacks. It is difficult to know in which direction these should weigh, for if a patient has survived previous attacks he may well survive the present one, although he would be exposed to the risk of recurrence in the future. In the case of a child who has recovered from previous attacks the parents would rarely consent to an operation which could be performed with much less risk when the acute attack had passed.

With regard to the operation, splenectomy should be undertaken if possible. Adhesions may render this difficult and the operator may have to be satisfied with ligation of the splenic vessels, the results of which operation are still uncertain. A blood transfusion should always be given at the time of operation, but it is not right to delay transfusion because the question of splenectomy may shortly arise.

RESULTS OF SPLENECTOMY

It is difficult to estimate with exactitude the dangers and results of splenectomy. Many of the patients who die after the operation would undoubtedly have died in any circumstances, but splenectomy is a serious operation in acute purpura haemorrhagica and is undoubtedly associated with a high operative mortality. It must also be remembered that many patients recover without operation, even when *in extremis*.

In favourable cases the haemorrhages cease with extraordinary rapidity after operation. It is said that haemorrhages can be seen to cease immediately the spleen is removed. The blood platelets rise rapidly, undoubtedly due to flooding of the circulation with reserves from the bone marrow, as happens after splenectomy for other conditions. In the course of two or three weeks the platelets fall to an ordinary level. Recovery from the operation may be uneventful and the haemorrhages completely disappear, and no subsequent symptoms may arise for a course of years. Nevertheless, it is known that even in such cases serious haemorrhages may recur after long intervals of freedom.

Occasionally the platelets rise to a high or a normal level with cessation of the haemorrhages and then subsequently fall to a low figure. Haemorrhages may not immediately recur, but they tend to do so later. This course is, however, more common in the chronic than in the acute form. In a few cases the blood platelets entirely fail to rise. In spite of this the haemorrhages may cease for a few days, but they then recommence, usually with a rapidly fatal termination.

In addition to blood transfusion and splenectomy many other methods of treatment have been advocated and supported by a record of cures, but in considering these the tendency to spontaneous recovery must be borne in mind.

OTHER METHODS OF TREATMENT

Good results have been claimed for vitamin C in the pure crystalline form of cevitamic acid. If this is correct it brings the primary haemorrhagic diathesis into line

with scurvy, which is not impossible; this method of treatment needs further testing. Cevitamic acid must be injected intravenously, being admittedly useless by the mouth, and the dose should be 150 mg. daily until the haemorrhages cease. This method is worthy of trial together with blood transfusion. There is no evidence that the injection of whole blood or of horse serum intramuscularly is of any value.

Several attempts have been made to use snake venom, the venom of certain snakes being coagulant, and good results have been claimed. Antivenin serum, prepared by immunizing horses against the venom of certain snakes, particularly the genus *Bothrops*, has been injected intramuscularly in 10 c.cm. doses. Another method has been the intradermal injection of filtered diluted snake venom. The venom of the copperhead snake has been tried in dilutions of 1 in 3,000 and 0.1 c.cm. injected daily for several days. The number of recorded cases is small, but it is not impossible that snake venom may prove helpful.

Attempts have been made to "block" the reticulo-endothelial system by the injection of various substances. The most recent method is by the intravenous injection of 10 c.cm. of a 1 per cent. solution of Congo red. It is known that such injections raise the number of blood platelets experimentally in animals, though the amount used has been much larger than is recommended for administration to human beings. Liver extracts in any form are entirely useless.

During convalescence the treatment should be on common-sense lines. The diet should contain a sufficiency of vitamins, and iron will be indicated for the treatment of the anaemia. All septic foci should be appropriately treated.

Chronic Purpura Haemorrhagica

The problem of treatment in this group differs essentially from that in the acute group, since there will be ample time to consider the appropriate measures. There will be no expectation that the tendency to haemorrhage will stop permanently. When beginning in childhood it may diminish with advancing life, but this is not invariable. In all cases septic foci should be carefully treated. The results of splenectomy have been satisfactory, and therefore an important question to decide is whether or not splenectomy is indicated. The operative mortality is about 8 per cent., although some surgeons have reported series with lower death rates.

Many (but not all) of the patients on whom splenectomy has been performed have remained free from all symptoms over a course of years. In some cases, however, the haemorrhages continue in a slighter degree for some weeks or months before ceasing; in others the haemorrhages continue permanently with diminished severity. It is important to note that some of the patients in whom the results have appeared entirely successful, no haemorrhages developing for several years, gradually return to a severe haemorrhagic state. A small proportion of cases show no benefit, but this is exceptional. Prognosis is difficult, and while the results are, in general, satisfactory the possibility of a less successful termination must be borne in mind and put before the patient or those responsible.

INDICATIONS FOR SPLENECTOMY

The first question that will arise is whether the severity of the condition is such as to allow life to continue without serious impediment to reasonable activities and without risk in the near future, in the absence of operation. The manifestations may have been so mild over a course of years and the general condition may be so good at the time of examination that the risk of an operation

would clearly be unjustifiable, but it should be remembered that the question may need to be reconsidered in the future. If operation cannot be dismissed on these grounds other circumstances which must be considered are: the age of the patient and the general physical condition; the previous history; the extent of the haemorrhages and their duration; evidence of increasing severity; the degree of anaemia; and whether the white cells are increased or decreased. With regard to the last point, leucopenia is evidence of exhaustion of the marrow, which may be temporary or due to advancing aplasia. Permanent leucopenia is a serious sign, for it will increase the risk of operation; on the other hand, it is evidence that the bone marrow is unequal to the demands made upon it, and it is therefore best to regard leucopenia as favouring splenectomy. If there is a definite leucocytosis then the bone marrow is able to react and the decision is of less urgency. The size of the spleen is not an important factor. If the number of platelets is below 100,000 per c.mm. it should weigh in favour of, and if above 150,000 it should weigh against, splenectomy. In the latter case there is a risk of subsequent thrombosis, and in the former the farther the number falls below 100,000 the greater evidence is it of the activity and severity of the haemorrhagic tendency.

ESTIMATING HAEMORRHAGIC ACTIVITY

The bleeding time and the capillary resistance test must be recorded, a great prolongation of the bleeding time being an important sign. These tests are a measure of the activity of the haemorrhagic tendency at the time of examination, and may be valuable as evidence that it can attain a high degree of severity. But in quiescent periods the tests may be normal, and this must not be regarded as an indication that serious haemorrhages will not occur.

A case of chronic purpura haemorrhagica must be watched, the various examinations repeated, and the decision as to splenectomy based on observations over a satisfactory period. Only rarely is it justifiable to decide to operate on the strength of a single examination. The risk of operation will be less when the bleeding time is normal.

Blood transfusion cannot have more than a temporary effect on the haemorrhages, but may benefit the anaemia considerably in chronic purpura haemorrhagica. Blood transfusions repeated from time to time may be sufficient to keep older subjects and borderline cases in a reasonably satisfactory state without exposure to the risks of operation. The amount injected should be from 500 to 700 c.cm. A pre-operative blood transfusion is always necessary.

OTHER METHODS OF TREATMENT

In addition to the methods of treatment described for the acute form there are others which have been used in the chronic. Calcium has been given in large doses, but its administration is valueless, for there is no shortage of calcium in the blood and no prolongation of the coagulation time.

Protein shock, either by injection of T.A.B. vaccine or of tuberculin, has yielded good results in children. I have had most unfortunate experiences of its use in adults, and would regard it as dangerous. There are well-authenticated cases in which haemorrhages have been prevented over many years by injections of adrenaline, 1 in 1,000 solution, 3 to 5 minims, and it is worthy of trial in cases beginning in childhood. It is only rarely effective, but in such cases its action is obvious in a few days. There is no evidence that ultra-violet light has any specific effect. Treatment with turpentine or with arsenic is also valueless.

(To be continued.)