THROMBOCYTOPENIA

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A fundamental difficulty in studying thrombocytopenia is the result of the technical difficulties of enumerating platelets accurately. Even with what seems to be a reliable method, that is to say one which gives consistently reproducible results, remarkable variations in the platelet count often seem to occur during the day. The mechanism of these alterations is unknown. They call to mind the striking diurnal variations in the eosinophil count, although a definite rhythm has not been convincingly demonstrated. It is not appropriate here to consider in detail the techniques available, but it may be said that methods involving direct enumeration of platelets in a counting chamber are generally to be preferred to other methods. Whatever procedure be selected it is desirable that the results should be checked against the examination of a blood film properly made and stained.

The unreliability of platelet counts and the marked diurnal variations that are observed in certain apparently healthy persons make it difficult to give, with any accuracy, a figure below which all counts can certainly be considered abnormal. Thrombocytopenia is therefore impossible to define exactly. It may, however, be said to be present when the count is consistently below 100,000 per mm.³. The possibility that there is a border-line zone, say between 100,000 and 250,000 per mm.³, within which meaningful alterations in platelet concentration can occur remains to be explored.

One of the first points that should be emphasized by anyone writing about thrombocytopenia is that this phenomenon may be quite temporary, lasting no more than a few days, or even transient, occupying but an hour or two. A second fact that it is necessary to be clear about is that thrombocytopenia, be it prolonged, that is to say continuing for weeks or months, or transient, is not invariably accompanied by purpura, by bleeding from mucous membranes, or into body tissues. Indeed, an abnormally low platelet count may

persist for years without any manifest bleeding tendency or even an undue liability to bruise. Such clinical observations, along with the well-established fact that laboratory animals made thrombocytopenic by injection of anti-platelet sera do not develop purpura or other evidence of increased tendency to bleed, make it quite clear that a low concentration of platelets in the peripheral blood cannot be the sole factor responsible for purpura. It is possible, though not proved, that lack of platelets may make an already established bleeding tendency worse. Further detailed studies of the processes that result in thrombocytopenia and more knowledge of the ways in which prolongation of the bleeding time is determined are required before the mechanism of the production of purpura can be fully understood.

There are four phenomena that frequently accompany thrombocytopenia, namely a prolonged bleeding time, abnormal clot retraction, decreased capillary resistance (increased capillary fragility) and incomplete consumption of prothrombin.

Repeated, and as closely as possible simultaneous, determination of these functions shows, however, that they are not invariably associated. Bleeding time (Duke's method) may be normal with thrombocytopenia, or with diminished capillary resistance or with both together. Thrombocytopenia is not invariably accompanied by grossly abnormal capillary resistance and certainly not by an unequivocally positive tourniquet test. Attempts to assess capillary resistance by a suction capsule, however, reveal that normal values are rarely found with thrombocytopenia, though grossly diminished resistance is not invariable. The lowest values for capillary resistance by this method have been found in subjects in whom the platelet count in the peripheral blood has been within normal limits. Thrombocytopenia is almost invariably accompanied by defective clot retraction and by abnormal prothrombin consumption, although both phenomena may be

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present either separately or together with a normal platelet count.

A prominent role in the mechanism of thrombocytopenia has hitherto been attributed to the spleen for the following reasons:

(1) A number of disorders of which enlargement of the spleen is a prominent feature, for example myeloid leukaemia, reticulosis, Gaucher's disease and Banti's syndrome, are often accompanied by thrombocytopenia. Sometimes this is associated with leukopenia and anaemia—so-called 'hyper-splenism.'

(2) Removal of the spleen is on occasion a life-saving operation. In a young female, for example, with extensive recurrent purpura, epistaxis, haematuria and bleeding from the gums and uterus, in whom repeated blood transfusion had arrested neither the bleeding nor a progressive fall in haemoglobin concentration, splenectomy as an emergency procedure stopped the bleeding within an hour. It must, however, be admitted that splenectomy is not invariably successful in similar circumstances.

(3) Splenectomy is followed by significant elevation of platelet count in some 90 per cent. of patients with so-called idiopathic thrombocytopenic purpura. Moreover, it accounts for permanent arrest of purpura, accompanied by a return of the platelet count towards normal, in about 60 per cent. of patients with that disorder, and is still the most effective method of treatment.

(4) It has been shown that splenectomy can prevent the fall in platelet count that follows the injection of small doses of anti-platelet serum into animals; large doses of the serum, however, cause reduction of the platelet count even in splenectomized animals.

(5) Several groups of workers have reported the extraction, from the spleens of patients with thrombocytopenic purpura, of anti-platelet substance, so-called 'thrombocytopen,' the injection of which into animals has produced marked reduction of the platelet count. Because other workers have not been able to confirm these results and because tissue extracts rather readily produce thrombocytopenia when injected into laboratory animals the significance of such experiments must remain in doubt.

There are three ways in which the spleen has been supposed to produce thrombocytopenia. One of the first suggestions was made by Kaznelson in 1916, who postulated that the platelets were destroyed in the peripheral blood as the result of a substance liberated by the spleen. Much later, in 1940, the results of minute histological examinations of the spleen using special staining techniques led to the suggestion of 'selective sequestration' of thrombocytes in the splenic pulp and

their destruction there either by lysis or by phagocytosis. These hypotheses are supported by the finding, not always confirmed, that platelet counts in blood taken from the splenic artery at operations in man usually exceed those in the splenic vein, and by the observation, agreed upon by all, that platelet counts in material obtained by splenic puncture much exceed counts made in the peripheral blood.

Frank, in 1915, first suggested that the spleen, through a humoral agency, exerted an inhibitory effect upon the production of platelets in the bone marrow. Following the development of the technique of sternal puncture, it was shown that in many patients with thrombocytopenia the numbers of megakaryocytes in the marrow were either normal or somewhat increased. More detailed cytological studies have, however, established that, certainly in some patients, these cells are abnormal in appearance, with strikingly little evidence of platelet production, and that there is a return towards normal within 24 hours of splenectomy.

It is difficult, then, to avoid the conclusion that, in some instances, perhaps the majority, the spleen plays some part in producing thrombocytopenia. Recent work has indicated, however, that thrombocytopenia may be produced in more than one way and it is now clear that theories based upon a central role for the spleen cannot always be invoked to account for it.

That platelets may suffer direct injury from substances present in the circulating blood is suggested by a number of observations. Abnormally low platelet counts have been recorded in approximately 50 per cent. of the surviving infants of mothers with thrombocytopenia, whether or not splenectomy has been performed previously in the mother. It is as a rule accompanied by purpura and is present for a few days to a few months. Such observations afford presumptive evidence for a toxic or inhibitory material transmitted through the placenta; it is presumably eventually destroyed or eliminated, since sustained thrombocytopenia in the infant is very rare.

Some of the best evidence in favour of platelet destruction in the blood has been obtained by the study of the thrombocytopenia and purpura that follows the taking of quinidine or the hypnotic Sedormid (allyl-isopropyl-acetyl-carbamide) by persons who have acquired a hypersensitivity to these drugs. Sedormid purpura has been studied extensively by Ackroyd. He found that very small doses of Sedormid, for example 1.4 µg., could produce purpura and that bleeding might develop as soon as 15 minutes after the drug was taken. A fall in the platelet count from 325,000 to 25,000 within two hours has been shown to follow the taking of quinidine. These findings

alone suggest that destruction of platelets is occurring in the circulation and this hypothesis is supported by Ackroyd's demonstration that, after the addition *in vitro* of Sedormid, the serum of patients who had recovered from Sedormid purpura rapidly produced agglutination of platelets and subsequently lysis together with impaired clot retraction. These phenomena could not be demonstrated in controls. Subsequent work clearly demonstrated that Sedormid becomes attached in some way to platelets (but not to red or white blood cells) to constitute an antigen. In the hypersensitive subject this antigen, in the presence of complement, reacts with an antibody to produce platelet lysis. Ackroyd did not claim that the thrombocytopenia caused the purpura. He did in fact demonstrate excessive capillary fragility during attacks of purpura in Sedormid-sensitive persons, and he believes that the capillary endothelial cells are also damaged in an antigen-antibody reaction. A close antigenic relationship between platelets and vascular epithelium had already been strongly suggested by the work of Bedson with anti-platelet sera in animals. It seems possible that the megakaryocytes could be involved in the same process.

Considerable impetus has recently been given to the notion that thrombocytopenia may sometimes be the result of destruction of platelets in the circulating blood by results from two independent laboratories. It has been shown that plasma from certain patients with thrombocytopenia, when transfused into healthy recipients, can regularly render them thrombocytopenic and even produce abnormal bleeding. The fall in platelet count may be noted within two hours and may persist for five to seven days. Conversely, the transfusion of platelet-rich preparations into some patients with thrombocytopenia is followed by very rapid destruction of the transfused platelets. To emphasize the importance of these observations an analogy between thrombocytopenia and acquired haemolytic anaemia has been postulated. In the latter disorder it is often possible, by using anti-globulin serum (Coombs' serum) to demonstrate an antibody adsorbed on the red cells. Some patients with acquired haemolytic anaemia also have thrombocytopenia. Furthermore, it has

now been found that in certain cases the same anti-globulin serum will agglutinate platelets.

A third hypothesis to account for thrombocytopenia, namely that platelets are taken up or 'utilized' in tissues, has received little experimental confirmation. There is evidence, however, that platelets can be removed from blood both in the spleen and in the lungs.

In conclusion it should be emphasized that recent work on the mechanism of thrombocytopenia, while indicating the probability that this is not always the same, has as yet not made it possible to separate patients with thrombocytopenia into clearly distinguishable groups and it has not so far led to any important therapeutic advance. The value of cortisone and adrenocorticotrophin has yet to be clearly assessed, though it seems probable that in certain patients their administration is followed by some, usually temporary, improvement in the tendency to bleed, though not necessarily as the result of an improvement in the platelet count. Splenectomy remains the best method of treatment and should always be considered in adults who have had thrombocytopenic purpura for more than three or four months, regardless of whether there are few or many megakaryocytes in the bone marrow. When thrombocytopenia occurs in either sex below the age of puberty, spontaneous remission is likely and splenectomy should be delayed as long as possible. When thrombocytopenia is found in association with infection or the administration of drugs known to produce reduction in the platelet count, remission is to be expected as the infection is treated or the drug withheld. Thrombocytopenia accompanying disease of the spleen or bone marrow is not as a rule susceptible to treatment, though splenectomy may have to be considered in the former group in order to arrest bleeding and prolong life.

The treatment of thrombocytopenia by means of blood containing a high concentration of platelets, for example from persons with polycythaemia vera, or with plasma in which the concentration of platelets has been artificially increased, can only be undertaken in specialized clinics and its value remains to be assessed.

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