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## Thrombocytopenic purpura hemorrhagica

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THROMBOCYTOPENIC PURPURA HEMORRHAGICA

Senior Thesis

University of Nebraska College of Medicine

Omaha, Nebraska

1 9 3 3

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## C O N T E N T S

		Page
I	Definition and Introduction	1
II	The Blood Platelets - Thrombocytes	7
III	Treatment	30
IV	Histology of the Spleen	44
V	Conclusion	45
VI	Case Histories	47
VII	Bibliography	63

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I

Definition and Introduction

## THROMBOCYTOPENIC PURPURA HEMORRHAGICA

Thrombocytopenic purpura hemorrhagica, morbus maculosus werlhofii; Werlhof's disease; hemorrhagic thrombocytopenia (57); hemogenic syndrome (Roskam); essential thrombocytopenic purpura (Frank); thrombocytolytic purpura (Kaznelson); primary or essential purpura; idiopathic purpura hemorrhagica, are all terms applied to one of the blood dyscrasias, of unknown etiology, characterized by the following clinical syndrome:

- (1) spontaneous bleeding from the mucous membranes, especially of the nose and mouth - at times also from the uterus, intestines, visceral organs, and brain;
- (2) purpuric skin lesions;
- (3) thrombopenia - low blood platelet count;
- (4) normal or only slightly increased clotting time;
- (5) non-tractility of the blood clot;
- (6) prolonged bleeding time - generally from above 10 minutes to several hours.

Idiopathic, or perhaps better still primary or essential purpura, is the better and more accurate terminology to use as it differentiates this condition from other similar ones in which purpura and hemorrhages occur from secondary or symptomatic causes; such as (1) toxins; (2) chemicals, (3) radioactive substances, (4) cellular infiltration or irritation, (5) scurvy, and (6) hemophilia.

Rubnitz (74) has lately made the classification of "central" in those cases which show platelet deficiency on a thrombopoietic basis due to hypothrombopoiesis; and "peripheral"

er the nonthrombopenic cases which do not show definite platlet pathology but rather a defect or alteration in the capillary walls, as from the secondary type. However, several recent authors have advanced the idea that it is due to an increased permeability of the capillary walls rather than to a thrombopenia which gives rise to the hemorrhagic manifestations. (36). As shall be brought out later, it is quite evident that both of these factors go hand in hand to produce the clinical picture of "essential purpura."

This condition occurs most frequently in children and young adults; and more frequently in women than in men - 3 to 1. (71). Although Piney (68) and others (82) state that, "no evidence of familial incidence can be found," according to Tice (83) and others (13), "heredity and familial examples have been described by Leschke and Wittkower, by Liebling and by Hess, but these are rare." Occasionally the spleen shows marked enlargement, however, in the majority of cases it is not enlarged.

There are two main types of this malady i.e., (1) acute and (2) chronic - intermittent and continuous. (13) Babcock (4) divides them into (1) purpura fulminans - malignant form and fatal within a few hours: this at times is mistaken for acute leukemia, (2) acute toxic form, and (3) the chronic form. The chronic form begins in adolescence, frequently in girls who have had poor health. Purpura is associated with severe constitutional disturbances and splenomegaly, and tends to be intermittently progressive. The onset may be abrupt after a few days of

general malaise, with severe and extensive ecchymoses, hemorrhages from the mucous membranes - nose, gums, stomach, bladder, uterus, and into the brain. It is a condition in which a hemorrhagic discoloration appears under the skin without apparent reason, ranging from small (petechiae) to large areas (ecchymoses, vitices) in size; these spots appear either temporarily or at intervals, or as a chronic condition. They exist in all degrees from quite harmless, quick healing "purpura simplex" to the 'foudroyant' deadly illness, "purpura fulminans." The more severe cases are, as a rule, associated with spontaneous or easily induced uncontrollable internal or external hemorrhages, "purpura hemorrhagica."

In morbus maculosis werlhofii there is malaise at the onset followed in a few days by severe and extensive ecchymoses and hemorrhages with joint pains and vomiting; nephritis and vomiting also occur. (4)

The chronic condition is estimated to be nine times as frequent as the acute type. This type may persist for years (13).

The acute cases differ only in their course from the chronic. When first seen the cases fall into three varieties: (1) may run a fatal course, (2) may recover spontaneously (apparently the first case reported by Werlhof belongs to this group) (74), and (3) the case may be the onset of the chronic type. In the case of the chronic type the blood may be perfectly normal between attacks (Frank) (5). The diathesis renews itself for each subsequent attack. In the continuous

type the abnormal state of blood in constant - thrombocyto-  
penia - though the clinical manifestations of the disease may  
not always be in evidence. Due to the fact that in the latter  
type there is frequently seen a high relative lymphocytosis  
following prolonged bleeding it may be confused with lymphatic  
leukemia. Evidence of secondary anemia are only seen in cases  
of long continued bleeding and are directly proportional to the  
extent and amount of the bleeding. A preponderance of poly-  
morphonuclear cells in cases of purpura is a favorable index  
of marrow activity.

This syndrome was first reported by Werlhof in 1735.  
With the exception of the French, it is quite surprising to  
find that until recently but little attention has been paid  
to the blood changes in this disease. The early reports on  
the diminution of the thrombocytes by Brohm (1881) and E. Krauss  
(1883) in Germany, were ignored until 1916 when Glazmann  
revived them. Deny (1887) made a similar observation. Hayem  
(1893) first called attention to the non-contractility of the  
blood clot. To Hayem and his pupils (Bensaude, Rivet and  
others) goes great credit for the preciseness of their observa-  
tions of the chief hematological changes in purpura. (74). Duke  
(1910-1912) first emphasized the relation of the blood plate-  
lets - thrombocytes - to the bleeding time: Hess (1915) first  
suggested that splenectomy might be beneficial in this disease;  
Kaznelson (1916) first referred a case of his for splenectomy  
with such remarkable success that he thereby introduced a



method of treatment which, in certain selected cases, is comparable to the removal of the spleen in cases of hemolytic jaundice.

According to Piney (68) "cases of chronic essential purpuras seem to be diagnosed less frequently than should be the case, because it is usually expected that a purpuric rash must accompany the exacerbations; this is by no means the case; the malady is a hemorrhagic one, but not necessarily a purpuric one."

In taking a history - especially if the patient is seen for the first time and is an adult - one must be most careful to avoid making grave mistakes in the diagnosis. He must carefully inquire into the history for any symptoms occurring in childhood, such as easily induced or spontaneous nose-bleeds, whether gastric or intestinal hemorrhages, though these are rare, have occurred, whether there has been prolonged bleeding following such minor operations as tooth extraction, if there have been incidences of extensive ecchymoses frequently following slight injuries.

The more common finding is that of occasional nose-bleeds or excessive menstrual flow which has been a source of intermittent annoyance for a long time, but has finally become sufficiently annoying to cause the patient to seek medical advice. Spontaneous recovery is the general rule with the anemia caused by the hemorrhages overcome, only, however to

reappear again when another attack occurs.

Due to the peculiar tendency to remissions, it is not surprising to find that the various tests give conflicting and discordant results in various cases but also different results in the same patient at different times. Small incisions are apt to bleed longer than normal, although the clotting time is not altered. However, at times the increase in bleeding time is not well marked. It is usually possible, even in periods of remission, to artificially induce "purpura." This may be done by placing a tourniquet about the arm for from ten to fifteen minutes after which time small petechial areas, either scattered point-like hemorrhages or a generalized petechial exanthem, will be observed on the arm below the tourniquet showing hyperpermeability of the capillary walls. This is the so-called Rumpel-Leed's test although Hess first called attention to it in 1916. However, this venous congestion of the arm by constriction with the resulting petechial manifestation cannot be relied upon too much as it can be produced in menstruating women who show no other signs of a hemorrhagic diathesis; as well as in cases of hemorrhagic nephritis. In cases of true purpura striking the skin over the sternum - or other boney prominence - with a percussion hammer will produce ecchymoses. A positive Hess test may be obtained in cases of scurvy.



## The Blood Platelets - Thrombocytes.

Since up to but very recently the marked decrease in the number of the blood platelets - thrombocytes - has been held to be the primary cause of the purpura and hemorrhages: some discussion as to their etiology, function, and reaction within the blood stream and hemolytic organs of the body might not be amiss.

Histologically the position of the thrombocytes is still unsettled and a much debated question. Buckmaster (cited by Starling (79)) regards them as artefacts due to the fact that if a drop of blood, which has been obtained by a platinum loop and carefully kept at body temperature, be examined microscopically, no blood platelets will be observed. Schilling (76) does not believe that they are preformed blood elements in spite of their "ameboid" motion; but rather are merely 'cell fragments'. Since specific granulations are absent it does not seem probable that they are leucocytic fragments. On the other hand, since hemoglobin cannot normally be demonstrated in them it is evident that they cannot be pieces of erythrocytes. Other observers (Engel, Preisich, and Heim) believe that with the observations to date it is plausible to assume that the thrombocytes are derived from the nucleus of the primary erythrocytes. Schilling (76) holds that the thrombocyte itself is the entire modified nucleus of the younger erythrocyte - hematoblast, partly detached and becoming free only in the circulation; e.g., by blood platelet thrombosis or during the preparation of the smear.

Other, older, ideas held that the thrombocytes were unorganized precipitates of blood plasma. It was later shown that what had been believed to have been amoeboid motion - when freshly placed on agar medium - was merely a change due to a difference of surface tension.

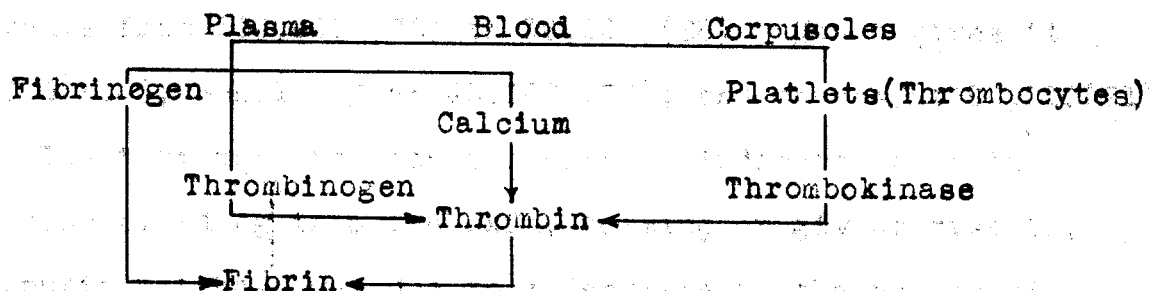
The idea which has the most support at the present time is that advanced by Wright that they are produced by peculiar giant cells - megakaryocytes - found in the bone marrow of all mammals. These cells have a protoplasm which stains a pale blue with Romanowsky mixture, containing large numbers of azurophil granules which arise as detached cytoplasmic processes. (6). Most of the recent authors are in accord with the idea that the blood platelets are preformed living elements (52).

Maximow (54) describes them as small, colorless corpuscles which have the form of round or oval, biconvex disks; which, when seen in profile appear like small, plump spindles or rods, and are found circulating in the blood of all mammals. Some authors describe them as irregular, elongated or pear-shaped corpuscles. They are not uniform in size, the average being  $3\mu$ . Chemically they have been found to contain proteins and lipids: a phospholipidprotein combination (52). They consist of two parts: one, which is highly refractile and contains purple granules - the chromomere; the other pale and homogeneous, staining pale blue - the hyalomere.

Mathews (53) states that the number of blood platelets is very variable and believes that it is a very suggestive fact

that the more care there is used in keeping the blood as near the living state as possible the fewer platlets are seen; that injury to the blood vessel wall greatly increases their number. Although he states that most authorities incline toward the preformed living element theory, he states that it is difficult to decide whether they are preformed in the living unchanged blood or whether they appear with great ease when the blood is disturbed. Emotion or the injection of adrenalin serves to increase their number by contraction of the spleen, which serves as a reservoir, and possibly a source, of them.

The entire case in purpura hemorrhagica has - up to the present time - hinged on the importance of the platlets in the formation of blood clots. According to the following diagram they release the substance thrombokinase - one of the essential elements in the formation of blood clots, hence the term thrombocytes (89).



Starling (79) states that filaments of fibrin are often seen radiating from the center of disintegrated blood platlets. That they are concerned in the production of blood clots is shown by the fact that in living blood vessels the thrombocytes aggregate around any injured spot in the vessel wall, later

fusing together so as to form an adherent thrombus or clot which covers up the seat of injury and aids in repairing the damage done and in preventing the escape of the contents of the blood vessels.

Still another point of difference is the actual number present normally, or at any one time, in the blood stream. The average usually given is between 250,000 and 400,000. However, since the various methods available at the present time for determining the number of platelets present per cu. mm. are subject to wide variations; not only between different technicians but also with the same individual at different times; some believe that the actual number lies between 700,000 and 800,000 but that about half of them disintegrate before they can be counted.

Various figures are also given below which spontaneous hemorrhages from the mucous membranes and into the skin occurred. These range from 100,000 (76) to 30,000 (68). Minot gives it as 60,000 (60); Schilling as 40,000 (76); and others at 80,000(71).

The term thrombocytopenic purpura indicated that the spontaneous bleeding into the skin, forming or giving rise to, the purpuric patches, was due to a decrease in the number of thrombocytes. This point of view has lately been challenged because there are cases reported (36) in which no hemorrhage occurred - at least that gave any clinical evidence - with a platelet count ranging as low as 10,000; while on the other hand are cases with a platelet count as high as 100,000 with clinical evidences of spontaneous hemorrhages. That some other factor

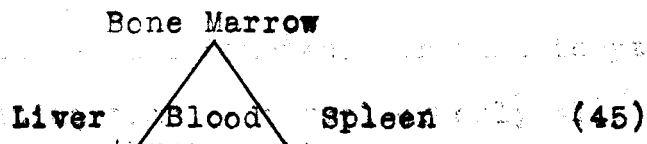
must be at work along with the thrombocytopenia seems to be confirmed by the fact that in cases in which splenectomy has been done even though after an initial marked rise in the number of blood platelets there has been a decrease considerably below that ordinarily regarded as indicative of spontaneous hemorrhage without any clinical evidence of hemorrhage.

There are two schools of thought as regards the etiology of the thrombocytopenia so universally seen in these cases (87): (1) that advanced by Kaznelson, and supported by Aschoff, Foa, Eppinger, Krumbhaar, Brill and Rosenthal that the thrombocytopenia is due to an increased destruction of the formed thrombocytes probably due to hyperactivity of the spleen: since this organ is generally regarded as being one of the places in the body in which thrombocytes are destroyed. He bases his opinion on the following findings: (a) the not infrequent occurrence of splenomegaly, (b) the presence of excessive numbers of megakaryocytes found in the marrow, and he has reported finding them in the splenic pulp; he looks upon these findings as evidence of a compensatory process, (c) the number of blood platelets in the spleen are greater than would be expected from the amount of blood which is found in the organ, and (d) the marked rise in the blood platelets following splenectomy. (2) that advanced by Frank, cited by Lewis(5), that there is some hormone or myelotoxin, possibly produced by the spleen, which inhibits the production of the thrombocytes by attacking only the megakaryocytes in the bone marrow. As stated elsewhere the former



theory has the most evidence on its side at the present time. This is considered to be a hyperactivity on the part of the reticulo-endothelial system with the most activity shown by the spleen, or at least some dysfunction of the spleen which activates the platlet distruction by the remainder of the reticulo-endothelial system and this is relieved by splenectomy.

The hemorrhagic triad may be illustrated by the following diagram:



Although numerous observations have been made on the physiology of the spleen in the last few years there is still much to be learned about its function. At the present time it is considered to be the largest member of the lymphoid and reticulo-endothelial system which has been described elsewhere. However, it must be kept in mind that because of its anatomical independence and size, and its relation to the liver it holds a certain dignity as an organ 'sui generis.'

The lymphoid system is most active in youth, sharing in the production of the lymphocytes; it gradually atrophies with age (64).

Seeliger (77) described pathological changes within the protoplasm of the megakaryocytes. In about 90% of the cells no granules could be found; in 6% the protoplasm was found to be partially granular; and in the remaining 4% it appeared to be normal. Due to the fact that there are frequently found abnormally large forms in the blood it is held that there is some

defect in the normal separation of the blood platelets from the parent megakaryocytes.

A phenomena first noted by Hayem in 1895 and which, at the present time, is (74) being considered as a more accurate and reliable finding and which - as far as is known at the present time - always associated with purpura hemorrhagica only-is that of the non-retraction of the blood clot and transudation of the serum. Normally, according to the method of Duke, clotting takes place in about four minutes. The bleeding time is from two to three and a half minutes. In thrombocytopenic purpura while the clotting time is normal or only slightly increased from 10 minutes to several hours, the most striking thing is that whereas the clot forms it does not retract and the blood is seen to ooze from beneath it. When the blood is tested for clotting it frequently shows no retraction of the clot after twenty-four hours.

It has been stated that clot retraction does not take place when the blood platelets drop below 80,000 (71). This has been verified by Lee and Minot. They hold the view that normally there are more thrombocytes present in the blood than are needed to produce clot retraction or complete coagulation. The degree of retraction of the clot depends upon the number of thrombocytes which do not undergo cytolysis during the process of coagulation. Thus, although the blood which is low in thrombocytes may clot, or coagulate, normally or within the normal time limit, yet - because all of the thrombo-

cytes are used up in the clotting process there are none left to produce or cause contraction of the clot and the bleeding continues. (88).

Rosenthal (74) states, "that the clot retraction definitely depends upon the integrity of the thrombocytes, and that Hayem's index of the reduction of the thrombocytes and the non-contractility of the blood clot are the two most important blood changes."

In observing the phenomena of coagulation under the dark field microscope, Burke and Tait saw the thrombocytes burst and globules of protoplasmic projections radiate in all directions. Along the course of these particles threads of fibrin were laid down. When the thrombocytes are removed from the blood it remains in a fluid state indefinitely unless tissue extract or thrombocytes are added. (72).

Another factor which has been receiving a great deal of attention at the present time, and which is being considered by some to be of more importance in the etiology of the hemorrhagic state than the thrombocytopenia, is the hyper-permeability of the capillary walls, or capillary weakness. (37). This may be present either alone or in conjunction with thrombocytopenia. If the thrombocytopenia alone exists the hemorrhagic phenomenon may not exist: possibly the explanation of the absence of hemorrhage following splenectomy without a resulting thrombocytosis.

Evidently some disturbance of either the contractile function or character of the walls of the capillaries has

taken place in addition to the thrombocytopenia. Frank (cited by Christain (13)) has suggested capillary stasis and the theory of "micro-traumata" as the immediate cause of the bleeding though most believe that the hemorrhages are truly spontaneous. This assumption that the capillary itself is a secondary important factor in purpura, helps to account for those patients with a low platlet count that do not bleed and for the cases of non-thrombocytopenic purpura. At the present time the thrombocytopenia is the only definite knowledge that we have in these cases. All of the other factors, etiological and otherwise, are, at present, entirely unknown. As has been previously stated the only other blood findings are those dependent upon the degree and extent of the hemorrhages - secondary anemia; the cells showing some achromia and the 'color index' tending to be low. There are slight variations in their size and shape, while some polychromatophilia and stippling occur. Occasionally normoblasts are seen, and reticulated blood cells appear in increasing numbers when appropriate stains are used. The leucocytes are moderately increased; there is a polymorphonuclearcytosis, both relative and absolute; at times a slight relative lymphocytosis is seen. These vary with different cases.

The serum obtained from the bloodclots in cases of purpura has been found to contain less thrombin than does ordinary serum, as measured by its action upon fibrinogen <sup>or</sup> hydrocele fluid.

As Hayem pointed out there was vulnerability in the viscousness and agglutination of the platlets to foreign bodies.

In normal individuals the platelets show an agglutinating power whereby they adhere to wounds which Hayem termed "clou hémostatique": or the method by which hemorrhages are prevented from the capillaries. However, in purpura, due to a lack in quantity and also a change in the quality of the thrombocytes, this function is greatly interfered with.

To arrive at some rationale for this it is necessary to consider, more fully, a system which has already been referred to i.e., the reticulo-endothelial system. The various organs considered to comprise this system are as follows:

(1) spleen, (2) bone marrow, (3) lymph glands, (4) the liver, and (5) peculiar contractile cells found in the capillary walls called Rouget cells.

The spleen is considered to be one of the principle hemolytotoxic organs of the body. Although it exercises several vital functions yet it itself is not essential to life as is shown by the fact that it may be removed without serious injury to the individual. It apparently does not function as a single organ but as a part of a system; in which the other members apparently compensate for it by increased activity. Since this is evidently the case it would not seem as though splenectomy would give any lasting results in purpura hemorrhagica. On the other hand it seems to confirm the theory that the biological factor is closely related to splenic function or activity - a toxin perhaps - since, in selected cases its removal is met with such immediate and lasting benefit.

The reticulo-endothelial system is composed of strongly phagocytic cells, and is widely distributed throughout the body. With the exception of its function as a blood reservoir, the spleen probably traces all of its activities, and especially those concerned with phagocytosis, erythrocytosis, bile pigment formation and lipid activity to these cells. Since the other members of this system carry on similar activities they are able to take over the function of the spleen when the need arises.

According to Piney (68) the mode of development of thrombocytopenia is essentially hematological in character. The thrombocytes not only decrease in number, but distinct abnormalities are found among those present in the blood; giant forms of thrombocytes are always found and are very characteristic of the disease. Histological changes typical of Werhof's disease forms important support for the view that the platelets are derived from the megakaryocytes in the bone marrow. It is justifiable to presume that there is an excessive stress placed upon the bone marrow, at least so far as thrombocytopoiesis is concerned, because parts of megakaryocytes can often be found in the blood, and as a rarity, even whole cells are seen.

There is now little doubt but that the regulation of the normal number of blood platelets is one of the functions of the reticulo-endothelial system, which has its greatest concentration in the spleen. Hypersplenism might be associated with a

normal thrombocytopoietic system. If this view were accepted the malady would have to be regarded as being "thrombocytolytic purpura."

It has often been contended that some unknown toxin was present which was capable of causing injury to the megakaryocytes without, at the same time, interfering with the other functions of the bone marrow. It is further known that splenectomy is followed by the stimulation of the myeloid function in all of its aspects. However, in but few cases of Werlhof's disease does the operation result in leucocytosis and emigration of immature erythrocytes, without any sign of the usual post-operative thrombocytosis. This seems to be the result of widespread, but selective destruction of the megakaryocytic tissue.

It appears to be clear that Werlhof's disease really represents a selective pathological process affecting the thrombocytopoietic mechanism of the body without at the same time involving the other functions of that tissue. It is, therefore, reasonable to inquire whether or not purpura is associated with a generalized aplasia of the bone marrow, and obvious example of this, of course, is found in myelophthisis, where all cytopoietic functions of the myeloid tissue are about equally involved and a severe hemorrhagic diathesis develops. There are cases of aplastic anemia in which reduction of erythrocytes is relatively more intense than are leucopenia or thrombocytopenia, in others leucopenia dominates the pic-

ture, whilst a few present a thrombocytopenia of great intensity, with less evidence of affection of the other functions of the marrow. It would seem, therefore, that each one of the cellular systems of myeloid tissue can be injured more or less independently of the others, and Werlhof's disease might, therefore, be regarded as being the mildest conceivable form of myeloid aplasia.

From the excellent results obtained in selected cases from splenectomy, it rather points to the intimate relation existing between the spleen and the blood platelets. This has been the subject of much investigation. The platelets are exceedingly fragile and, as has been stated before, tend to disappear or disintegrate rapidly with the ordinary methods of blood examination now employed. They disintegrate when exposed to the air, in changes of the hydrogen-ion concentration of the surrounding media, or tension of CO<sub>2</sub>. Their importance to the process of blood coagulation has been mentioned and they have been shown to contain not only thrombogen (Morawitz), but also they may liberate a substance which is capable of neutralizing anti-thrombin (Bayne-Jones). (50).

No satisfactory explanation has been advanced to account for the relation of the spleen to the life of the blood platelets. That the disorder is particularly related to the spleen is shown by the fact that it is not taken over - or not entirely - by the rest of the system following splenectomy.

The life of the blood platelets has been estimated to



be from three to five days. (13).

A further function of this system, so designated by Aschoff, is the destruction of the formed elements of the blood. Thus it has the job of devouring the used up erythrocytes and leucocytes and thrombocytes of the circulating blood, and to metabolize them.

A striking morphological characteristic of the cells of this system is their vital staining, i.e., the uniform granular deposition of a dye-stuff 'in solution' in the living cell bodies without in anyway injuring them.

Evidently a system of cells, such as the reticulo-endothelial system, whose particular function is to digest worn out blood cells, may show variations of dysfunction both in degree and distribution of site of dysfunction. Thus one form of dysfunction would seem to be definitely limited to the reticulo-endothelial cells of the spleen as is seen in hemolytic jaundice where the extirpation of the spleen results in a cure.

In another form of dysfunction, as in Gaucher's disease, it is not limited to the spleen but to reticulo-endothelial cells located in the lymph nodes, bone marrow, and liver. Splenectomy in this case would remove only a major portion of the lesion.

Inasmuch as the reticulo-endothelial cells get rid of jaded or excessive thrombocytes, it is logical to think that in a disease such as thrombocytopenic purpura, in which a lower absent platlet count is a prominent feature, that some part

of this system is overactive. If these overactive cells are largely limited to the spleen, then its removal would promise immediate good and probably permanent results. However, if the entire reticulo-endothelial circle is involved, splenectomy would do no more than remove a part of the overactive apparatus, and such a major procedure in the presence of a profound vascular disturbance, as in the acute forms of purpura, would be extremely hazardous to the patient.

In some of the blood diseases involving the blood-forming apparatus, there is apparently an associated disturbance or over-activity of the blood-destroying or reticulo-endothelial apparatus as well. Thus in some cases of aplastic anemia and certain of the leukemias, there is noted a marked decrease in the thrombocytes and a tendency to bleed. However, splenectomy in these cases is illogical because the lesion is not limited, even partially, to this organ. These are two diseases which must be carefully differentiated from thrombocytopenic purpura.

As has already been stated the general opinion is that the thrombocytes are the most important formed elements in the phenomena of blood clotting, by the production of a thromboplastic substance. The severity of the bleeding would, therefore, seem to depend upon the following factors: (1) the intensity of thrombocytolysis, (2) the extent to which certain cells in the reticulo-endothelial system are engaged in thrombocytolysis and are distributed in the spleen, liver, bone marrow, and lymph nodes, (3) the permeability of the capillaries to the

circulating blood. This latter consideration is the least understood of the three. The thrombopenia may favor a ready egress for the erythrocytes through the potential spaces between the living endothelial cells of the capillaries. On the other hand, the Rouget cells - classed by Aschoff as belonging to the reticulo-endothelial system, may play an important part in the permeability of the capillaries. Krogh and his pupils made most valuable contributions to the study of the capillary system. Rouget in 1873 first called attention to the existence of peculiar contractile cells on the walls of the capillaries, whose ramified prolongations of cell body protoplasm irregularly encircled the capillary wall. Vimtrup, working in Krogh's laboratory, confirmed Rouget's long forgotten findings and named these cells Rouget cells, after their discoverer. Aschoff disputes the findings of Vimtrup as regards the contractility of the cell bodies but considers them a unit of the reticulo-endothelial system. It is conceivable, therefore, that these Rouget cells, stimulated by some agent that is active in other parts of the reticulo-endothelial system, might disturb the permeability of the capillary wall to the blood stream facilitating escape of the blood units into the tissues (86): or actually exerting a destructive action upon the thrombocytes present in the blood stream within the capillary bed.

It has been stated that the hemorrhage is due to diapedesis of the erythrocytes in which they take on ameboid action. The bleeding being due to the extreme thrombocytopenia and the peculiar action of the blood upon the cells of the cap-

illary walls which permits the extravasation of blood through them. However, this action is not apparent on the larger vessels, thus making surgery possible in severe cases where splenectomy is indicated. (65).

If the spleen produces a toxin (17), it will effect the reticulo-endothelial system in three ways: (1) by increasing the thrombolytic power of the spleen, (2) by effecting the megakaryocytes in reducing the number of platelets produced as well as affecting the quality of those that are produced, so that their thrombocytic power is diminished, (3) it affects the Rouget cells of the capillaries, so that they are rendered more permeable to extravasation of the blood from within. Cessation of the hemorrhages following splenectomy, even when there is no increase in the number of platelets is evidently due to the fact that the quality or normal thrombocytic power has been restored. Months after the splenectomy the marked decrease in the number of platelets noted is undoubtedly due to hypertrophy of the lymphatic glands and tissue throughout the body with assumption of the thrombocytolytic powers formerly possessed by the spleen, however, apparently without the ability to reduce or destroy the thrombocytic power of the thrombocytes. In cases where splenectomy apparently fails, in cases of long duration, it is possible that the Rouget cells had become so deeply affected that even after the removal of the toxic element elaborated by the spleen they were unable to completely recover their normal function.

That the normal spleen does destroy thrombocytes is favored by the fact that there is practically always a sharp rise in the platelet count following splenectomy, both in experimental animals and in clinical cases. One would, therefore, expect to find a larger number of thrombocytes in the splenic artery than in the splenic vein. However, comparative counts made on the number of thrombocytes in the splenic artery, splenic vein, and the peripheral veins, by Halloway and Blackford, do not confirm this view. Cited by Lewis(51).

However, there are other factors which cause thrombocytolyses, either by direct action or by overstimulating the elements of the reticulo-endothelial system that normally destroys the thrombocytes. Cole, 1907, first demonstrated that the platelets could be destroyed in one animal by injecting into it anti-platelet serum developed in another animal. Other workers have reproduced clinical signs and blood changes characteristic of purpura by subcutaneous injections of anti-platelet serum.

Cohen and Leman (50) suggest that the spleen also elaborates some capillary poison which disturbs the tone of the peripheral capillaries, and is also related to the prolonged bleeding time. This toxin may be related, as above suggested, to a selective action on the Rouget cells.

The entire mechanism involved in thrombocytolysis is not clear. Besides the phagocytosis, the anti-platelet serum mentioned elsewhere, we have definite evidence that in acute

infections produced by the streptococci and staphylococci thrombocytolysis occurs as a result of these infections; so that a theory has been advanced that possibly essential purpura will ultimately be found to be toxic in origin.

The same results have been noted in cases of infection by the streptococci and pneumococci. It is definitely known that the 'lighting up' or failure to drain a streptococcus foci of infection, such as in sinus or antrum infection, will result in greatly diminished thrombocytes, and the appearance of petechiae and purpuric bleeding. It may be that poisons from bacteria may stimulate some element in the reticulo-endothelial system to excess thrombocytolysis. This factor of infection is most important and may be the underlying cause even in the so-called idiopathic purpura cases.(37).

On the other hand Leschke and Wittkower (cited by Lewis(50)) are convinced that the fundamental cause of this disease is a constitutional insufficiency in the platelets produced: a sort of thrombocytic diathesis; and cite the case of a mother with purpura hemorrhagica who gave birth to an infant who had no platelets and was covered with petechiae. Brill and Rosenthal (50) believe that the spleen acts directly on the platelets and affects in a harmful way the nature and agglutinative properties of these bodies.

From the foregoing it is apparent that there are three factors involved in the production of hemorrhages, i.e., thrombocytes, per se, permeability of the capillary endothelium, and

the blood plasma. In purpura where the hemorrhage involves diapedesis of the erythrocytes through the unbroken capillary walls, the thrombocytes, which are markedly reduced in the majority of cases, and the capillary endothelium have both variously been held responsible. Both Denys and Frank later considered that the thrombocytopenia was the primary factor. However, since not infrequently there is little or no reduction of the thrombocytes: at times marked reduction without any noticeable bleeding: Tidy would classify those cases without free bleeding but showing petechial hemorrhage as 'purpura simplex.' He regards the reduction of the thrombocytes in the general circulation as secondary to their becoming adherent to the damaged capillary walls in an attempt to prevent diapedesis. Bedson experimentally showed, in rabbits, that neither condition existing alone was able to produce purpura, only when both factors are combined.

Pathological bleeding has been ascribed to separate or combined action of the following factors: (a) scarcity or absence of the thrombocytes, (b) inferior quality of the capillaries that affect their contractility and permeability of the endothelium. Earlier writers, including Duke and Frank, believed that the prolongation of the bleeding time and the severity of the hemorrhages corresponded to the degree of thrombocytopenia present, and supported the hypothesis that the thrombopenia alone was responsible for all of the hemorrhagic manifestations observed. A second group, includ-

ing Nagy and others, held that it was due to a condition of the capillaries. His opinion was that the thrombopenia resulted rather than caused the bleeding. Finally, a third, and larger group, believe in the coexistence of both factors. At present the origin or nature of the injurious agent producing these conditions is unknown.

From a pathological standpoint it appears as though we had a 'platlet-capillary' complex in purpura producing the hemorrhages. (87).

#### Some Differential Diagnosis

Although it is not the purpose of this paper to go into all of the various types of blood dyscrasias which might be confused with thrombocytopenic purpura, a brief outline of the ones most commonly confused with this condition will be given. The following text-book differentiation between thrombopenia and hemophilia is given: (87)

Findings	Thrombopenia	Hemophilia
Hereditary tendency	Rare	Present
Sex	Male & Female	Male, Transmitted by Female; Female reported but rare.
Hemorrhage	Frequent Spontaneous	Following direct Injury
Petechiae	Usually present	Absent
Tourniquet test	Positive	Negative
Thrombocytes	Reduced	Normal
Bleeding Time	Prolonged	Normal
Clotting Time	Normal	Prolonged



Findings	Thrombopenia	Hemophilia
Clot	Retraction Defective	Fragile
Spleen	Frequently Enlarged	Not Enlarged

Schilling (76) gives the following summary of differentiation between athrombopenic purpura, thrombopenic purpura, and hemophilia.

	Athrombopenic purpura; Vascular Injury	Thrombopenic Purpura (Werlhof) Lack of Thrombocytes	Hemophilia Disturbed Coagulation
Nature			
Etiology	Infectious anapylactoid condition (serum disease, rheumatic condition, etc.	According to Frank "essential" other-wise special constitutional condition reacting in latent infections etc.; also associated with leukemias, osteosclerosis, endocrine disorders	Congen. almost exclusively among men, transmitted by apparently healthy women, aggregated family-wise, (familial) subject to hemophilia
Blood Findings	Coagulation normal sometimes shortened Normal or somewhat extended time of bleeding. Thrombocytes normal increase or slightly decreased. Slightly infectious leucocytic finding. Later an anemia	Coagulation normal, retraction ability absent. Bleeding time much prolonged Thrombocytes much decreased or absent At times infectious leucocytic findings After unfavorable course, severe aplastic anemia	Coagulation prolonged in various degrees. Time of bleeding often diminished. Thrombocytes normal, or lymphocytes.
Clinical	Purpura-exanthemata hemorrhages from gums, tissue hemorrhages. Least harmful course, seldom agonal.	Purpura-exanthemata (often very much extended) Hem. of mucous membrane, intestinal Hem. etc. acute or chr., benign or foudroyant malignant course. Frequently splenic tumors.	Sudden Hemorrhage from small or internal wounds. Blood effusions into joints. Periodically increased. Often fatal hemorrhages from slight cause.

Nature	Athrombopenic purpura:Vascular Injury	Thrombopenic Purpura(Werlhof) Lack of Thrombocytes	Hemophilia Disturbed Coagulation
Therapy	Directed against etiology; other- wise symptomatic	Symptomatic with careful Kaseosan treatment, blood transfusions, or roentgenray treat- ment to spleen. Clander or Coagu- len. Finally splen- ectomy. Vitamine (Nateina) is rec- mended	Increase of coagulation by gleatin. NACL solution 10% (5-10cc. intra- venous coagulen): blood transfu- sions, roentgen- ray treatment to spleen.

Scurvy must also be differentiated from purpura hemorr-  
hagica. However, the general clinical features such as spongy  
gums, hemorrhagic infiltration of the muscles, especially of  
the lower leg, and subperiosteal hemorrhages should distin-  
guish them. The absence of thrombopenia should be enough.  
It does, however, give a positive Hess test.(13).



## TREATMENT

With the various clinical findings in mind, the treatment resolves itself into an attempt to combat or remedy the existing conditions, i.e., either to restore the platlet count and capillary endothelium to normal or to remove the cause for the thrombopenia, and thus permit the thrombocytes to again reach their normal level, or function. The treatment therefore, consists of two kinds: (1) medical - or the attempt to stimulate the thrombocytopoietic organs to greater activity with a resulting thrombocytosis, and (2) surgical - the removal of the spleen as it is regarded as the larger part of the thrombocytolytic system. It must be kept in mind, however, that a number of cases get well spontaneously.

The medical treatment consists of blood transfusions, both from a standpoint of increasing the number of thrombocytes and the induction of a reaction on the part of the recipient from the foreign protein - the latter possibly being the better of the two as the life of the thrombocytes is so brief. Direct rather than indirect transfusions would appear to be the better of the two as the sodium citrate used to prevent coagulation has been shown to be thrombocytolytic in action. Recently Jones and Tocantins (36) have shown that small frequent transfusions are much more efficient in controlling the hemorrhages and advocate 300 cc as the standard adult dose, and vary this according to the square meter body surface of the individual.

Due to the fact that the reaction is probably the

important factor intrusions and that small amounts act as well, or better, than larger ones, many men use from 10 to 20 cc of whole blood intramuscularly with very satisfactory results in some cases. Piney(69) states that the use of injections of adrenalin; 2 to 3 minims three to four times a day; causes a lymphocytosis, which is followed by neutrophilia and thrombocytosis, and this is of transient value in some cases of Werlhof's disease.

Although roentgenray treatment of the spleen has been tried in an effort to reduce the size of the spleen and hence its thrombocytolysis, not much success has attended its use.

Laurens and Sooy (78) studying the effect of light and darkness upon the constituents of the blood, observed a stimulating effect of the latter on the number of erythrocytes and thrombocytes in white rats. They further observed a more pronounced stimulation of these blood elements after exposing the white rats to the mercury vapor quartz lamp after three daily exposures of six minutes at a distance of two feet.

With this knowledge in mind and knowing that thrombocytopenia is one of the most characteristic findings in idiopathic purpura it seemed to Sooy and Moise that a rational method of treatment was suggested. During a year's time they treated ten cases of this disease: five were observed during an acute phase and the other half were of the chronic type. The treatment was used in two cases to prepare the patients for operation; in another to prepare a woman for the extrac-

tion of several teeth, she having bled profusely for three days following a recent tooth extraction; and in another patient with marked hemorrhagic diathesis, on whom a tonsillectomy was indicated. These procedures were followed by normal convalescence without any bleeding.

Their method of treatment is as follows:

"On the first day the patient was given two exposures of six minutes each, at a distance of thirteen inches, on the entire dorsal and ventral surfaces of the body. The exposures were increased daily by three minutes for five days, after which the exposure may be increased in daily increments of ten minutes. It is rarely necessary to increase the exposure beyond twenty-eight minutes."

"This procedure gives a massive exposure and may produce a somewhat painful hyperemia. In such cases, the treatment is omitted on the following day. No serious burns have been observed."

A report of a case of theirs will appear under 'case histories'.

Although not much work has been done with this form of treatment it would seem as though this might prove to be of some real benefit, in some of the milder cases, at least.

Building up the resistance of the individual with cod-liver oil, high nutritive diet, etc. is also advised. However, in a number of cases the medical treatment is largely empirical, or else it is resorted to in an attempt to prepare the patient for surgical intervention. Some authors contend that instead of checking the bleeding, transfusions increase it. (50).

The above was the situation regarding the treatment of thrombopenic purpura up to 1917 when Kaznelson, of Prague, first had a splenectomy performed on a patient of his who was suffering from this malady. He is usually given the credit for the introduction of this type of therapy although Hess, of New York, advocated it in 1916, cited by Whipple (86). The results of the splenectomy in Kaznelson's case were so striking that the procedure was soon widely adopted. In 1924, Engel reviewed twenty cases which had been reported in the German literature, including five cases of Kaznelson and he added reports of four of his own. During the past few years this type of treatment has been used with increasing frequency, especially here and in Germany. Giffin and Halloway reported nine cases from the Mayo Clinic treated in this way over a period of two years, in 1925. In more recent reviews on this subject, made by Whipple, Seschke, Wittkower, and Williamson in 1926 showed a total of almost 100 cases in which splenectomy had been done in the ten year period.(51).

Even with the brilliant results frequently observed following splenectomy this procedure is but little more than empirical along with the blood transfusions, etc., as it does nothing to remove the known cause. Its only rational lies in the fact that frequently splenomegaly is found in these cases. However, this may be that there are two good reasons for the professional enthusiasm regarding splenectomy and its continued use: (1) many cases fail to respond to medical regime to control

their main symptom, i.e., bleeding, (2) because in the majority of chronic ~~chronic~~ cases of purpura there is an amazing immediate improvement, both subjective and objective, in the patient's condition. Furthermore, at present, it is the only mode of treatment which really gives good results. However, the beneficial effects are not invariable, nor indeed always effective in the same degree. It is especially indicated in chronic cases which have developed a severe anemia from the continued hemorrhages; but the results of the operation need to be realized, fully, before the decision is reached as to its advisability.

Certain cases in which splenectomy is performed give very disappointing results. The usual thrombocytosis appears: in most cases following splenectomy there is a marked and often, sharp rise in the thrombocytes reaching, and not infrequently, exceeding the normal numbers: this, however, seldom, if ever, persists, for gradually there is a fall below the normal level - sometimes without a reappearance of the hemorrhagic symptoms - at other times these appear rather soon after, while some are thought to have been permanently alleviated, though this cannot be stated with certainty, as yet, as not enough time has elapsed for unequivocal records to be available: but very soon the number falls again and the hemorrhages again appear. There is a much greater tendency for variations in the number of the platelets, than was seen in the blood picture prior to the operation. At times it may



be possible, by splenectomy, to convert a persistent case into an intermittent disease: where there is a fluctuation of the thrombocytes following splenectomy - at times so low as to be unable to prevent the occurrence of the symptoms, while at other times the numbers rise above the number apparently necessary for the health of the individual (critical value).(68).

Then there are those distressing cases in which this procedure has absolutely no effect for following the splenectomy there is no lessening of the clinical symptoms and the platlets fail to rise above the critical value.

It would seem as the efficacy of splenectomy in cases of purpura hemorrhagica would depend upon whether the major part of the thrombocytolysis is taking place within the spleen as well as upon the exciting cause or agent. This would seem to be the case in the so-called chronic type with a hypertrophied spleen, for it is in this type of a case in which the brilliant and apparently lasting results are obtained.

Rosenthal (cited by Nelson) (65) gives the following two conditions in which splenectomy is indicated; (1) where there is essentially a disturbance of the spleen and there is a return of the thrombocytes to their normal level following its removal; (2) where there is a possible disorder of the platlets, so that they remain at a normally low figure. Nevertheless, the spleen is apparently responsible for the hemorrhages, because in a majority of the cases there is an immediate cessation of them following splenectomy.

The favorable results of splenectomy appear to be largely limited to the chronic cases because of the high mortality associated with the acute cases. This may be done at any time in the chronic cases, although it is better to do it during a remission period. In the strict sense not all are cured as occasionally mild forms are seen after the operation. However, reports of patients ranging from four to eight years postoperative show lasting and beneficial results.

The gravity of each case is decided by the abnormal bleeding which is present, as this is the essential feature and the amount, persistence, and at times the location of the hemorrhages must be considered.(50).

On the whole the results of splenectomy are favorable. Many are symptomatically well. In others a severe purpura is converted to a purpura simplex or a very mild case of persistent hemorrhage. These are generally found in connection with colds or an increase in the activity of the lymphoid system on an infectious bases.

What is needed, if such a procedure is possible, is to develop some method whereby one could determine whether or not a particular patient will benefit from splenectomy. Such a procedure would be of great value. It has been suggested that possibly the injection of adrenalin would be able to supply the necessary information. It seems that those cases which fail to show a thrombocytosis following adrenalin injection will fail to show one following splenectomy.(69).

However, case I shows a contradiction to this theory.

Splenectomy is indicated as an emergency measure in cases of excessive bleeding which fail to respond to the ordinary medical regime of rest, internal therapy, local applications, radiation of the spleen, or transfusions. It is the procedure of choice in the chronic cases, and due to the exceedingly favorable results so frequently seen in these cases it has been suggested that it may be extended to include the milder forms which produce anemia because of their long duration. (51).

The types of cases which appear to be the most suitable for splenectomy are characterized by the following five fairly definite findings:

1. Low or absent platlet count
2. Prolonged bleeding time
3. Failure of clot retraction
4. Normal clotting time
5. Appearance of petechiae following Hess test.

A summary of 81 cases in which splenectomy was performed shows the following types - 73 chronic and 8 acute, deaths - 6 from the chronic varieties and 7 of the 8 acute cases operated on died. The following results were obtained in 61 followed cases: 51 gave good results, 4 fair and 6 poor. (86).

Here again, in the operative significance in splenectomy, there are differences of opinion as to the results obtained. Kaznelson emphasises the fact that there is generally a splenomegaly and he believes that these cases are

~~are~~ especially favorable for operative intervention because with an increase in size the spleen has increased its thrombocytolytic powers. However, the fact that the spleen is not palpable is not a contraindication for splenectomy. Many cases have been reported which show that the results obtained and the benefits derived from the operation bear no definite relationship to the size of the spleen.

Concerning the operation 'per se' there is not much to be said. As it has become more common the technique has improved and the mortality and the morbidity have decreased. In cases weakened by continuous hemorrhages and with a marked anemia the patient should be fortified by a blood transfusion prior to the operation and immediately following if at all indicated.

The removal of the spleen is followed almost instantly by a checking of the bleeding, in fact the mere ligation of the splenic artery is sufficient to cause the hemorrhages to cease at once. This has led some to advocate merely the ligation of the splenic artery, leaving the spleen 'in situ' and thus reducing the shock of the patient. This procedure, either splenectomy or ligation of the splenic artery, appears to correct the hemorrhagic tendency with a promptness difficult to explain. At such an early stage, the thrombocytes cannot as yet have been put into the circulation. The hemorrhages seem to stop even in cases where a blood platelet crisis fails to appear. Franck(3) concludes that not only is splen-

ectomy a forcible stimulant of blood platlet crisis, but also an intervention upon the autonomy of the capillary motor apparatus which forces the capillary regions to respond to trauma and obstructing pressure, by constriction and condensation of their parietal colloids, as well. This would seem to confirm the theory of a localized capillary preparedness to bleeding as a factor of the disease, without, however, clearing the pathologic process. One speaks, quite in general of capillary defect, capillary injury, endothelial injury or endothelitis, also of an "accidental capillary constellation." Franck (3).

If one must exclude the functional humoral factor as a basis for the immediate effect of splenectomy, there must be some nonspecific influences. Among these one may assume that the lowering of the blood pressure, the cooling of the patient, the psychic effect, etc., combined with such a serious surgical intervention, is the cause for the immediate diminishing or arrest of the bleeding, while the specific functional humoral influence later perfects and fixes it. (3).

Not only is a normal healing of the wound to be expected, but there is no more bleeding from the incision than would be found in an ordinary individual undergoing an abdominal operation. This is quite as a surprising fact as is the early arrest of the hemorrhages. Roskam (3) believes that the various parts of the body have various bleeding times. Franck (3) believes that the capillaries possess regional independence.

A few authors (Vogel, Kaznelson, Herfarth and Schloffer) have reported increased local bleeding during the operation.(3).

Whatever may be the relation between the local bleeding thrombopenia and splenectomy, it has been proved in 100 cases that the danger of an alarming or fatal bleeding in the operation field need not be feared. However, in essential thrombocytopenia it is a serious intervention, especially when it is done as a last resort in patients in poor condition.(3).

The mortality in the acute cases is very high, ranging from 70% to 80%, whereas in the chronic cases it is between 6% and 8%.(3). From cases collected it appears that death in the acute cases is usually due to shock soon after the operation, or persisting hemorrhages if death occurs later. It appears as though the younger patients have a more favorable prognosis.(3). In the chronic cases, when death does occur, it is usually due to intracranial hemorrhage, sepsis, cardiac failure or anesthetic accidents.

Post-operative complications which may prove to be rather sequelae are chiefly shock and hemorrhage. However, as has been stated with improved technique and gentle with thorough hemostasis these may be largely avoided. Local fat neurosis may result with an elevation of the temperature. The tail of the pancreas, which lies against the spleen must be carefully pushed away and kept from being traumatized. Not infrequently infection has followed splenectomy.

The loss of the spleen, whether this organ is diseased

or healthy, is usually well tolerated by the individual. As has been mentioned it may be replaced by the other members of the reticulo-endothelial system even to its pathological functions. Accessory spleens may also be present, with a tendency to regenerate, so that they should carefully be watched for: Beer found one such organ in one case and four in another(3). Finally, one never knows whether the pathogenesis was the same in all of the reported cases of so-called essential thrombocytopenia; especially, whether the spleen always played the same role under apparently identical conditions. This is a field of modern medicine which is just beginning to be explored and much will depend upon the pioneer work done by the surgeons. It is, therefore, important that all cases operated and observed over a long period of time be reported.

So far there is not too much available data at hand regarding the late or permanent results of splenectomy. The reports that are available vary. About 50 cases have been observed for a sufficient period of time to form some conclusions concerning the permanency of the results of the operation. However, it seems as though the results are permanent if the thrombocyte count remains high, although, there are some fairly good results if it did not (3).

There have been various explanations offered to account for the beneficial effects on the thrombocytes following splenectomy. Since only one portion of the reticulo-endothelial

system is removed some observers doubt the permanency of the results. Basing his results on splenectomized and non-splenectomized animals with experimentally produced purpura, Bedson believes the effects to be only temporary. Since he does not believe that either the splenic activity or the thrombopenia are essential factors in purpura, Nagy is skeptical of any beneficial results. He takes the view that chronic purpura hemorrhagica is due to dysfunction of the ovaries or other internal secretory glands, and that the direct cause of the hemorrhages is due to the fragility of the thrombocytes. The reduction of the platlets being the result, rather than the cause, of the bleeding, since these bodies are numerically exhausted in exercising their normal function of forming platlet thrombi in the presence of capillary hemorrhage (cited by Lewis (50)).

Whipple and Kaznelson (cited by Lewis (50)) trace the results directly to the removal of the spleen. In their opinion, although as there undoubtedly is more or less compensation on the part of the remaining reticulo-endothelial system of lymph glands, bone marrow and lymphoid tissue in the liver and possibly the Rouget cells in the capillaries, it is not sufficient to vitiate the good results of the splenectomy. Attention has been called, in this connection, to the parallelism existing between purpura hemorrhagica and hemolytic jaundice. In the former there is the destruction of the thrombocytes with bleeding and anemia, in the latter destruction of the erythrocytes with jaundice and anemia. In both



cases there is a marked improvement following splenectomy - one portion of the reticulo-endothelial system.

Brill and Rosenthal (cited by Lewis(50)) are of the opinion that the bleeding in purpura hemorrhagica is due to changes in the blood vessels plus the faulty production of the thrombocytes which affects both their quantity and quality. The removal of the spleen restores the thrombocytes to their normal agglutinative and retractive properties. In their opinion the improvement in the quality of the thrombocytes accounts for the absence in the renewal of the bleeding even in those cases in which the thrombocytes again sink to a very low level shortly after splenectomy.

Quite a few cases, after eight years, have been found to be physically fit and symptomatically well.

The spleen is a large, soft, spongy organ that is located in the upper left part of the abdomen. It is about the size of a fist and is covered with a thin, fibrous capsule. The spleen is made up of a mass of small, irregular nodules called splenic nodules. These nodules are arranged in a regular, repeating pattern. Each nodule is made up of a central artery and a central vein, surrounded by a mass of small, round cells called splenic sinusoids. The sinusoids are lined with a thin layer of cells called endothelial cells. The spleen is an important part of the immune system and is involved in the production of antibodies and the destruction of old, worn-out red blood cells.

#### IV

### Histology of the Spleen

The spleen is a highly vascularized organ, with a rich blood supply. The blood enters the spleen through the splenic artery and exits through the splenic vein. The spleen is divided into two main parts: the red pulp and the white pulp. The red pulp is the larger part of the spleen and is made up of a mass of small, irregular nodules called splenic nodules. The white pulp is the smaller part of the spleen and is made up of a mass of small, round cells called splenic sinusoids. The spleen is an important part of the immune system and is involved in the production of antibodies and the destruction of old, worn-out red blood cells.

## HISTOLOGY OF THE SPLEEN

With so much emphasis placed upon the spleen as either an etiological factor of great prominence or at least involved to a greater or less extent in this malady, it would seem as though grossly as well as histologically there would be very definite and characteristic findings. However, strange as it may seem, there is very little to be seen which varies from the normal. Although some consider splenomegaly as characteristic this is not a constant finding at operation. In some cases the spleen appears to be packed with platelets, many of which are undergoing phagocytosis. In other cases no apparent lesion in the spleen can be demonstrated. Some cases show myeloidization and pulp hyperplasia probably associated with the existing anemia. No constant lesions have been observed in the bone marrow (64).

In cases of enlargement it is probably due to an increase in the lymphoid tissue and to diffuse myeloid metaplasia (Hamilton and Waugh - cited by Lewis) (50) Kaznelson and Suliger found an accumulation of thrombocytes in the spleen, but this has not been confirmed by many subsequent observers. (50). For other changes noted see Case I.

In one of Engel's cases (cited by Ausschütz)(3) the extirpated spleen showed vacuolized endothelia, a hyperplastic pulpa, dilated sinuses, and increased connective tissues.

V

**Conclusion**

## CONCLUSION

As has been shown, the disease entity commonly referred to as thrombocytopenic purpura hemorrhagica appears to be not due merely to a thrombopenia, as was early stated and long held to, rather a phase of a deranged reticulo-endothelial system, than a distinct entity. Whether this is a constitutional diathesis, a toxicity from some infective condition, a hypo-activity on the part of the megakaryocytes due to some myelotoxin liberated by the spleen, a thrombocytolysis by the spleen 'per se' upon the thrombocytes, or an increased permeability of the capillary walls to which the thrombopenia is secondary is the question and problem which faces modern medicine in this particular blood dyscrasia.

Be that as it may, with the introduction of splenectomy we have at our disposal a means of curing many and materially aiding many others who find themselves suffering from this malady. We must not forget, however, that this is not a panacea, as it only is beneficial when used in well selected cases, and it does not attack the basic etiological factor of the disease.

As in the past, again we shall undoubtedly find that history will repeat itself. In the next decade many cases will be splenectomized without rhyme or reason and for a time the use of splenectomy in thrombocytopenic purpura will be discredited. But as time goes on and only properly selected cases are subjected to this procedure, surgery will have offered a

means of combating a serious disease in a way which is as certain as it is spectacular. Although it may not prove to be a cure, it certainly has proven itself already a life saving measure, temporarily if not permanently. "To see a child who is bleeding from every mucous membrane, and from bleeding spots on face covered with all sorts of styptics suddenly stop bleeding when the pedicle of the spleen was ligated, as occurred in our case, is something not to be soon forgotten and hardly credible if not personally observed. The miracles of the scientist are certainly more wonderful than those of the fanatic fakers(72)."

The first part of the report deals with the general situation in the country and the progress of the work during the year. It is followed by a detailed account of the work done in the various departments, and a summary of the results achieved. The report concludes with a list of the names of the staff and a statement of the total expenditure for the year.

**VI** **Case Histories**

The following are some of the cases which have been reported during the year. They are given in the order in which they were reported, and are numbered for reference.

1. A case of acute inflammation of the lungs, occurring in a young man, aged 25, who had been suffering from a severe cold for several days. The patient was admitted to hospital on the 15th of the month, and died on the 20th. The post-mortem examination showed that the lungs were completely consolidated, and that there was a large amount of purulent material in the bronchi.

2. A case of chronic inflammation of the lungs, occurring in a woman, aged 45, who had been suffering from a cough and shortness of breath for several months. The patient was admitted to hospital on the 10th of the month, and died on the 15th. The post-mortem examination showed that the lungs were completely consolidated, and that there was a large amount of purulent material in the bronchi.

3. A case of acute inflammation of the lungs, occurring in a young man, aged 20, who had been suffering from a severe cold for several days. The patient was admitted to hospital on the 12th of the month, and died on the 18th. The post-mortem examination showed that the lungs were completely consolidated, and that there was a large amount of purulent material in the bronchi.

## Case 1

### Essential Thrombopenic Purpura, Treated Surgically.

A girl, aged 16, was admitted to the University Hospital in Omaha, on January 23, 1932. There was nothing of importance in her past history. On January 13, following a throat infection, she first noticed dark red spots on her left forearm. Lesions of the same type appeared on her body and neck the following day. Soon large "black and blue marks" appeared on different parts of the body without any trauma. A hemorrhagic spot made its appearance in the sclera of the left eye on January 19. On January 21 a severe nose bleed occurred which required packing. The only findings of any import on physical examination were numerous petechial and purpural spots on upper and lower extremities, "blood blisters" on the tongue, numerous purpuric spots on the throat, and slight bleeding from the gums.

Blood examination on admission: Hb. 85%, R.B.C. 4,800,000, W.B.C. 9,200 of which more than 60% were granulocytes. Clotting time 10 minutes, bleeding time 20 minutes. The clot was nonretractile. The platlet count varied from 48,000 to 118,000. Between the date of entrance and March 5 she had frequent attacks of epistaxis. The nares were packed many times but only with temporary benefit. Between February 13 and March 5 she received twenty-one injections of adrenalin  $M_{277} 4$  hours and three transfusions with little or no benefit.



She was on general diet, fluid intake over 2000 cc. per day, and cod-liver-oil .5 oz. twice a day. She was also given 20 c.c. of whole blood intramuscularly. The above constitutes the general medical regime in these cases. On March 2 her blood examination was as follows: Hb. 56%; R.B.C. 2,990,000; W.B.C. 6,800; platlets 70,000; differential - polys 67%, segmented 56%, staff 11%, Lymphocytes 39%, Myeloblasts 2%, lymphoblasts 1%, Endothelial Leucocytes 1%, Neutrophilic Myelocytes 1%, bleeding time 20 minutes, pulse 98, blood pressure 106/74 - 32. Ophthalmoscopic examination failed to show the presence of any hemorrhages into the retinae. No improvement resulted from the medical treatment, the patient was becoming very restless and discouraged so splenectomy was considered and on March 5 the spleen was removed. When exposed the spleen was found to be approximately twice normal size - although it had been impossible to palpate it on abdominal examination - it was attached by a broad pedicle with resulting difficulty in excision and hemostasis. It was very friable. The platlet count rose from 48,000 immediately after operation to 222,000 one hour later. The following table gives a graphic comparison of the platlet count throughout her stay in the Hospital:

<u>Date</u>	<u>Platlet Count</u>	<u>Clotting Time</u>	
1-25-32	118,000	11 Min.	7 Min
2-3-32	86,000		
2-4-32	87,000	Clot non-retractile	10 Min. 20 Min.
2-6-32	73,000		
2-8-32	75,000		
2-10-32	66,000		
2-15-32	56,000		
2-29-32	74,000		
3-3-32	78,000	Serum Ca. 10.1 mg. %	8 Min 18 Min
3-5-32	Operation 68,000	7:30 a.m.	
	Ended 48,000	9:15 a.m.	
	9:00 A.M. 222,000	10:20 a.m.	
	200,000	12:15 p.m.	
	150,000	1:30 p.m.	
	86,000	2:30 p.m.	
	88,000	4:30 p.m.	
	88,000	6:30 p.m.	
	86,000	8:30 p.m.	
3-6-32	148,000	8:00 a.m.	
	124,000	12:00 M	
	255,000	7:30 p.m.	
3-7-32	195,000	9:00 a.m.	
3-9-32	200,000		13 min. 3.5 Min Some Retraction of Clot
3-10-32	280,000		
3-12-32	318,000		
3-15-32	320,000		
3-16-32	325,000		
3-22-32	312,000		

The recovery was uneventful. The pathological report on the spleen was as follows: Gross: Weight, 180 grams. Appearance, normal in size and shape. Capsule elevated over lateral surface by the presence of fluid which proved to be principally blood. Sections across the spleen shows nothing unusual in its gross appearance. Impression: Negative Spleen. Microscopic: Each section stained by routine eosin and hemotoxin, by phosphotungstic acid and hemotoxin and by Mallory's aniline bluid. Where present the capsule was thin and showed no particular change. Trabeculae showed no increase in size or

number. The pulp was moderately congested. The germinal centers were rather numerous and quite active. A considerable number of the arteries showed an unusual amount of thickening for a person of this age. Scattered through the pulp were considerable numbers of polymorphonuclears and occasional eosinophilic cells. Careful examination showed also a fair number of young forms of granulocytes showing that granulopoiesis had apparently been proceeding within the spleen. There was a slight increase in the number of phagocytic cells but this was not particularly prominent. The special stains done brought out the fact that there was an increase in the amount of fibrous reticulum throughout the spleen and showed up the thickening of the vessel walls quite strikingly. Diagnosis: Hyperplastic Spleen with Granulopoiesis.

The patient ran rather a septic type of fever from March 5 to March 23. Careful physical checkups failed to isolate the etiological factor for it. No mention of this could be found in the literature with the exception of Nelson (65) who states that especially in early cases of splenectomy the tail of the pancreas was at times traumatized during the operation causing a destruction of fat. Some trauma of the closely associated tail of the pancreas due to the difficulty in removing the spleen in this case may have caused the fever curve noted though I hardly believe it sufficient to account for its extended duration.

The writer had this case on his medical clinical clerk service. It was reported by Rubnitz (74). A letter from this

patient's doctor on February 21, 1933, stated that she had improved steadily since her return from the hospital and was in fairly good health at the present time. She had had a few subcutaneous hemorrhages and had complained of legache. A few months ago she did not feel so well but her doctor believed that this was largely due to too much activity on the part of the patient. She has been in school all year. She probably has not always had the proper nourishing foods as the family are rather poor so that this might be a further contributing factor for her present symptoms. However, this case illustrates the striking result which can be obtained by the use of splenectomy in properly selected cases.

#### Case 2

##### Essential Thrombopenic Purpura, Treated Medically

A girl, aged 5, entered the Mercy Hospital of Council Bluffs, Iowa, on June 11, 1931. Her previous history was negative. Six weeks before admission she began to have nose bleeds and oozing from the gums. A rash was noticed by her parents consisting of elevated red macules and small dark red spots within the skin. There was some itching with the rash. After a period of two weeks the bleeding stopped and the rash faded. One week before admission she had a reappearance of the same condition. On examination, purpuric spots were found in the mouth, under the eyes, and on the dorsum of the hands. Large ecchymoses were found over the inner aspect of the right

thigh and over the vulva. A macular eruption was also found on the trunk, the macules showing surface excoriation.

The blood examination: Hb. 58%; R.B.C. 3,620,000; W.B.C. 6,000 of which 55% were polynuclears. There was some polychromatophilia, and basophilic granules were found frequently in the red cells. The platlet count was 66,000 per c. mm. The clotting time was 5 minutes and the bleeding time 15 minutes. The clot was soft and did not retract in 24 hours.

During her first week in the hospital the temperature was near normal, reaching 100.4 as the maximum. She had frequent nose bleeds, some of them very profuse. Whole blood was given intramuscularly with apparent benefit. New crops of purpuric lesions kept on appearing frequently. On June 28 she became very restless and showed signs of meningeal irritation. A lumbar puncture done on June 29 disclosed a clear fluid, under pressure; 30 c.c. were removed. It contained 50 cells per c. mm., mostly mononuclear. The fluid proved to be sterile. The meningeal irritation subsided but the purpuric manifestations repeatedly came back. Intramuscular blood injections seemed to be of decided benefit in arresting each new flareup. During the month of July she was more than "holding her own." On August 4th she developed a severe diarrhea with bloody stools. Nose bleeds were very frequent. The same treatment was intensified. She commenced to show definite signs of improvement about September 10. The last recorded nose bleed was September 15. From then on she improved steadily and left the hospital on

October 6 in good physical condition. She was seen last by her family physician in March 1932. She has fully regained her health and has not had any sick spell since she left the hospital(36).

### Case 3

A girl, 15 years of age, entered the hospital on October 17, 1931, with a nosebleed of seven days duration. She never had been very strong, had never had any specific diseases of any sort. She had had a nosebleed seven years ago following drainage of an abscess at the angle of the jaw which lasted two days. She had no more bleeding until two years ago when she had a severe nosebleed and spots all over her body. She was in a hospital three weeks and made an uneventful recovery. She had severe hemorrhaging from the gums lasting two days following the extraction of a tooth. Since that time she has had occasional bluish spots on her body and slight bleeding from the gums. Seven days prior to her entrance to the hospital she had a severe nosebleed lasting four days which was finally stopped by a doctor by packing; since that time it has continued to ooze. She had a severe cough and was very hoarse.

Family history negative; no childhood diseases. Always had a poor appetite and ate very little meat.

Physical examination showed a very drowsy, pale girl. There were a few bluish spots on the lower legs and breasts - 12 in all. She was bleeding slightly from gums, and there was

dried blood on the nose. Small red spots were seen on the pharynx and tongue. Temperature 99.3°, respiration 25, pulse 100. Trace of albumine was in the urine. W.B.C. 35,200; R.B.C. 1,746,000; Hb.35%; no platlets were found. Bleeding time 21 minutes. No retraction of clot after 24 hours.

Fifty c.c. whole blood was given intramuscularly. The next day 400 c.c. transfusion was given. She was thought too sick for splenectomy and daily transfusions were advised. The drowsiness was thought to be due to cerebral hemorrhage.

She died October 19th from bronchopneumonia(12).

#### Case 4

#### Essential Thrombopenic Purpura Treated by Mercury Vapor Quartz Lamp (28)

A girl, aged 12, was referred to the New Haven Hospital June 4, 1925, by Dr. William McQuire, with the complaint of frequent bleeding from the nose. The family and personal history were irrelevant.

The present illness commenced three years previously, with occasional slight bleeding from the nose. The bleeding was small in amount, and occasionally came on while the patient was asleep. The bleeding gradually became more frequent and more profuse. One year previously the bleeding came on twice a week. Since that time she had rarely had a free interval longer than three days. She had frequently bled as often as often as twice a day. The bleeding was usually small in amount,

its duration varying from two to fourteen hours.

In January 1925 the patient bled for three hours from a small laceration in spite of attempts to control it by pressure. A few weeks later she bled profusely following the extraction of two lower molar teeth. The bleeding stopped after an intramuscular injection of whole blood.

May 11th epistaxis commenced and continued for the ensuing twenty-nine hours. She was confined to bed for three weeks. She had had two subsequent severe hemorrhages; during the latter she was seen by Dr. McGuire, by whom she was referred to the New Haven Hospital.

She was quite pale and anemic. The nostrils were packed with blood stained cotton. There were numerous petechiae and ecchymoses over the trunk, back, and extremities. They varied in size from minute spots up to ecchymoses 5 cm. in diameter. The physical examination was otherwise negative.

Blood examination showed: R.B.C. 2,500,000; platlets 108,000; W.B.C. 11,600. coagulation time was five minutes and the bleeding time twenty-eight minutes. Complete retraction of the clot required ninety minutes. The diagnosis was idiopathic purpura hemorrhagica.

Treatment with the mercury vapor quartz lamp was commenced immediately. The effect of the treatment is shown in the accompanying table.

February 13, 1925, the patient was able to attend school for the first time in three years. Her general condition had been good. There had been no clinical manifestations



of purpura. The blood platlet count had remained normal. At the present time the blood examination shows: R.B.C. 4,100,000; platlets, 468,000; W.B.C. 9,100; bleeding time 4 minutes; coagulation time 5 minutes; complete retraction of clot, 39 minutes.

Effecto of Mercury Vapor Quartz Lamp Treatment on Blood Findings

Date	Treatment in Min.*	R.B.C.	Platlets	Coag. Time Min.	Bleed. Time Min.	Complete Retract. Min.
6/4/25	4	2,500,000	108,000	5	28	90
6/6/25	4	2,500,000	138,000	5	21	86
6/8/25	4	2,500,000	242,000	4	13	59

The patient had a severe cold and did not come to the hospital for treatments. Jun 13, 1925, she had slight epistaxis.

6/13/25	12	2,200,000	152,000	5	22	76
6/15/25	12	2,600,000	192,000	5	21	75
6/17/25	12	2,900,000	206,000	4	15	59
6/19/25	12	3,200,000	320,000	4	11	51
6/21/25	12	3,400,000	406,000	4	11	48
6/23/25	12	3,600,000	500,000	4	7	41
6/25/25	12	3,900,000	546,000	4	7	41
6/26/25	Treatments discontinued					

\*The figures represent the duration of each exposure as given on the dorsal and ventral surfaces of the body (78).

Case 5.

This case shows the excellent result which may be obtained with splenectomy.

Female, married, age 28, admitted to the hospital on April 20, 1924.

Family History: Negative

Past History: Patient has had typhoid, pneumonia

and measles. Married at 21 years. No children. Had what was supposed to have been a miscarriage at 25.

Present Illness: At the age of 11 she began to have attacks of epistaxis and bleeding from the gums associated with petechiae and ecchymoses in the skin. The patient bruised easily and black and blue spots resulted from slight trauma. At times her ankles were swollen and tender. At the age of 14 she had an attack of headache, dizziness, and a period of unconsciousness followed by internal strabismus of one eye and diminished vision which suggested meningeal and retinal hemorrhages. Catamenia began at 14, always has been excessive in duration and quantity. Sometimes flowed six weeks. Two years ago she consulted a gynecologist who found no pelvic cause for the menorrhagia. A diagnosis of chronic purpura hemorrhagica was made at this time from the blood examinations (Minot).

Blood: April 26, 1923 R.B.C. 2,712,000; Hb 35%; W.B.C 7,600; Diff. polys 75%, Lym. 18%, large mononuclears 7%, blood smears characteristic of secondary anemia. Fragility began 0.42, complete 0.20. Blood platelets strikingly diminished; very few observed (under 1000). Coagulation time normal. Clot rather soft, non-retractile.

For the past year patient had persistent slight nose bleed. Her periods were always prolonged. The anemia and attendant symptoms varied with the amount of bleeding.

Physical Examination: A well developed and nourished female. Heart and lungs were negative. Abdomen soft, not distended. Liver and spleen not palpable. Pelvic Examination

negative.

Skin: Petechiae and ecchymoses especially numerous over legs below knee and on arms in the region of the elbows. Few minute purpuric spots on the eyelids. On thighs and buttocks several black and blue areas 4 to 5 cm. in diameter were observed. Temperature normal, Pulse 85, Urine Albumin 0: Sugar 0; Sp.gr. 1.018; Sediment negative.

Blood: April 22, 1924 R.B.C. 4,000,000, Hb(Tallquist) 75%, Van Slyke method for venous blood 78.5%, W.B.C. 5,800, Diff. Polys 65%, Lym 27%, Large mon. 8%. Stained specimen neg. Bleeding time 40 minutes. Coagulation time - 2 cc. V.bl. 12 minutes. Clot somewhat soft in consistency. No retraction at the end of 24 hours. Blood platelets markedly diminished. The few observed seemed to average larger than normal.

7 Splenectomy: April 23, 1924, a nonadherent normal-sized spleen was removed without difficulty. There was no unusual bleeding during the operation.

Pathological report on spleen:(Dr. J. H. Wright) A spleen 4.5 inches long. On section cut surface red, homogenous, without visible follicles. Tissue little firmer than normal. Microscopic examination shows infiltration of reticulum with small round cells resembling lymphocytes and collections of large lymphocytes in the follicles. No other abnormality recognized.

Convalescence normal. Wound healed by first intention without hematoma.

Postoperative Report: Blood specimen taken one half

hour after splenectomy showed no clot retraction at the end of 24 hours.

Six Hour Report: Platelets did not appear to have changed in number. W.B.C. 12,000

Twenty-Four Hour Report: W.B.C. 16,000. Platelets definitely increased by estimation to slightly below normal.

April 30, 1924: 7 days after operation. Platelets increased to normal. Clot shows firm retraction.

June 16, 1924: R.B.C. 3,900,000; Hb 80%; W.B.C. 62,000 Platelets somewhat diminished below normal; not as high as a week after operation. Coagulation time 8 minutes. Clot retraction normal. Bleeding time less than 3 minutes.

April 13, 1925: Eleven months after operation patient reported in perfect health. Has gained 14 pounds since operation. No bleeding or petechiae. Periods normal in every respect.

Blood Examination: R.B.C. 4,480,000; Hb 85-90%; W.B.C. 7,800, platelets normal or slightly below normal in number. Among them are a few rather unusually large and slightly more granular than normal. Bleeding time normal. <sup>n</sup>Touriquet test negative. Coagulation time 25 minutes. Clot retraction normal.

This patient was last seen in November 12, 1926, two and a half years after operation. The blood examination showed R.B.C. 5,460,000; Hb. 80% W.B.C. 11,100; platelets 200,000. Coagulation time 10 minutes. Clot retraction normal. Bleeding time 5 min. <sup>n</sup>Touriquet test negative. There has been no tendency to bleed since removal of the spleen. Six months after operation two

teeth were extracted without unusual bleeding. The petechiae disappeared one week after operation and have not returned. Two weeks after operation there was a normal period of four days duration, the first normal period the patient ever had. Since then every period has been normal and a chronic invalid has become a perfectly healthy woman. (5Q).

#### Case 6

J.M., female, age 7, admitted to the Royal Waterloo Hospital July 1931 suffering from purpura. On admission great numbers of purpuric spots were seen on the front and back of the patients body, limbs and a few in the mouth. Most of these were small being but slightly larger than a pinhead; there were some large areas of ecchymoses. There was continuous oozing of blood from the gums and both nostrils.

Temperature 100°; pulse 120 - at first was 170; respiration 25. All organs appeared normal, the spleen was not enlarged.

R.B.C. 4,000,000; Hb 70%; C.I. 0.88; W.B.C. 9,500, Polys 69%, Eos. 2%, Bas. 1%, large Hyal. 5%, Lymph 23%.

Patient had usual childhood diseases. No history of previous attacks of purpura; no history of it existing in the family.

After 48 hours the oozing was materially increased, the patient looked pale from the loss of blood. Adrenalin plugging proved useless in controlling the bleeding.

Capillary resistance test was positive in 3 minutes, bleeding time over 1 hour, blood platlets 16,000, clotting time normal.

The condition became distinctly worse and splenectomy was advised. No splenculi were found. Within 10 minutes all bleeding from the mucous membranes had stopped. The patient had an uninterrupted recovery. Three days after the operation the platlet count was 45,000.

The patient was seen 3½ months later and looked the picture of health. There were no further appearances of purpuric spots in the skin or bleeding from the gums or nostrils.

R.B.C. 4,660,000; Hb. 90%; C.I. 0.97; W.B.C. 6,800, Polys 68.5%, Eos. 1.5%, Bas. 1.0%, large Hyal. 5.5%, Lym. 23.5% Capillary resistance test negative after 3 minutes. Bleeding time 2½ minutes.

Report on the spleen: There was a marked deficiency of red pulp and very atrophic looking Malpighian corpuscles, but no other apparent abnormalities. (56).

Report of two cases six years after splenectomy for purpura. Both had severe hemorrhages endangering their lives.

Bleeding time, W.B. 20 min.; E.D. 15 min. before splenectomy. The capillary resistance test was markedly positive in each case. In W.B. the platlets were almost absent, E.D. 60,000, fever on occasions.

Both have been in perfect health since, without any

signs of purpura. Bleeding time normal (3 min) in each;  
capillary resistance test negative in both.

Mrs. E.D. now 35; W.B. 17.

Blood counts 2/3/32 were:

	E.D.	W.B.
R.B.C.	4,200,000	4,400,000
Hb	81%	80%
C.I.	0.9%	0.9%
W.B.C.	8,000	6,500
Polys	68%	63%
Eosin	2%	2%
Bas.	0.5%	1%
L.Hyal	6.5%	8%
Lumph	23%	26%
Platlets	130,000	185,000

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