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ESSENTIAL THROMBOCYTOPENIC PURPURA

WITH CASE REPORT

by

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ESSENTIAL THROMBOCYTOPENIC PURPURA

Essential Thrombocytopenic Purpura Hemorrhagica belongs to one of the heterogenous groups of affections generally classified as belonging to the hemorrhagic diseases; thought as late as the beginning of the century to be dependent upon a hemorrhagic diathesis, -- diathesis referring to a tendency, inherited or acquired to bleed -- chiefly from the capillaries. In order that we may relegate this condition to a distinct category, let us briefly review the more distinctive features of the affection.

Thrombocytopenic Purpura is an affection, proceeding through an acute, subacute, or chronic course, characterized clinically by hemorrhage into the skin and mucous membranes that cannot be controlled by the use of ordinary hemostatics.

The condition is usually not hereditary, but congenital and familial forms have been described. It occurs chiefly in adolescence but may occur at any age. The acute attack may appear, run its course in two or three days ending fatally; or after two to three weeks may eventually cease as abruptly as it began or pass into the subacute or chronic stages.

The condition usually starts with petechial and ecchymotic hemorrhages into the skin, -- over the entire body in more severe cases. These petechiae also occur in the buccal mucous membrane, palate and pharynx. Hemorrhage from the gums, nose, and less frequently the stomach, intestines and kidneys are

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prominent features when present and girls may present menorrhagia or metrorrhagia.

The vulnerability of the capillaries is an outstanding feature since the slightest trauma or static resistance (capillaryresistance test) results in a shower of petechiae. The continued loss of blood results in a marked anaemia and the patient may become weak, incapacitated and bedridden. Remissions are common but exsanguination may eventually result leading to a fatal termination. Fever may be present but usually accompanies the extravasation of large amounts of blood where absorption of the blood clots leads to hyperpyrexia. As Rosenthal (96) describes the typical sufferer --

" - - - - The picture is that of a young ghastly white, blanched faced individual, bedridden, with dried blood crusts on the lips, the teeth covered with clotted remnants of blood arising from bleeding gums; and from the nostrils may be seen extruding, hemorrhagic clots from which oozes fluid blood which trickles down over the lips. - - - - "

Attempts at stopping this bleeding by such ordinary agencies as tamponage, transfusions, calcium salts, thrombakinase, etc., meet as a rule with no success.

Examination of the blood of these patients give certain characteristics of the disease which reveal at least in part, the pathogenesis and individualize it from other forms of purpura.

First, there is a marked dimunition in the number of platelets, usually from the normal of 250,000 to less than 100,000,

more rarely to total absence. It is this characteristic of the disease that gives it the title of Thrombocytopenic purpura.

Secondly, if the blood is permitted to clot, which it does in normal time, the clot remains unretracted instead of shrinking from the walls of the tube as it does normally, exuding serum as the process occurs. This at once differentiates the condition from hemophilia where the clotting time is markedly delayed and imperfectly executed, and though, after the clot forms, retraction occurs.

The third important hematological finding is an increased bleeding time -- the time necessary for capillary bleeding to cease. Normally, a small puncture wound ceases to bleed from one and a half to three minutes; but in this affection may take ten or more minutes before cessation of the capillary oozing.

In other respects the blood picture shows only compensatory changes as a result of the hemorrhage. The leucocyte picture is variable, but a moderate leucocytosis is the rule. The red blood cells are usually markedly diminished along with the hemoglobin, although there is a hypochromia, the color index being less than one. Smears show a tendency for the red cells to be microcytic with occasional normablasts appearing.

The present accepted classification of Purpura is offered by Pratt (92) and Leschke (65).

I. Thrombocytopenic Purpura

A. Essential or primary (Werlhof's disease)

B. Symptomatic

1. In blood diseases (aplastic anaemia, leukemia, pernicious anaemia)
2. Infections (sepsis, subacute bacterial endocarditis, typhoid, tuberculosis, etc.)
3. Intoxications (benzol, arsphenamine, snake venom, etc.)
4. Radiation (X-ray, radium, etc.)
5. Diseases associated with splenomegaly (hemolytic icterus, Gaucher's disease, etc.)
6. Tumors, metastases, sclerosis of the bone marrow.
7. Anaphylaxis
8. Avitaminoses

II. Nonthrombocytopenic Purpura

A. Essential or primary

1. Anaphylactoid (purpura of Schonleim and Henoch, and erythema of Osler.)
2. Miscellaneous (purpura simplex, purpura fulminans, purpura senilis, purpura cachectica, mechanical purpura and familial and hereditary purpura)

B. Symptomatic or secondary Purpura

1. Various chronic diseases (chronic nephritis, cardiac or hepatic diseases)

2. Infections (scarlet fever, typhoid, etc.)
3. Intoxications (benzol, arsphenamine, iodine, snake venom, etc.)
4. Avitaminoses (scurvy)

HISTORY

Essential Thrombocytopenia was first separated from the heterogenous group of purpuras by Werlhof in 1735. Although there have been no controversions of his classical description, still certain additions have been made and other types of purpura described.

In 1883 Krauss (60) reported the observations of Brohm that the platelets were markedly reduced in number at the time hemorrhage occurred. Denys (20) a french histologis by independent work also observed this phenomena, and Hayem (42) not only confirmed these observations but demonstrated the role of the platelets in clotting and the non retractility of the clot in Purpura hemorrhagica.

Duke (26) in 1912 reported that the bleeding time was prolonged in this affection. He also noted that the purpuric manifestations closely followed the platelet count and produced the disease in rabbits by reducing the platelet count with diphtheria toxin and benzol.

In short until recent years, at least; the history of

thrombocytopenic purpura has paralleled that of the platelet -- and were more known of the physiology of the platelet today, more might be known of purpura hemorrhagica. Pure skepticism however, finally backed by experimental and clinical data has reduced the importance of the thrombopenia in this affection.

THE BLOOD PLATELET AND ITS CLINICAL SIGNIFICANCE AS RELATED TO THROMBOCYTOPENIA PURPURA

The platelet in health may be defined as a round or oval disk-like body with an average diameter varying between two and three microns, and with a hyaline cytoplasm containing numerous granules. It was discovered as early as the middle of the last century by Donne and Arnold (23) and called "blood platelets" by Bizzozero (12). The existence of a third morphological blood element has been repeatedly affirmed and denied. Mathews (77) believed the blood platelet to be merely a precipitate formed in altered blood plasma. Roskam (98) on the other hand showed that the particles of precipitated plasma bore no resemblance to blood platelets in size, shape or staining reactions. Bizzozero (13) was the first responsible for asserting their independence as blood elements. Hayem (41) and Kemp (56) thought the platelet to be erythroblastic in origin and this idea ultimately prevailed until 1906 when Wright (117) made a comprehensive study of the platelets, their morphology and relation to the myelogenous

tissue. He found the platelets to correspond closely in structure to the megokaryocyte of the marrow, having a red and purple granular central area surrounded by a hyaline blue border. These megokaryocytes he found to have pseudopods, segmented at intervals with granulated center, having the appearance of a stock of platelets connected to the giant cell. It was his conception that these pseudopods, extending into the marrow sinusoids became broken off, the resultant irregular fragments becoming platelets. This work was confirmed by Bunting (17) and others. Aschoff (3) considers it a closed question. Also, in support of this conception Wright and others point out the parallelism between the number of circulating blood platelets and the number of megokaryocytes in the bone marrow. Both are increased in regenerative states following on hemorrhage and toxemia, in inflammatory states, in myelogenous leukemia (118) in Hodgekins disease, in experimental conditions following the innoculation of diphtheria toxin (24) and antiplatelet serum (67). More direct proof is offered by the observations of Sabin (101) who watched the clumping of granules and fragmentations of the cytoplasm into typical platelets, in megokaryocytes of the bone marrow in vital preparation. In some instances, small plate-like portions of the cytoplasm became attached to the periphery of the cell by a narrow stalk until ultimately the cytoplasm of these cells had become almost completely fragmented into small irregular oval and granular masses lying free in the surrounding medium. Bedson and Johnston (6) on the other hand interpreted

this appearance as degenerative and not productive. After injecting antiplatelet serum they saw no megokaryocytes in the stage of active platelet budding but did note an increased number of megokaryocytes in the bone marrow which is in support of Wright's theory. Le Sourd and Pagniez (67) found that like the platelet, the megokaryocyte produced retraction of the clot, concluding a genetic relationship between the two.

It may be added that although these considerations eliminate the erythrocyte and leucocytes as precursors of the platelets, still evidence is not overwhelming in favor of the megokaryocyte. This is because most of the evidence is based on morphological and tinctorial observations. However it seems reasonable to suppose that the platelet is an independent element and has orgin in the bone marrow if not other potential hemopoetic tissues in time of stress. (23)

Like the red blood cells, however, the platelets are supposedly destroyed by the phagocytic action of cells of the reticuloendothelial system, a system discovered mainly by the efforts of Aschoff (3). In the strict sense, this system is composed of the reticulum cells of the splenic pulp, the cortical nodules and pulp cords of the lymph nodes and remainder of lymphoid tissue, the reticulum cells of the sinuses of the lymph nodes, the blood sinuses of the spleen, the capillaries of the liver lobules (Kupffer's cells) and the capillaries of the bone marrow, adrenal cortex and hypophysis. This destruction capacity has been dif-

ficult to demonstrate on human beings. The spleen constantly contains large numbers of platelets in health and may be seen in the splenic sinuses when a portion of that organ is teased out in a suitable medium and properly stained (6,7). Splenectomy, experimental or therapeutic is followed by an increase in the circulating platelets (6,7) and blood of the cubital vein and splenic artery contain more platelets than blood from the splenic vein (16).

In contradistinction it must be remembered that an increase in platelet count follows other operative procedures, experimental or therapeutic (6,8,7). Furthermore an increase in the numbers of circulating platelets does not always follow splenectomy (15) although Spence (102) believes this is due to a diseased extra-splenic reticulo-endothelial system. One must also consider that the spleen acts as a reservoir for red blood corpuscles and therefore the platelets may be retained for storage purposes and not for destruction. Proof is offered here in that injection of ephedrine or adrenalin which produces splenic contraction is followed by a rise in the number of circulating platelets.

Some investigators claim to have observed phagocytosis of degenerated platelets within the endothelial cells of the spleen. It is interesting to note that when the function of the reticulo-endothelial system is "blocked" such as by the injections of trypan blue, there is an increased number of platelets in the circulation (7, 59, 112). If splenectomy is performed after blocking, the platelet count does not rise further. However,

the blocking is only temporarily effective and it may be that other tissues take over the function of the reticulo-endothelial system.

It is quite probable that a great number of platelets are produced and destroyed each day. Duke (24, 25) found that the total number of circulating platelets could be regenerated within three to five days. Mackay (76) in counting the platelets of thirty health subjects found the count to range from 250,000 to 450,000 with individual variations amounting to as 200,000 in the same day. Thus it would appear that the platelets delicate structure and its ease of degeneration and regeneration, its life is probably short.

PATHOGENESIS

The most thought-provoking phenomena found in this affection is the thrombopenia, not only because it aids in the differentiations from the forms of purpura, but because it supposedly was responsible in whole or in part for the symptomatology and tended to reveal, at least in part, the pathogenesis.

Assuming, as we must for the present, that the genesis of the thrombocyte is from the megokaryocyte of the bone marrow, and its doom in the phagocytosis of the reticulum cells, then it might be supposed the ultimate cause for such depletion either lies in an inhibition of formation or increased destruction at

these two terminals.

Frank (33), professor of Internal Medicine in the University of Breslau in 1915 proposed the theory that this thrombopenia was due to an inhibitory action on the megokaryocytes of the bone marrow by a myelotoxin. Kaznelson (54) on the other hand believed the spleen to be responsible for an excessive destruction of the platelets. In dogmatic fashion he did not believe the condition could exist without the thrombopenia. He boldly executed his theory by removing the spleen on one of his patients with phenomenal results. Frank explained Kaznelson's success by suggesting the spleen to be the source of some toxic agent acting upon the bone marrow. These two theories have added proponents and up to the present day are still antagonistic.

The histopathological reports on autopsied material has certainly added no light to the subject. (83, 80, 14, 78, 89, 102, 106, 36) If permitted to draw any conclusions, whatsoever, from these reports it shall have to be in generalizations for the findings are not constant. In the final analysis, the bone marrow reveals an increased number of megokaryocytes and it is highly probable that this increase represents a compensatory hyperplasia rather than a pathological state. The spleen, on the other hand, gives a rather constant picture of splenitis, acute or chronic.

Experimental and clinical data, however, do not conform with the theory that the platelet deficiency is the sole cause

of the purpura. Of primary evidence of this, we have the massive amount of data compiled by Cole (18), Le Sourd and Pagniez (69), Ledingham (62, 63), and Bedson. It was Bedson who finally perfected the antiplatelet serum so that it produced no hemagglutination, and the new antisera, when injected into experimental animals was capable of producing purpura. But the pertinent point of Bedson's experiments was that agar serum injections, which produced a marked thrombocytopenia did not produce purpura unless anti-red cell sera was added. He thus concluded that two conditions were necessary for the production of purpura.

1. Removal of the platelets from the circulation.
2. Toxic injury to the capillary endothelium.

Clinically, the return of a thrombopenia after splenectomy without a return of the purpuric manifestations in evidence that the thrombopenia is not the sole factor. Furthermore, though the purpuric symptoms closely parallel the platelet count in most cases, this is not invariable (82, 113, 102). In aplastic anemia, where all cellular elements of the blood are all decreased, along with the platelets, purpura does not occur. Mackay (76) demonstrated that prolonged bleeding could occur in the presence of a normal platelet count, and normal bleeding time and the absence of hemorrhage in the presence of a diminished platelet count.

In the early experimental work it was difficult to reduce

the platelet count without also injuring the capillary endothelium. As has been pointed out, Bedson (9) could considerably reduce the platelet count with agar serum, but not produce purpura without damaging the endothelium of the capillaries. Whittkower (114) by means of X-ray, reduced the platelet count to 19,000 without producing purpura. Pulvertoft (93) on the other hand, by injecting streptococcal toxin into rabbits produced a picture of fulminating purpura without any diminition in the platelet count.

Kaznelson (55) and Rosenthol (96) attempt to explain purpura in the presence of normal platelet counts by suggesting a qualitative defect in the platelet and point out the variation in morphology of the platelet in this condition. Mackay (76) however could find no evidence of this. He believed the platelet reduction to be on a toxic basis, perhaps from a metabolic or secretory deficiency, as in pernicious anaemia where the platelet count is greatly increased on liver therapy. According to this theory the platelet reduction is merely a superimposed phenomena -- and is probably due to an interference with normal platelet formation.

Tidy (108, 109) believes the platelet reductions to be secondary to endothelial damage and hemorrhage; yet he fails to explain why in other conditions such as scurvy, where damage to the capillary endothelium exists, there is no pronounced thrombocytopenia.

Evans (28) recording the platelet count following splenectomy in a case of thrombocytopenic purpura found that it took ninety

days for the count to return to normal limits. He believes two factors are responsible:--

1. The reticulo-endothelial system taking over the function of the spleen.
2. Some toxic agent removed by remaval of the spleen.

However the results of splenectomy are not so constant that Evans' theory is applicable to all. Piney (91) divides the essential thrombopenia purpuras into three groups, those in which there is:

1. A rapid rise in platelets to a normal level which is sustained.
2. A rise after operation followed by return of purpuric symptoms.
3. No change in the platelet count though there was a marked thrombopenia before operation. These cases often show clinical improvement in spite of the platelet count.

It is quite obvious that the role played by the spleen varies in these three groups. In the first group, the spleen is evidently responsible for the low platelet count (either because of marrow inhibition or increased destruction) and the purpura. Splenectomy would be specific in such a condition. In the second group, the fall of the platelet count to former levels might be explained on the basis that the rest of the

of the reticulo-endothelial system has compensated for the loss of the spleen. In the third instance, the spleen was probably not the seat of the trouble.

Lescher and Hubble (66) believe that the purpuras should be divided into two groups depending on the cause:-

1. Deficient production of megokaryocytes
2. Defective separation of the platelet from the megokaryocyte.

Possibly a third cause might be mentioned, mainly the excessive destruction by the spleen.

De Sanctis and Allen (21) believe that some agent activates the reticulo-endothelial system to unusual thrombolytic activity. The fact that splenectomy in acute cases has no effect bears out this opinion. They believe recurrences due to the fact that the reticulo-endothelial system has partially taken over the function of the spleen following extirpation of that organ.

Askey and Toland (4), in regards to the rapid rise in the platelet count following splenectomy, suggest the presence in the blood stream of a toxin which tends to lower capillary resistance yet is so transient in its effects that a continuous supply is necessary for sustained action. They believe the spleen to be the source of the supply since that organ is the only one to be cut off from the general circulation in thereapeutic splenectomy. Yet many cases showing clinical improvement with relief of homorrhage

after surgical removal of the spleen, fail to show improvement of the blood picture, the platelets remaining low, the bleeding time prolonged, the tourniquet test positive and the clot non-retractile. They thus conclude that the whole reticulo-endothelial system is involved and that the removal of the spleen is only a quantitative reduction in the extent of the disease.

Whatever the etiological agent may be, it still remains obscure, although recent advances may clarify the situation to quite an extent. Whipple (113) and Tocantis (110) are impressed with the fact that infection often precedes the onset of purpuric symptoms and Stewart (105) believes that bacterial toxins stimulate the reticulo-endothelial system to increased destruction of the platelet. These observation have led to the eradication of all foci of infections as a supportive measure, an important adjunct to all therapeutic procedures.

The most enlightening work however has just been received from Troland and Lee (111) who took the spleen of three patients with Thrombocytopenic purpura directly from the operating room, chopped each into small pieces and placed them in acetone reagent. The supernatant fluid was drained off after a few weeks, the residue shaken with distilled water and filtered. Injection of the filtrate into rabbits in all three cases produced a reduction in theplatelet count from 650,000, 640,000, and 610,000 to 58,000, 70,000 and 100,000 respectively in twenty four hours. Repeated injections caused the platelet count to remain low but

no purpura was evident. The red and white cell counts were not appreciably changed. They suggest the name "thrombocytopen" for the unknown active principle. As a control, four organs from non-purpuric patients including the spleen of a patient with hemolytic icterus, were treated likewise but produced virtually no decrease in the platelet count. The report, however, is preliminary and will be followed by a more complete report in the near future.

BLEEDING TIME AND CAPILLARY PERMEABILITY

With such pertinent facts as supplied by Bedson (9) we know that the platelet alone is not responsible for the purpuric manifestations, -- and this will be further substantiated in the forthcoming discussion. We must assume that the toxic agent acts directly upon the endothelial lining of the blood vessels. As we have stated, Pulvertoft (93) has shown that a fulminating purpura can be produced inthis way without any thrombocytopenia.

Duke (24) pointed out the relation of spontaneous capillary hemorrhage, bleeding time and the number of ciruclating platelets. Accordingly, he found that the bleeding time and the purpura were inversely related to the number of platelets. He discovered that purpura rarely occurred when the platelet count exceeded 40,000. It was a natural assumption to regard the thrombocytopenia as the cause of the purpura. Evidence of this relation-

ship exists in other diseases such as acute leukemia, pernicious anaemia, diptheria, hemorrhagic small pox, and in such experimental work with diptheria toxin (5, 53) benzol (7) and anti-platelet serum (10). Duke believedthe platelets adhered to the edges of the injured endothelium, thus closing the wound and preventing hemorrhage.

Frank (33) in 1913 stated that a normal intact capillary will not permit diapedesis or hemorrhage with resultant purpura. He believed that there must be some damage, or at least an increased povosity of the capillaries. The capillary resistance test of Hess (43) impresses us with the same idea. Normally after a tourniquet has been firmly applied to the upper extremity so that the venous return but not the arterial supply is obstructed, petechiae do not appear distal to the tourniquet. In thrombocytopenia, however, small capillary hemorrhages appear below the point of constriction. Such bleeding is produced by an increase in the venous pressure.

The pathology is not definitely known. Rouget (99) in 1873 first called attention to the existence of peculiar contractile cells on the walls of the capillaries. Aschoff (3) denied that these cells were contractile but stated they were part of the reticul-endothelial system. Whipple (113) states it is conceivable to suppose, since the cells of Rouget belong to a system stimulated by the same agent as other parts of the reticulo-endothelial system, then these cells might be responsible for

the disturbed permeability of the capillary walls, allowing the passage of blood into the tissues. Aschoff believes that there is some softening of the intra-cellular cement substance.

Bedson (9) describes the typical vascular lesion present in all cases of Thrombocytopenic purpura. Histological examination revealed changes in the vascular endothelium similar to those described by Findley for experimental scurvy; namely a swollen edematous appearance of those cells. He placed the mesenteric vessels of an anaesthetized guinea pig under observation and experimentally produced purpura by innoculation of anti-platelet serum. Within a short time hemorrhages were observed under the microscope along the course of the vessels, yet there was no appreciable slowing of the current nor plugging of the vessels. The majority of the hemorrhages appeared to be an exaggerated form of diapedesis. Bedson suggests that the hemorrhage probably would not occur with an adequate number of platelets for the platelets and the white blood cells flowing at the periphery would block the escape of the centrally moving red cells. Were the blood stream appreciably slowed by the swollen endothelium it might be argued that the platelets, adhering to to the lining cells would eventually plug the vessels and lead to its rupture. However there is not much evidence to support this view.

Kemperer (57) did find this to be the case in four cases of clinically acute thrombocytopenic purpura. The vascular lesions

appearing in the capillaries and smaller arterioles. The affected vessels were dilated and the lumen completely occluded with granular thrombi. The lining endothelium at these sites showed swelling and proliferation and in many places the thrombus showe actual invasion with proliferating endothelial cells resembling houng fibroblasts. Various stages of organization could be seen in the same organ, some thrombi were still mural. They believed the vascular thrombosus occurred in repeated attacks and the endothelial proliferation to be a response to the thrombolytic occlusion of the lumen. In ten other cases of acute and seven of chronic thrombocytopenic purpura no such pathology could be observed. These investigators believe the depletion of platelets to be due to the vast number composing the thrombi, a theory that is similar to that of Tidy (108). It was interesting to note that a brother of one of the four cases cited above also had purpura, clinically identical but no such pathology was observed.

The vaso-constriction action, concomitant with hemorrhage, has long been known. As early as 1869, Ludwig (75) and Schmidt, perfusing the muscle of a dog with blood serum, encountered an unexpected resistance to the flow of defibrinated blood. Early investigation believed the effective element to be epinephrin. O'Connor (84) however found that the action of the serum was not the same as for epinephrin and that the stimulating agent entered the blood during the process of clotting. Janeway and Park (49) confirmed this. O'Connor (84) also mentioned that extracts of

of platelets produced a powerful vaso constrictor action on the arterial ring. Stewart and Tucker (103, 104) appended a foot note to this effect, for it fitted in with their findings, offering a relation between the vaso constricting action of the serum and the formed elements of the blood. These investigators found that the pressor action was due to a substance formed when the formed elements of the blood were shed. This change occurred concomitantly with some of the changes preliminary to clotting and not as the fibrinogen was converted into fibrin. Their results also implied that the vaso constrictor effect of the serum was an important adjunct in the role of sealing of important vessels. Janeway, Richardson and Park (49) verified the findings of O'Connor that the extracts of platelets produced a powerful vaso constriction action but could produce no such effect with the extract of erythrocytes or leucocytes. Since the circulating plasma of normal animals produce no vaso constriction and since plasma can be taken from the vessels without vasoconstriction occurring, they were led to conclude that the substance responsible was liberated after the plasma escapes from the blood vessel.

Hirose (44) found that the effect of defibrinated blood on the carotid artery was roughly proportional to the platelet count. In cases where the platelet count was extremely low, the defibrinated blood had little or no vaso constricting property. That there is a relation between capillary tone and the blood platelets seems to be true. Furthermore, loss of capillary tone leads

to increased capillary leakage. We may thus conclude that any great quantitative or qualitative change in the platelet preventing the supply of vaso constrictor substance would encourage the loss of vasomotor tone and the production of capillary hemorrhage.

McLean (78) on the other hand, states that the severity of capillary bleeding is not in proportion to the number of platelets, severe bleeding occurring in the presence of platelet counts varying from 10,000 to 140,000. He believes the lowered capillary resistance to be due to the activity of the same agent responsible for the change in quality or number of platelets and also for the irritation of Rouget's cells and the softening of the intracellular cement substance of the capillary walls. Mackay (76) fully agrees with McLean due to variations in his own cases where no hemorrhage occurred when the platelet count on two patients were 14,000 and 40,000 respectively. The constancy with which the low platelet count parallels the bleeding time is due both to vascular permeability and platelet reduction. Leschke (65) states that the contraction of the capillaries is absent or diminished in purpura and Mackay thinks that the hemorrhage is due tothe inability of the walls to contract. Bermuth (11), on the other hand, observed normal capillary response in this disease. It is quite obvious that more experimental work will have to be done on this point before its relative importance can be properly evaluated.

CLOT RETRACTION

Normally when whole blood is taken from a vein before it has mixed with any tissue juices, and allowed to stand in a container, it becomes gel-like in consistency after two to six minutes so that the container can be inverted without spilling the blood. Soon the agglutinum begins to retract from the edge of the vessel, exuding serum as the process occurs. Under standard conditions, this process is complete in eighteen hours.

In essential thrombocytopenic purpura hemorrhagica, the clotting time is normal, but retraction is either delayed or does not occur. The normal clotting time and failure of retraction was first noted by Hayen (42) in 1896. Glanzmann (38, 39), LeSourd and Pagniez (70) believed a platelet ferment to be the cause because platelets were the only blood elements to undergo decompostion during the process of coagulation. Frank (34) thought retraction to be due to shrinkage of the platelets. The process of coagulation is an intricate phenomenan and not clearly understood in spite of wast amounts of research. At present Howell's theory (45) of coagulation is accepted. Briefly, the theory states that the circulating plasma contains three essential factors of coagulation, fibrinogen, prothrombin, and calcium salts. Coagulation is prevented because prothrombin is kept inactive, even in the presence of the calcium ion by an inhibitory substance, heparin. When

blood is shed without coming into contact with the tissue, the platelets degenerate and liberate a thromboplastic substance related to cephalin which neutralizes heparin and allows prothrombin to be converted into the active principle, thrombin. The fibrinogen then reacts with the thrombin to form a firm deposit of fibrin crystals which in vivo prevents further escape of blood.

Reuben and Clemens (95) state that blood deprived of its platelets content will not clot unless tissue extracts or platelets are added. Brill and Rosenthal (14) believe that the failure of clot retraction is due to a qualitative change in the platelet.

The failure of syneresis to occur has also been noted in pernicious anemia, aplastic anemia, and Banti's disease (97) where the platelets fall below 100,000. If a splenectomy is performed, the clot retracts coincident with the platelets increase (19, 107, 84).

It has been experimentally shown that retraction occurs in proportion to the number of platelets in blood plasma (70) or in hydrocoele fluid (71). Furthermore in animals that have been deplatetized there is a failure of clot retraction until the platelet count returns to normal (62, 64), then two agents which modify or destroy platelets likewise affect syneresis (70, 72).

Wide variations in relation to retraction and the platelet

count have been clinically reported (113, 19) but this variation is probably due to errors in laboratory technique. This is largely due to an adhesive property between the clot and its container preventing retraction when, under standard conditions, retraction would occur (46, 90). Mackay (76) believes this relation of platelet and retraction doubtful due to variance in his own cases.

Archard and Aynand (2) found that blood which was deplatetized with gelatin, gum and lecithin injections, retracted. This has also been noted after deplatelization with peptone and thymus nucleic acid (90).

Le Sourd and Pagniez (73) found that a change in the hydrogen ion concentration, by addition of calcium, caused retraction which was known to be absent at the time of experimentation, demonstrating that the plasma is an important factor.

Howell, (46) found that when the blood was increasingly alkalinized, a point could be reached when the fibrinogen became transparent yet which would not retract. Furthermore free oxylated plasma or pure fibrinogen showed marked retraction properties when thrombin was added and Howell believes the platelet may be a source of this material.

Mackay (76) believes that the retraction property of blood is inherent in the plasma, and that the platelet only augments this property. Thus we must assume that where no retraction occurs, there is a fundamental alteration in the plasma. Tocantis (110) is quite in sympathy with this theory and believes that syneresis

is not dependent upon the platelet although this element promotes retraction and prevents adhesion between clot and container.

DIAGNOSIS

To mention that the diagnosis should be assured before the more radical types of treatment are resorted to, perhaps seems inconsequential, yet the mistake has been made more than once of subjecting a patient to splenectomy when the affection turned out to be a myelogenous leukemia in an aleukemic phase. The differential diagnosis should never be lightly considered. Chiefly among the affections to be eliminated are:-

1. Hemophilia
2. Aplastic anaemia
3. Leukemia

The diagnosis from hemophilia can be made on the basis of non-traumatic origin of bleeding, lack of familial history, normal clotting time, prolonged bleeding time, absence of clot retraction and thrombocytopenia. In acute aplastic anaemia all elements of the blood are depleted. There are no nucleated reds and there is a decisive leukopenia whereas in the thrombocytopenic purpura, aleucocytosis is the rule. The chief diagnostic point in leukemia is the presence of young white cells in the blood.

Not only the diagnosis of typical cases but also the recognition of a typical case will give the practitioner much diffi-

culty. Recognition of new groups within the general heading of Essential thrombocytopenic purpura is to be expected at a future date. Some cases appear to be hereditary or familial. Prolongation of the bleeding time without paucity of the platelet has been described. Further study will be necessary before a correct subdivision can be accurately made.

TREATMENT

The types of treatment for thrombocytopenic purpura are many and varied. To a great extent therapy depends upon the phase and severity of the disease, the age of the patient, degree of exsanguination, etc. For practical purposes we may divide the treatment into conservative and radical, i.e., non-operative and operative.

Transfusions seem to be the most popular type of conservative therapy. Larrabee (61), Jones (52), Moffat (81) and Tacantis (110) report cases where repeated transfusions have produced remissions without subsequent recurrences. Such treatment, however, is far from being uniformly successful, but when effective, controls hemorrhage, increases the red cells and platelets and in general is a valuable supportive measure even when not curative.

Other conservative mthods have been tried with varying degrees of success. Jones (52) recommends the administration

of calcium or parathormone. Dixon (22) reports four cases treated successfully with autogenous blood. Liver therapy has been tried successfully with Jacob (47) and Jones (52). Pancoast, Pendergrass, and Fitz Hugh (85) believe that roentgen rays should be given for temporary relief. Rudisill (100) treated 6 cases with X-ray producing rapid relief in each case and no remissions. Mettier, Stone, and Perviance (79) treated five cases with X-ray and found the platelets to rise as much as 250,000 or 500,000 in nine days. McLean, et. al. (78) treated six cases with ultra violet. Four of the cases were chronic and two, clinically acute. Of these six, one died due to inability to find a donor for transfusion; but the rest suffered no recurrences during the entire period of observation (eight months to five and one half years), and the platelet count remained within normal limits in three cases for over two years. Jones (51) and Giffin (37) also recommends its use and believes that a high vitamin B and D diet should be administered to these patients. Thromboplastin has also been tried therapeutically (51) and non-specific protein shock with horse serum, milk and human blood have been tried with a lesser degree of success (30).

The use of anti-venom as a therapeutic agent has also come into limited use by certain clinicians. Taylor (107) reported rapid recovery in four of five patients treated with antivenom, and recommends its use in fulminating cases where splenectomy carries such a high mortality rate. Peck (87) expresses the

view that the action of antivenom is on the capillaries and the mechanism of coagulation. If this is so, the effect should be (and is) temporary, and thus like other forms of conservative therapy is not curative but produces remission of symptoms. Peck and Rosenthal (88) treated 13 cases with antivenom and found nine cases showed improvement, with symptomatic and hemotological relief in four. Four cases showed only slight temporary relief. Rosenthal (88) however, believes that the remissions may be spontaneous. He concludes that this type of therapy is of aid in shortening the period of convalescense in patients in the early stages of a remission. Greenwald (40) had similar success and recommended it along with transfusions to be used before splenectomy and in cases where operative procedure did not actively curtail the hemorrhagic diathesis.

Splenectomy has long been the treatment of choice in this affection since Kaznelson first achieved his brilliant results. Eliason and Ferguson (27) in 1932, reporting two hundred thirteen cases in literature, including those compiled by Whipple (113) and Spence (102) and five of their own, give the following results.

The total mortality rate prior to 1932 was 13.1%, a reduction of 7% for the figures given prior to 1928. There were 81.2% of the operated cases cured or definitely improved.

Among the acute cases, there was a total mortality rate of 34.3%. However, the figures for the period between 1928 and 1932 were only 13.6% in comparison to that of 83.3% reported by

Spence in 1938.

In the chronic cases, there was a mortality rate of 7% for the whole series against a 11.8% mortality rate reported by Spence. In these cases there was cure or improvement in 88.1% of the cases.

Among the acute cases all but one died on the operating table following operation. In all probability these patients were well exsanguinated at the time of operation. The phenomenal decline in the mortality in these cases is explained by Eliason and Ferguson as due to earlier surgery and more adequate preparation before surgery.

The above statistical data proves conclusively that the chronic cases are better surgical risks than the acute ones. But just what to call a chronic or an acute case of purpura hemorrhagica is often difficult to ascertain. Whipple (113) states that a case is chronic when the patient has recurrent attacks of bleeding from the gums and nose, petechiae and ecchymoses, menorrhagia in women, but no bleeding into the alimentary canal or parenchyma of the internal organs. Because splenectomy produces a cure in these cases, he believes they represent a true disturbance of the reticulo-endothelial system -- a system in which the spleen plays a major role.

Spence (102), Fitz Hugh (31), and Jones (50) as well as others are in agreement with this theory. Williamson limits operation to those cases in which the patients development and health are interferred with or where the bleeding is so profuse

as to endanger the patients life.

Giffin (35) offers the following results of splenectomy at Mayo Clinic and draws his own conclusions. He believes that chronic cases of mild severity should be treated symptomatically, with elimination offoci of infection, diet, iron and transfusion if necessary. In twenty five cases of moderate and severe chronic cases operated at Mayo's, the mortality rate was zero. But recurrences occurred in seven cases which, for the most part, were mild. In nine cases of acute exaceriations of chronic purpura, there was only one death, and that due to an intracranial hemorrhage before operation. All had mild recurrences but are well. Giffin believes the patient should be given every opportunity for spontaneous remission before splenectomy is resorted to. He believes it doubtful if patients, showing acute exacerbations can be cured by splenectomy if they do not respond to transfusion. On the other hand if transfusions do not produce a response, operation should not be delayed longer than is necessary. In the acute cases he believes that splenectomy is only indicated when, in spite of transfusions, etc., that patient is on a down-hill course. This is probably the general attitude at present among medical men. However, the trend is definitely toward splenectomy regardless of the chronicity.

CASE REPORT

A white schoolgirl, age nine, entered the University Hospital on February 28, 1938. Two weeks prior to Christmas, 1937, while convalescing from a sore throat and cervical adenitis, small, slightly elevated black spots spontaneously appeared on the hips, arms, and legs. These areas gave the appearance of bruise marks although there was no history of trauma. A few days before Christmas the patient had three spontaneous nose bleeds of moderate severity and another on Christmas day, which lasted several hours and left her pale and weak. Her physician, seeing her for the first time, ordered her to bed and gave her a high vitamin C diet, believing the condition to be scurvy. She improved considerably until January 3, 1938, when the bluish spots reappeared spontaneously over the entire body and the temperature rose to 102 degrees. On January 17, she had another severe nose bleed and fainted. She was immediately transfused. She suffered three recurrences the following month, including hemorrhage from the nose and gums, and a transfusion was the method of treatment in each case. Ordinary hemostatics seemed useless in attempts to curtail the hemorrhage. On February 21, she received the fourth transfusion. Since that date she has shown considerable improvement, the skin has cleared, and she has had no more active bleeding. She was sent into the University hospital by her physician with a diagnosis of Essential Thrombo-

cytopenic purpura.

No hereditary nor familial relationship could be found in the history. She had had pneumonia, small pox, measles, mumps, chicken pox, pertussis, and frequent sore throats accompanied by cervical adenitis.

On entrance, the patient was well nourished but very pale. There were blood crusts in the external nares and the nasal mucous membrane was dry and crusted. The lips were pale and the gums had a purplish tinge. There were two carious teeth. The tonsils were large and moderately inflammed and there was a moderate bilateral submaxillary adenitis. The lungs were clear. A faint systolic murmur was audible over the apex of the heart and there was a questionable enlargement of the heart to the left. The spleen was not palpable but percussion showed it to be enlarged and subsequent X-rays of the abdomen gave the impression that it was twice normal size.

There was no active bleeding. A bluish discoloration over the right iliac crest measured 10x4 cm. There were also ecchymotic spots in the right anti-cubital fossa and on the right thigh. The tourniquet test was strongly positive, the bleeding time prolonged--($7\frac{1}{2}$ minutes), the platelet count only 96,000, and no clot retraction in the face of a normal clotting time of ten minutes.

Dr. Hamilton thought it advisable to pursue a conservative course to allow for observation and thorough hematological studies.

The patient was placed on a general diet and givenan additional six ounces of orange juice a day.

As can be seen from the accompanying table, the platelet count slowly fell to the low level of 40,000, yet no bleeding occurred. The tourniquet test was strongly positive, however, and the least trauma produced ecchymosis. On March 11, she was transfused with 300 cc. of citrated blood, but though the red cells showed a substantial increase, the platelet count remained unaltered and the bleeding time prolonged. On the 16th, reticulogen was began and following a latent period of three days the platelet count jumped to 102,000. This rise in all probability should be interpreted as a spontaneous remission for a week later the count dropped to a new low level of 32,000. On the 26th, she had a nasal hamorrhage and vomited twice, the vomitus containing bright red blood.

On March 30th, following surgical consultation it was decided to make one more conservative attempt,--this time with moccasin venom. After the first administration the bleeding time increased to two hours, but the platelet count remained around the same precarious level. The following day she had a slight nasal hemorrhage and there was a persistent oozing until April 3, when she was again transfused andthe snake venom discontinued. There has been no bleeding since transfusion. She will probably be transfused once again and then splenectomy will be performed.

The case is quite typical of an acute thrombocytopenic purpura which has now passed into the chronic phase. It is this type of case most amendable to treatment by splenectomy, and since her physical condition is excellent at present, operation should result in marked relief or cure.

DATE	PLATELETS	W.B.C.	R.B.C.	Hb %	Ret.%	BLEEDING -- TIME	CLOTTING -- TIME
2-28-38	96,000	---------	----------	---	---	7½ minutes	10 minutes
3-1-38	102,000	6,900	2,280,000	36	---	----------	----------
3-2-38	98,000	9,850	---------	---	---	7½ minutes	----------
3-3-38	91,000	10,050	---------	---	2.7	----------	----------
3-4-38	75,000	7,200	2,440,000	32	2.2	----------	----------
3-5-38	68,000	8,500	---------	---	2.1	----------	----------
3-7-38	66,000	-----	---------	---	---	----------	----------
3-8-38	68,000	-----	---------	---	1.8	8 minutes	28 minutes
3-9-38	64,000	8,300	---------	---	2.3	----------	----------
3-10-38	54,000	-----	---------	39	---	----------	----------
3-11-38	Indirect Blood Transfusion---300 cc. Citrated Blood						
3-12-38	54,000	8,550	3,580,000	47	2.9	----------	----------
3-14-38	54,000	------	---------	---	1.7	----------	----------
3-15-38	46,000	------	---------	---	1.2	----------	----------
3-16-38	46,000	7,650	3,900,000	52	.8	----------	----------
3-16-38	Reticulogen--½ cc / day / hypo started.						
3-17-38	40,000	-----	---------	---	---	9½ minutes	----------
3-18-38	42,000	10,550	3,350,000	58	.8	----------	----------
3-19-38	102,000	8,850	3,550,000	56	.8	----------	----------
3-20-38	-------	7,350	3,320,000	54	---	----------	----------
3-21-38	98,000	7,200	3,270,000	50	.8	----------	----------
3-22-38	126,000	-----	---------	---	.9	----------	----------

DATE	PLATELETS	W.B.C.	R.B.C.	Hb %	Ret.%	BLEEDING -- TIME	CLOTTING -- TIME
3-23-38	36,000	------	---------	---	1.0	----------	----------
3-24-38	38,000	6,850	3,490,000	---	1.0	----------	----------
3-25-38	38,000	------	---------	---	1.7	----------	----------
3-26-38	32,000	------	---------	---	1.3	----------	----------
3-27-38	------	13,4000	3,470,000	---	---	----------	----------
3-28-38	36,000	-------	---------	---	1.3	----------	----------
3-29-38	38,000	-------	---------	---	1.2	----------	----------
3-30-38	Reticulogen discontinued. Moccasin Venom began.						
3-30-38	36,000	12,200	3,410,000	48	---	2 hours 1½ min.	11 minutes
3-31-38	40,000	------	----------	---	---	16½ minutes	7½ minutes
4-1-38	42,000	------	----------	---	2.4	13½ minutes	17½ minutes
4-2-38	------	------	----------	---	1.5	----------	4 minutes
4-3-38	Indirect Blood Transfusion -- 350 cc. -- Citrated Blood						
4-4-38	54,000	14,200	4,310,000	68	---	14½ minutes	----------
4-5-38	56,000	------	3,370,000	64	3.1	7½ minutes	5½ minutes
4-6-38	88,000	13,600	3,280,000	65	2.9	5½ minutes	4 minutes
4-7-38	76,000	------	---------	---	2.9	7½ minutes	4 minutes

ADDITIONAL LABORATORY DATA

Sedimentation Rate: 24 mm. in 1 hour and 23 minutes.

Fragility Test: From .4% Na Cl to .18% Na Cl.

Kahn and Kline (diagnostic): Negative

Differential Blood Count: Segmented forms----------39
Staff---------- 2
Eosinophiles---------- 1
Monocytes----------10
Lymphocytes----------48

*Subsequent differentials, in search of young white cells not recorded. No immature cells found.

Blood Smear: Reveals variation in size and shape of the red cells with a preponderance of microcytes; moderate achromia and slight polychromasia.

No abnormal white cells.

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