Thrombocytoasthenia and Thrombocytopathia—Old Names and New Diseases

By H. Braunsteiner and F. Pakesch

Among hemorrhagic disorders, those due to qualitative platelet defects have remained most obscure even though they were described very early. This obscurity reflects the lack of precise knowledge of the normal function of thrombocytes. Platelets are cytologic objects with interesting chemistry, and only recent advances in electron microscopy and in protein chemistry have revealed some basic facts on their role in normal and pathologic conditions.

A beginning in the study of qualitative platelet diseases was made by Glanzmann in 1918. He described several cases of purpura, some with thrombocytopenia, and also some with normal numbers of platelets but defective clot retraction. His work was criticized severely, and barely accepted outside the German-speaking countries. These criticisms, offered from valid reasoning by excellent specialists such as Quick and MacFarlane, have proved, at length, to be not justified. Glanzmann's concept of thrombocytoasthenia was initially based on "intuition," but this disease does exist and, as we shall see, its name is singularly evocative.

Further impulse to the question of qualitative platelet diseases was given about 15 years later by Willebrand and Jürgens. These authors described a familial disease on the Åland island next to Finland, characterized by purpura and extremely prolonged bleeding time with normal clot retraction. It was defined as thrombocytopathia.

A certain number of cases which could be related to "thrombocytoasthenia" or "thrombocytopathia" were reported in the following years, but further progress was not made before 1948 when Bernard and Soulier described a case of thrombocytopathia with giant, lymphocyte-sized platelets and strongly defective prothrombin consumption. Later, they proved that this case also had a defective thromboplastin generation by platelets.

Since 1952, a disease was defined in this laboratory, based on electron microscopic examinations, which is characterized by the inability of platelets to form pseudopods and especially to spread in contact with a wettable surface. These cases show also either a manifest or a latent defect of clot retraction as revealed by thrombelastography. We found it logical, therefore, to call them thromboctoasthenias.

By cooperation of several research laboratories in Austria, Switzerland, France, Germany and on the Åland islands, and with the financial aid of the Austrian State Board of Education and the Hoffman-La Roche Corporation in Basel.
Switzerland, we have been able to examine or to reexamine a considerable number of patients with presumptive qualitative platelet diseases. A short account of the result of the analysis of 23 cases, a provisional classification, and a basis of pathogenesis will be given below. First, however, we shall briefly try to review the functional morphology and hemostatic factors of platelets, as far as they are necessary for a correct understanding of pathologic processes.

The normal circulating platelet is round or oval, but as soon as it comes in contact with a wettable surface numerous pseudopods form after a few seconds and within a short time the hyaloplasm spreads thinly, whereas the granulomer coalesces to a central pseudonucleus (fig. 1). This behavior is not basically influenced by addition of anticoagulants and it is also found when washed platelets are suspended in isotonic saline or plasma substitutes. Pseudopod formation and spreading can be diminished or abolished, however, by changes of the viscosity of the medium, by addition of strong platelet agglutinins, by addition of cocaine and, finally, by an inherent defect of platelets to be considered below.

Pseudopod formation and spreading represents the first line the adhesive faculty of platelets.

This adhesive faculty has to be strictly distinguished from aggregation or cohesion, i.e., the ability of platelets to stick one to another. Aggregation can be diminished or abolished by addition of anticoagulants or by suspension of isolated platelets in saline. It can be strongly enhanced by addition of thrombin or fresh serum (viscous metamorphosis) which leads also to consecutive disintegration of platelets (figs. 2 and 3). In practice, adhesiveness and aggregation frequently go hand in hand, for instance during formation of thrombi. Conventional methods for measurement of “platelet adhesiveness” in fact measure an inconstant proportion of adhesiveness and aggregation.

Finally agglutination is an independent serologic phenomenon. It derives its
practical meaning from pathologic states such as I.T.P. Agglutination generally diminishes adhesiveness. Only a strict distinction of adhesiveness, aggregation and agglutination of platelets gives a clear understanding of their functional morphology.

During coagulation most of the hyalomere disintegrates and the coalesced chromomere or aggregates of chromomerces form the centers of the fibrin-net (fig. 4). Formation of these centers seems to be in a certain relation to clot retraction. In all instances where pseudopod formation and spreading is absent there is no formation of “chromomere centers” and clot retraction is inhibited.
As is well known, several biochemical factors have been defined in platelets in relation to blood coagulation. Platelet factor 1\textsuperscript{10,11} seems to be identical with plasma factor V,\textsuperscript{12} platelet factor 2\textsuperscript{13} accelerates the transformation of fibrinogen to fibrin in the presence of thrombin. Platelet factor 3 contains the thromboplastic activity of platelets and acts with different plasma factors (VIII, IX, X, V, VII) to form active thromboplastin.\textsuperscript{14-16} Platelet factor 4 has antihemorrhagic activity,\textsuperscript{17} and, finally, serotonin,\textsuperscript{18} which is absorbed by platelets and released when they disintegrate, causing vasoconstriction and possibly influencing retraction.\textsuperscript{17}

The 23 patients we examined presented a uniform clinical picture with severe bleeding tendency from all mucous membranes, hemarthrosis in 3 instances, strongly prolonged bleeding time (up to 24 hours), some petechiae and ecchymoses, normal platelet numbers and normal plasma coagulation factors. There was no detectable circulating anticoagulant. The following specialized laboratory examinations have been carried out: Electron microscopic examination of platelets, examination of platelets on the smear, coagulation time, bleeding time, tourniquet test, clot retraction, thrombelastography (in some cases), prothrombin time, prothrombin consumption test, heparin tolerance test, thromboplastin generation test, in some instances a quantitative determination of plasma factors V, VII, VIII, platelet factors 1, 2, 4, "platelet-like activity of serum" (Soulier and Alagille)\textsuperscript{19} and capillary microscopy. We obtained the following results:

1. With 5 patients there was a very definite entity characterized as follows: Electron microscopic examination revealed a severe defect of pseudopod formation and an absolute lack of platelet spreading (figs. 5 and 6). On smears, thrombocytes were strictly isolated (fig. 7). Clot retraction was manifestly disturbed or a latent disturbance could be revealed by thrombelastography (fig. 8). The defect was not corrected by addition of serotonin. Thromboplastic generation, prothrombin consumption and all known coagulation factors were within normal limits, and no platelet agglutinin was present.
Fig. 5—Defective pseudopod formation and lack of spreading of platelets from thrombocytoasthenia. (Compare with fig. 1.)

Fig. 6—Platelets from thrombocytoasthenia in normal plasma. The defect persists.

Fig. 7—Platelets from thrombocytoasthenia are isolated on smears. Isolation, however, may also be found in some cases of thrombocytopathia.

Fig. 8—Normal thrombelastography (tracing I) and thrombelastography from thrombocytoasthenia (tracing II).

The disease starts in early infancy, it is not sex-linked, and hereditary factors were manifest in 2 patients (siblings) and questionable in another. Parents never showed signs of disease. Thus it could have a recessive pattern. None of the patients had children.

As to the pathogenesis the following results have been obtained: The lack of pseudopod formation and especially of spreading must be inherent to the plate-
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Fig. 9—Coagulation in plasma from thromboctoasthenia. Platelets form no centers. The fibrin net is without orientation.

Platelets. Normal platelets in plasma or serum of diseased persons behaved normally, whereas pathologic platelets in normal plasma or serum behaved in the same pathologic way. The disease, therefore, is essentially different from all other conditions in which some inhibition of pseudopod formation or spreading can be observed. (e.g., cryoglobulinemia or presence of a strong platelet agglutinin).

Further researches revealed a very remarkable fact. Pathologic platelets which did not spread in normal or pathologic plasma or serum, heated serum or barium adsorbed serum, spread absolutely normally if they were suspended in saline or isotonic solutions of plasma substitutes (fig. 10). There must be, therefore, a factor in normal serum, which, in contact with pathologic platelets, inhibits pseudopod formation and spreading.

Until now it has not been possible to isolate or to identify this serum factor. It does not seem to have any relation to coagulation factors, it is active in a more than tenfold dilution and it seems to be more concentrated in globulin fractions than in albumin.

On the basis of these results there can be no doubt that there is a very well defined disease caused by a constant, well reproducible platelet defect. Since our description, the lack of pseudopod formation and spreading has been confirmed by other investigators in 7 cases. Going over the literature there are at least 44 cases (24 females), where a similar pathologic mechanism is probable. In about half of the cases there is the possibility of a non-dominant and sex-independent hereditary pattern.

The terminology of qualitative platelet disorders is controversial and confusing. Almost all possible terms have been interchanged for all possible diseases, which were often vaguely determined. Two names, however, have been con-
1-

Platelets from thrombocytopenia in saline (or plasma substitutes). Normal pseudopod formation and spreading.

stantly used: Thrombocytopenia and thrombocytopenia. It seems reasonable, therefore, not to introduce new terms, but to give a better definition to these old and accepted names based on reproducible experimental facts. This is certainly possible for the cases mentioned above. It might be somewhat arbitrary to label just this group as "thrombocytopenia." We think it justified, however, by the following reasons: A defect of clot retraction was given as a characteristic by Glanzmann in his original description and is also found in our group, and

Fig. 10—Platelets from thrombocytopenia in saline (or plasma substitutes). Normal pseudopod formation and spreading.

Fig. 11—Giant platelets from thrombocytopenia may spread over 20 μ in diameter.
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finally the term of “asthenia” is particularly evocative for platelets which lack pseudopod formation and spreading

2) In the remaining 18 cases, results were much less uniform and the classification remains difficult. There was normal pseudopod formation and normal spreading in all cases. Retraction and thrombelastography were also normal. On the basis of coagulation tests, however, the patients could be divided into the following groups:

a) Five patients had a constantly and severely disturbed prothrombin consumption and platelet thromboplastin generation test. All known coagulation factors were normal. In 3 of these patients the platelets in the smear were very large (up to 6 μ in diameter) and had a lymphocyte-like appearance. They were also isolated on the smear. When they spread on the membrane, they often attained more than 20 μ in diameter (fig. 11). Two patients had no giant platelets, but the platelets were also to a high degree isolated on the smear. Capillary microscopy revealed no pathologic features.

These cases very closely resemble the cases published by Bernard et al. and Hirsch, Favre-Gilly and Dameshek. Four patients had a familial history, but only siblings had a similar hemorrhagic disorder, and parents were always healthy. One patient had a brother who presented moderate bleeding, prothrombin time and thromboplastic generation being normal. Another patient had a severely bleeding sister, who showed, in addition to a probable platelet defect, a temporary diminution of plasma factor VIII.

This group (a) is characterized by a deficient thromboplastic activity of the platelets (diminution of platelet factor 3 and/or 4) and was defined as “thrombocytopathia.” Isolation of platelets on the smear seems due, in these cases, to a deficiency of aggregation (not adhesivity), which might be the consequence of the lack of a thromboplastin generating factor in platelets.

This group is relatively well determined, especially the cases with manifest morphologic platelet anomalies and possibly different hereditary pattern. It would indeed seem logical to separate them completely, as Bernard and Soulier have done, but we have not yet done this, because one patient had a brother with markedly prolonged bleeding time but no disturbance of prothrombin consumption or thromboplastic generation. It is not very probable that there are two different diseases in one family, and patients with normal coagulation test may perhaps only present the incomplete picture of a common disorder. More cases should be described.

It should also be considered that one patient of this group might be related to a syndrome described by Alexander and Goldstein, and Larrieu and Soulier, characterized by a deficiency of plasma factor VIII and prolonged bleeding time, since his sister temporarily showed a diminution of this factor. In the patient himself, however, normal values were found on several examinations.

b) In 9 cases prothrombin consumption and thromboplastin generation were only temporarily pathologic or on the limit of pathologic values. This group includes 3 cases of the original thrombocytopathia of Willebrand-Jürgens from the Åland islands. In two cases (1 from the Åland islands) platelets were strictly isolated on the smear. At least 6 patients showed a dominant, sex-independent
hereditary pattern. Capillary microscopy performed in some of these cases revealed no abnormal features.

This group (b) was designated as "probable thrombocytopathia," provisionally, to reflect the actual fluctuating state of researches. It is hoped that new methods will soon be available which will allow more accurate evaluation of the basic defect of platelets, or of some hitherto unknown factor. The term thrombocytopathia is used, because it expresses a deficiency of thromboplastic activity of platelets—even though this deficiency is not absolutely ascertained—and because this group includes 3 cases of the original patients of Willebrand and Jürgens from the Åland islands, where this term has been inaugurated.

c) In 4 cases thromboplastin generation and prothrombin consumption were normal, although the clinical course could also be rather severe. In two instances, however, there was a very markedly disturbed "platelet-like activity of serum." Heredity was dominant and not sex-linked in all cases. In one instance the disease could be followed through 4 generations with 2 mortal bleedings. Platelets on the smear looked normal. Capillary microscopy revealed no abnormal features.

This group (c) was designed as "possible thrombocytopathia." We realize that most laboratories would classify this group—and possibly also some cases of group (b)—under the term of "vascular pseudohemophilia." In our opinion it seems impossible at present to give decisive experimental arguments for the cause of prolonged bleeding in these patients. We can only list the facts which speak in favor and against a capillary or thrombocytic origin of this disease or group of diseases.

In favor of capillary origin speaks the normal thromboplastic generation test and absence of platelet abnormalities. Capillary microscopy has in the hand of some investigators revealed evidence of disturbed capillary function.  

In favor of thrombocytic origin one may argue that presently available tests may not be sensitive enough to register a platelet disturbance. With a new test, measuring the "platelet-like activity of serum," Soulier and Alagille have found pathologic results in cases where conventional tests seemed to show normal results, and this has been confirmed in this study. Furthermore in the opinion of some investigators and also in our own, changes which have been described by capillary microscopy are not always constant and may also be found in patients without bleeding tendency. Finally from a clinical standpoint, proven vascular diseases, as hereditary teleangiectasia, worsen with age, whereas coagulation diseases rather improve. Cases we have seen all had a tendency to improvement.

In the literature there are about 120 cases, 60 per cent of them males, that could be classified into one of the three groups of thrombocytopathia. Heredity seems dominant and not sex-linked, with the possible exception of group (a).

**SUMMARY**

Thrombocytoasthenia is a well defined disease, due to defective pseudopod formation and lack of spreading of platelets, i.e., defective adhesivity in contact with wettable surfaces. This defect persists in pathologic or normal plasma, serum, heated serum and barium adsorbed serum. The platelets behave normally, however, in saline or plasma substitutes. There is a manifest or latent defect of clot retraction, which can be revealed by thrombelastography. This
disturbance seems to be in relation with the primary platelet disorder, and can not be corrected by addition of serotonin. Coagulation factors are normal.

Under the name of thrombocytopathia, possibly heterogenous diseases have been provisionally classified into three groups. In some patients a diminution of thromboplastic activity of platelets is ascertained. The platelets may also show marked morphologic anomalies. This group has been designated as “thrombocytopathia.” In the majority of patients a deficiency of thromboplastic activity of platelets is only found temporarily or the results are only moderately pathologic. This group has been designated as “probable thrombocytopathia.” The third group includes patients with a normal thromboplastic activity of platelets. As indicated with existing methods; more sensitive tests, still on trial, may give positive results. This group has been designated as “possible thrombocytopathia.”

Capillary microscopy gave normal results in patients of all three groups. The relation to “vascular pseudohemophilia” is briefly discussed.

SUMMARIO IN INTERLINGUA

Thrombocytoasthenia es un ben-definite morbo, debite al defective formation de pseudopodos e al inefficace extendimento del plachettas, i.e. lor defective adhesivitate in contacto con superficies humectabile. Iste defecto persiste in pathologic o normal plasma o sero, in sero calefacite, e in sero adsorbite a barium. Tamen, le plachettas se comporta normalmente in solution salin o in substitutos de plasma. Il ha un manifeste o latente defecto del retraction del coagulo, le qual pote esser revelate per thrombelastographia. Iste disturbance es apparentemente relationate al disordine primari del plachettas e non pote esser corrigite per le addition de serotoninina. Le factores de coagulation es normal.

Sub le nomine de thrombocytopathia, morbos de character possibilemente heterogenee ha essite classificate provisorimente in tres grupplos. In certe patientes un diminution del activitate thromboplastic de plachettas es constatate. Le plachettas etiam pote monstrar marcate anormalitates morphologic. Iste gruppo ha recipite le designation de “thrombocytopathia” (sin adjectivo qualificatori). In le majoritate del patientes un deficientia del activitate thromboplastic de plachettas es trovate solmente temporarimente, o le resultatos es solmente moderamente pathologic. Iste gruppo ha recipite le designation de “thrombocytopathia probable.” Le tertie gruppo include patientes con normal activitate thromboplastic de plachettas, in tanto que pote esser determinate per le methodos nune disponibile. Tests de plus alte grados de sensibilitate, que es currentemente sub verification experimental, va possibilemente producir resultatos positive in le casos de iste gruppo. Le gruppo ha recipite le designation de “thrombocytopathia possible.”

Resultatos normal esseva obtenite per microscopia capillari in patientes de omne le tres grupplos. Le relation a “pseudohemophilia vascular” es discutite brevemente.

REFERENCES

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