Symposium: What Is Hemophilia?

Deuterohemophilia: Plasma Thromboplastin Factor B Deficiency

Plasma Thromboplastin Component (PTC) Deficiency, Christmas Disease, Hemophilia B

By Paul M. Aggeler, M.D., Sidney G. White, Major, MC, USAF, and Theodore H. Spaet, M.D.

A new hemorrhagic disease which resembles hemophilia so closely that it is indistinguishable from it by ordinary laboratory methods has recently been described. Unfortunately, a multiplicity of names for this new disease has already appeared. A brief historical review of knowledge relating to this condition is therefore in order.

Pavlovsky\(^1\) first observed that the clotting time of mixtures of the blood of two patients who were thought to suffer from hemophilia was shorter than the clotting time of either specimen alone. He found that transfusion of 100 cc. of blood from one of these patients to the other produced the same effect as transfusion of an equal quantity of normal blood. He also noted that the coagulant activity of antihemophilic globulin made from the plasma of some supposedly hemophilic patients was almost equal to that made from normal plasma. These results were not interpreted as indicating that these patients might suffer from different diseases, nor was it suggested that an unknown blood coagulation factor might be involved in these reactions. On the contrary, Pavlovsky doubted that the antihemophilic globulin fraction was implicated in the pathogenesis of hemophilia and interpreted the results of his experiments as evidence that the clotting defect in hemophilia is due to variations in the concentration of an anticoagulant factor.

Koller, et al.\(^2\) reported in 1950, on a hemophilia-like disease, which they called "Moëna's anomaly" (after the family name of their patients). The clotting time of the blood was normal or only slightly prolonged, yet prothrombin utilization was markedly impaired. Mixtures of blood from these patients with that from patients with classical hemophilia showed normal coagulation times and normal prothrombin utilization. The prothrombin utilization of the normal female conductors of the trait was also said to be impaired. No further studies differentiating the deficient factor in Moëna's anomaly from the antihemophilic factor were reported.

Aggeler, et al.\(^3\)\(^,\)4 and White, et al.\(^5\) studied the case of a 15 year old boy with no siblings, who had no family history of hemorrhagic disease. They found that the whole blood clotting time was prolonged and prothrombin utilization was

From the Department of Medicine, University of California School of Medicine, the Medical Department, Veterans Administration Hospital, and the Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

Opinions expressed are those solely of the authors and in no way reflect the official views of the United States Air Force.
impaired, despite the presence of normal quantities of all previously described coagulation elements in the blood. The coagulation defect could be corrected by the addition of tissue thromboplastin and by "platelet-free" hemophilic plasma. The authors concluded that the patient lacked a plasma factor, the "plasma thromboplastin component (PTC)," which appeared to be as necessary biologically as the antihemophilic factor for the production of thromboplastin in the blood. They were the first to demonstrate the characteristics that differentiate this substance from the antihemophilic factor (AHF). These characteristics are:

1. PTC can be adsorbed by barium sulfate from oxalated plasma, as can prothrombin and the stable prothrombin conversion accelerator (SPCA, proconvertin, factor VII, co-thromboplastin).

2. PTC can be completely adsorbed from normal plasma by all previously described prothrombin adsorbants and by Seitz filtration, and it can be eluted from the adsorbant by sodium citrate. A purified PTC reagent, free of the antihemophilic factor, prothrombin, and both prothrombin conversion accelerators can be prepared by this process.

3. PTC is present in the 40 to 50 per cent saturated ammonium-sulfate fraction of normal plasma, and is not present in the 0 to 33 per cent saturated fraction which contains the antihemophilic factor.

4. PTC is present in serum, as well as in plasma.

5. PTC is present in normal quantities in the plasma in classical hemophilia.

6. PTC is not present in fraction I of Cohn, which contains the antihemophilic factor and fibrinogen, and is obtained by ethanol precipitation at low temperatures.

Schulman and Smith reported the case of a hemophilia-like disease in a male infant who had no family history of hemorrhagic disease. The patient was found to have normal quantities of all previously described blood coagulation elements, including the antihemophilic factor. They found that when prepared from normal plasma, Cohn's fraction I + III, which contains the antihemophilic factor, fibrinogen, prothrombin, beta globulin, and small amounts of alpha and gamma globulins, was effective in shortening the clotting time of the patient's blood. A similar fraction prepared from hemophilic plasma was equally effective in shortening the clotting time of their patient's blood, but had only a slight effect on the clotting time of hemophilic blood. A fraction prepared from the plasma of their patient was ineffective in correcting his defect, but corrected the hemophilic defect. These authors concluded that the patient lacked a "plasma factor X" which, together with the antihemophilic factor and platelets, is necessary for the production of thromboplastin in the blood. No further studies differentiating this factor from the antihemophilic factor were reported.

Biggs, et al. published a report on seven patients who, by ordinary tests, would be said to have hemophilia. (Two of these patients were members of the same family, and it appeared that the hemorrhagic disorder had been inherited as a sex-linked recessive characteristic.) These investigators found, however, that when a small proportion of the blood or plasma of their patients with "Christmas disease" was added to hemophilic blood or plasma, the clotting time of the latter was greatly reduced. They also noted, as had Aggeler, White, et al., that the missing factor was necessary for the production of thromboplastin in plasma, that it was adsorbed by aluminum hydroxide and by Seitz filtration, that it was not present in the 0 to 33 per cent saturated ammonium-sulfate fraction of normal plasma, but was present in the 33 to 50 per cent fraction, and that it was present in the serum, as well as in the plasma. They further showed that this clotting factor was heat labile, stable on storage in the refrigerator, and was contained in a crude ether fraction precipitated from plasma in association with alpha and beta globulins, but was not present
in the ether fraction precipitated from the plasma in association with fibrinogen. These authors also showed that even when there was little or no abnormality in the clotting time or prothrombin utilization test, "Christmas disease" could be differentiated from hemophilia by the thromboplastin generation test of Biggs and Douglas. The results were markedly abnormal when either hemophilic plasma or "Christmas disease" serum was substituted for its normal counterpart in the test.

Rosenthal, Dreskin, and Rosenthal reported the case of a 4 year old boy who had episodes of bleeding since birth, but who had no family history of hemorrhagic disease. His coagulation defect was shown to result from PTC deficiency by the demonstration that it could be corrected by hemophilic plasma, normal serum, and a purified PTC preparation. It was not corrected by barium sulfate-adsorbed plasma or by plasma of the patient studied by Aggeler, White, et al.

Poole described the case of a 5 year old boy whose blood and that of a number of patients with classical hemophilia were mutually corrective. He did not report any further studies, and his case is included among those of Biggs, et al.

White, Aggeler, and Glendening published in detail the observations contained in their earlier reports. They called attention to the fact that the effect of transfusion was much more prolonged in PTC deficiency than in hemophilia, and reported that in their patient prothrombolytic plasma transfusions, given at ten to fourteen day intervals for four years had produced beneficial results. They also confirmed the findings of Biggs, et al. regarding the heat lability of the PTC factor. In addition, they noted that the PTC factor is highly resistant to inactivation by changes in pH, that it is about equally present in the euglobulin and pseudoglobulin-albumin fractions of serum obtained by acidification and dilution, that the PTC potency of tissue thromboplastins is almost completely destroyed by heating to 60 C. for 20 minutes (as is also the AHF potency), and that brain cephalin-lecithin preparations appear to have no PTC potency. They also presented an improved method for making a PTC preparation from acidified serum.

Lewis and Ferguson reported three cases of PTC deficiency, in two of which there was a typical family history suggesting hemophilia. The third patient, whose family history was unobtainable, had previously developed an anticoagulant following repeated transfusions. Only traces of the anticoagulant were detectable at the time he was investigated for PTC deficiency. In these cases the diagnosis was established by the demonstration that the patient's blood and that of known hemophiliacs were mutually corrective and that the coagulation defect could not be corrected by the addition of barium sulfate-adsorbed normal plasma, but could be corrected by a purified PTC preparation made from the citrate plasma of a patient whose serum had been used to adsorb the normal plasma.

Van Creveld and Paulsensen reported the case of a 10 year old boy who had no family history of hemorrhagic disease, but who, by the ordinary tests, would be thought to suffer from hemophilia. The coagulation defect was corrected by hemophilic blood, but not by fraction I of Cohn nor by the euglobulin fraction of a normal plasma obtained by acidification and dilution. This is of interest in view of the fact that White, Aggeler, and Glendening found that the PTC factor was divided about equally between the euglobulin and pseudoglobulin-albumin fractions obtained from normal serum by a similar procedure.

Soulier and Larrieu discovered four cases of "hemophilia B" in a group of thirty-three male patients, all of whom had previously been thought to suffer from classical hemophilia. They confirmed the findings of previous investigators that the deficient factor is heat labile, stable on storage in the refrigerator, present in dicumarolized plasma and in normal serum stored at room temperature for 48 hours, and that it is removed by barium sulfate adsorption or filtration through 20 per cent asbestos pads. Two of their four patients had a family history suggesting hemophilia, and two had developed a circulating anticoagulant following repeated transfusions. They also reported another patient who appeared to have a combination of "hemophilia B" and AHF deficiency. This diagnosis, however, cannot be accepted as proved, since it was based entirely on the failure of the patient's plasma to correct the clotting defect of either "hemophilia A" (AHF deficiency) or "hemophilia B" (PTC deficiency).

Cramer, et al. reported two cases of "hemophilia B", in which the personal history, family history and the results of the usual laboratory tests suggested hemophilia. How-
ever, the clotting abnormality in both cases could be corrected by hemophilic, as well as by normal, plasma and serum.

Beaumont, et al. reported the case of a 3 year old boy with a congenital hemorrhagic syndrome resembling hemophilia. The coagulation defect could be corrected by normal serum, hemophilic plasma, platelet-poor normal plasma, and normal plasma aged for 30 days at 5°C or for 48 hours at 37°C. It could not be corrected by barium sulfate-adsorbed serum or plasma. The plasma of their patient also failed to correct the clotting defect when added to that of a patient with "hemophilia B" previously reported by Soulier and Larrieu. These authors also appear to be the first to confirm the observation of White, Aggeler, and Glendening that transfusion has a much more prolonged effect in this condition than in classical hemophilia.

Bergsagel demonstrated the existence of PTC deficiency in two brothers who had a relatively mild hemorrhagic tendency and whose blood showed normal clotting times and normal prothrombin utilization. The diagnosis was established by means of the thromboplastin generation test and by the fact that the plasma and serum from one of the brothers failed to improve prothrombin utilization in the patient studied by Aggeler, White, et al.

MacMillan observed a mild bleeding tendency in twelve male members of a French Canadian family. A study of five generations of the family showed that the tendency was transmitted as a sex-linked recessive characteristic. Spontaneous bleeding was uncommon, and clotting times and prothrombin utilization tests were either normal or only slightly abnormal. By means of the thromboplastin generation test it was shown that the defect was due to a lack of the "Christmas factor" rather than of the anti-hemophilic factor.

It is probable that factors other than the plasma thromboplastin component (PTC), the anti-hemophilic factor (AHF), and a platelet factor may be required for the production of thromboplastin in blood. Rosenthal, Dreskin, and Rosenthal noted the existence of another hemophilia-like condition which affects both males and females. This disorder is apparently due to the deficiency of a third thromboplastin factor, which they named "plasma thromboplastin antecedent (PTA)". The coagulation defect in patients suffering from this disorder can be corrected by normal serum, barium sulfate-adsorbed normal plasma, the citrate eluate of the barium sulfate used to adsorb the plasma, and by both hemophilic and PTC-deficient plasmas. Spaet, Aggeler, and Kinnsell have found evidence of a possible fourth plasma thromboplastin deficiency. The characteristics of the coagulation defect in this condition are similar to those found in PTA deficiency, except that the plasma and serum of the patient suffering from this disorder and those of a patient with PTA deficiency studied by Rosenthal were mutually corrective. Furthermore, it was found that when either aluminum hydroxide-adsorbed plasma or serum from this patient was substituted for its normal counterpart in the thromboplastin generation test, markedly abnormal results were produced. Johnson discovered that in the activation of purified prothrombin, the reaction of the plasma and serum of this patient was similar to that in classical hemophilia and quite different from that in PTC deficiency. In view of these findings it is apparent that a diagnosis of PTC deficiency cannot be established merely by showing that the clotting defect can be corrected by normal serum or hemophilic plasma, or that it can not be corrected by the anti-hemophilic fraction of normal plasma.

To establish the diagnosis with a greater degree of certainty in those patients who show impaired prothrombin utilization, it should be demonstrated that the

* Since the submission of this paper for publication, Rosenthal and Sanders have reported another case of PTC deficiency in which a similar prolonged effect of transfusion was observed.
defect cannot be corrected by adsorbed normal plasma nor by the addition of plasma or serum from a patient with proved PTC deficiency. In patients in whom prothrombin utilization is normal, the diagnosis can best be established by the characteristic result obtained in the thromboplastin generation test or by the demonstration of the inability of the patient's plasma or serum to restore normal prothrombin utilization in a case of proved PTC deficiency. It cannot be said with certainty, therefore, that the patients reported by Pavlovsky,1 Koller, et al.,2 Schulman and Smith,3 Poole,4 van Crevel and Paulissen,5 and Cramer, et al.6, 7 suffered from PTC deficiency. On the other hand, the cases of Biggs, et al.,7 Rosenthal, Dreskin, and Rosenthal,8 Lewis and Ferguson,9 Soulier and Larrieu,10 Beaumont, et al.,8 Bergsagel,11 and MacMillan12 appear to have had the coagulation defect originally described by Aggeler, White, et al.3-5 It is apparent that within a brief period of time a relatively large number of patients previously thought to have hemophilia have been found in reality to suffer from PTC deficiency.

White, Aggeler, and Emery23 recently investigated the PTC potency of various fractions of plasma obtained by Cohn's methods. They discovered that the PTC potency was concentrated in fractions III and IV. Little activity was found in fractions I and IV. None was found in fractions II or V. Since fraction III contains thrombin and fraction IV was poorly soluble, neither was suitable for intravenous use in highly concentrated form. Pronounced shortening of the whole blood clotting time and a decided reduction in the residual serum prothrombin followed the intravenous administration of the whole fraction IV. The results appeared to be superior to those achieved by the use of fraction I in classical hemophilia.

Since fraction IV is a waste product in the process of plasma fractionation, its substitution for plasma in the treatment of PTC deficiency would seem desirable. Furthermore, it appears to be quite possible that a concentrated therapeutic agent can be made from fraction IV in a manner similar to that already used to prepare PTC from serum and plasma. PTC deficiency can also be treated with moderately aged plasma and with serum. Since these agents are of little or no benefit in classical hemophilia, definite therapeutic advantages would result from segregation of PTC-deficient patients.

Johnson22 has found that in the presence of a platelet factor and calcium, the activation of purified prothrombin is less rapid by normal serum than by normal plasma. On the other hand, hemophilic serum gives the same reaction as hemophilic plasma, and both reactions are similar to those of normal serum. PTC-deficient plasma is less active than hemophilic plasma, but PTC-deficient serum, like normal serum, is less active than the plasma.

The name “plasma thromboplastin component (PTC) deficiency” was used by Aggeler, White, et al.3-5, 11, 22 to describe specifically a new disease caused by a deficiency of a previously undescribed blood clotting factor. The term was chosen in order to indicate the pathologic physiology of the disease. Objections have arisen to the use of this name, since it could also be used to indicate the pathologic physiology in classical hemophilia. Biggs, et al.7 proposed the designation “Christmas disease” from the surname of the first patient studied by them in detail. There are many objections to the use of an eponym, particularly one such as this which has other semantic connotations.
Soulier and Larrieu\textsuperscript{14, 15} and Cramer, et al.\textsuperscript{16, 17} have used "hemophilia A" for classical hemophilia and "hemophilia B" for PTC deficiency. The deficient factors in the two diseases would then be called AHF-A and AHF-B, respectively. It is now apparent that in personal history, family history, physical manifestations, and results of the usual laboratory tests, PTC deficiency may mimic hemophilia exactly. There is much merit to the argument that the name for this new disease should indicate this close similarity. On the other hand, this nomenclature seems to imply that PTC deficiency and hemophilia are actually different clinical types of the same disease, whereas the contrary would appear to be true, i.e., they are two distinct diseases which present very similar clinical pictures. Even though they are both plasma thromboplastin deficiency diseases, the characteristics of the deficient factors are distinctly dissimilar. Furthermore, although both diseases may be inherited as sex-linked recessive characters, there is no evidence that the defect in both resides in the same unstable gene. This terminology, then, would be more appropriate for use in segregating different types of true hemophilia according to the particular blood-clotting pattern observed.\textsuperscript{18-20} "Hemophilia A" might be used to designate the classical pattern, "hemophilia B" the type in which the clotting time is normal but prothrombin utilization is deficient, and "hemophilia C" the type in which both clotting time and prothrombin utilization are normal.

The need for a uniform system of nomenclature to distinguish between the various plasma thromboplastin factors is readily apparent; however, these components should not all be called antihemophilic factors (AHF). It has been suggested by Spaet, Aggeler, and Kinsell\textsuperscript{21} that they be grouped under the term "plasma thromboplastin factors" (PTF), which would allow the antihemophilic factor to be designated as PTF-A, the PTC factor as PTF-B, the PTA factor as PTF-C, and a possible fourth factor as PTF-D. If desired, the diseases characterized by these deficiencies could be known as "PTF-A deficiency," "PTF-B deficiency," and so on. Unfortunately, the exclusive use of this physiologic nomenclature would require the abandonment of the time-honored name of hemophilia, which is neither possible nor desirable. Instead, it is a clinically descriptive label for the new disease that is required. Designations containing Greek prefixes such as "parahemophilia" and "pseudohemophilia" have already been used to distinguish hemorrhagic disorders which in some ways resemble hemophilia but which are by no means variants of it. The terms "heterohemophilia" and "metahemophilia" might be employed in a similar manner. On the basis of this tradition, "deuterohemophilia" could be utilized to designate PTC deficiency, without necessarily implying that it is a second type of the classical disease. "Deutero-hemophilia" has an added advantage: by the simple expedient of changing the Greek numerical prefix, sufficiently distinctive terms, suggesting both a similarity with hemophilia and with each other, can be provided for any number of thromboplastin deficiency diseases.

Full agreement on nomenclature can probably only be reached by a conference of all those intimately concerned with the problem. However, pending such agreement, it is proposed that the name hemophilia, without prefixes or suffixes, be retained for the classical disease, and that the new disease, previously called "plasma thromboplastin component (PTC) deficiency", "Christmas disease", and "hemophilia B", be known as "deuterohemophilia". It is further proposed
that the deficient factor in hemophilia be called “plasma thromboplastin factor A” (PTF-A), that the deficient factor in deuterohemophilia be known as “plasma thromboplastin factor B” (PTF-B), and that this system of nomenclature be extended to include other thromboplastin factors as their identity is definitely established.

**SUMMARY IN INTERLINGUA**

Es presentate un summario historic del differentiation inter hemophilia classic (causate per un deficiencia del “factor antihemophilic”) e le distincte morbo (symptomatologicamente affin) que es causate per un deficiencia del factor nominate “componente plasmo-thromboplastic.” Seque un revista del casos reportate de iste secunde deficiencia que ha variemente essite nominate morbo Christmas, hemophilia B, etc. Es proponite pro illo le termino deuterohemophilia. Le termino hemophilia (sin affixo o epitheto) esserea applicate exclusive mente al morbo causate per un deficiencia del “factor antihemophilic.” Le factores deficientes in le duo morbos poterea esser designate como “factores plasmo-thromboplastic.” Le factor antihemophilic devenirea “factor plasmo-thromboplastic A” e le componente plasmo-thromboplastic esserea “factor plasmo-thromboplastic B.” On nota como avangate del sistema le possibilitate de su extension futur a tritojemophilia, tetartoemophilia, etc. como etiam le possibilitate de distinguere altre “factores plasmo-thromboplastic” per le uso de altere litteras del alphabeto.

**REFERENCES**

P. M. AGGELER, S. G. WHITE, AND T. H. SPAET

19 Bergsagel, D. E.: Personal communication.

Discussion

I wish to point out how much I appreciated the studies published by P. M. Aggeler and his co-workers.

The discrimination established by Aggeler and his co-workers between PTC and AHF factors seems to be essential, and it emphasizes once more the complexity of the development of intrinsic thromboplastic activity.

In spite of our insufficient understanding of that main point, I agree with the authors who admit the existence of two types of hemophilia, which can be observed in both hereditary and in so-called sporadic forms.

As the clinical symptomatology is similar in both types, and as the latter cannot be distinguished by classical laboratory tests, I regard it as logical to maintain—for both types—the term "hemophilia", specifying however whether it is the classic form or not (A or B hemophilia).

On the other hand, the question whether those conditions can be attributed merely to a quantitative deficiency of either the specific factor PTC or AHF, seems to me as yet an unsolved problem. The authors who believe in a simple deficiency should at least be able to offer a satisfactory explanation—in accordance with their conception—of the results obtained by L. M. Tocantins and by myself on the correction of the coagulation defect in hemophilic plasma by simple dilution with physiologic saline, or by contact with certain mineral substances (Kaolin powder, etc.).

R. Feissly

From the Clinique “La Pensée”, Ouchy, Lausanne, Switzerland.

PAUL M. AGGELER, SIDNEY G. WHITE and THEODORE H. SPAET