

CLINICAL CONFERENCE

Disorders of Coagulation of Blood

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DR. SCHULMAN: The case we would like to discuss is one chosen for its own intrinsic interest, and also because it provides a good opportunity to illustrate some of our newer knowledge of coagulation in general, and hemophilia in particular.

The patient is a 4-year-old boy who was referred to this hospital for investigation of a hemorrhagic diathesis. His birth was normal and at the age of 7 days he was circumcised without difficulty. At 1 year of age he developed bleeding from a traumatic laceration of the left upper eyelid, which persisted for 5 days. At the age of 3 years he apparently fell and bit his tongue. This led to persistent bleeding for a period of 14 days, despite the administration of three transfusions. At 3½ years of age, an upper central incisor became loose, resulting in bleeding for 3 days. At 4 years he suddenly developed a painful swelling of the right knee, which increased in severity for 5 days. Joint aspiration yielded 20 ml of blood. At no time did this boy have any other manifestations of bleeding. There had been no nose bleeds.

The members of the family are indicated in Figure 1. This patient has two brothers who are unaffected and three sisters who are also unaffected. The mother and father are unaffected. However, the mother's paternal uncle had a severe hemorrhagic disease and, in addition, the mother's sister has two sons who also have bleeding manifestations. The disease, then, apparently occurs only in males. It skips a generation and is apparently transmitted by females. This is the classic sex-linked, recessive inheritance which we have come to associate with hemophilia.

The major difficulty with this patient was that in repeated studies prior to admission—and these were studies which were more than routine—no abnormality was found. The bleeding time and the clotting time were consistently

normal. Platelets, prothrombin, fibrinogen, calcium, clot retraction, and tourniquet tests were also normal (Table I).

This, then, is a situation in which a boy has a strong family history of bleeding, a definite history of bleeding himself, but more than routine studies fail to disclose any abnormality. So we are left with the problem: Does this boy have a hemorrhagic disease? And if so, how is a diagnosis established?

The current concept of the coagulation mechanism, somewhat simplified, is shown in Figure 2. You will note that the clotting of blood takes place in three major phases. In phase 1 we have a group of plasma proteins, designated here as plasma thromboplastin-precursors, which react with the platelets to form thromboplastin. Until 5 years ago we believed that a deficiency of only one plasma protein led to the disease of hemophilia. At the present time, however, we recognize that not one but probably six, different plasma proteins act in this locus, and react with the platelets to form thromboplastin. The three plasma thromboplastin precursors which are clinically most important are: 1) antihemophilic globulin (AHG); 2) plasma thromboplastin component (PTC); and 3) plasma thromboplastin antecedent (PTA). A severe deficiency of any of these three factors may give the entire clinical picture of classic hemophilia. Previously hemophilia was thought to be an all or none situation. It was considered to exist when the patient could not produce any antihemophilic globulin at all. We know that that is not true; there are all grades of deficiency of AHG, and there are all grades of deficiency of PTC and PTA as well. At present, therefore, we must define "hemophilia" in regard to the specific factor lacking and the degree of the deficiency.

In the second phase of clotting the thromboplastin which is formed in phase 1 reacts with prothrombin and calcium, in the presence of

This presentation was part of a Clinical Conference conducted under the Chairmanship of Dr. Samuel Z. Levine at the New York Hospital, New York City, for the Annual Meeting of the Academy, October 11, 1956.

ADDRESS: 525 East 68th Street, New York 21, New York.

PEDIATRICS, January 1958

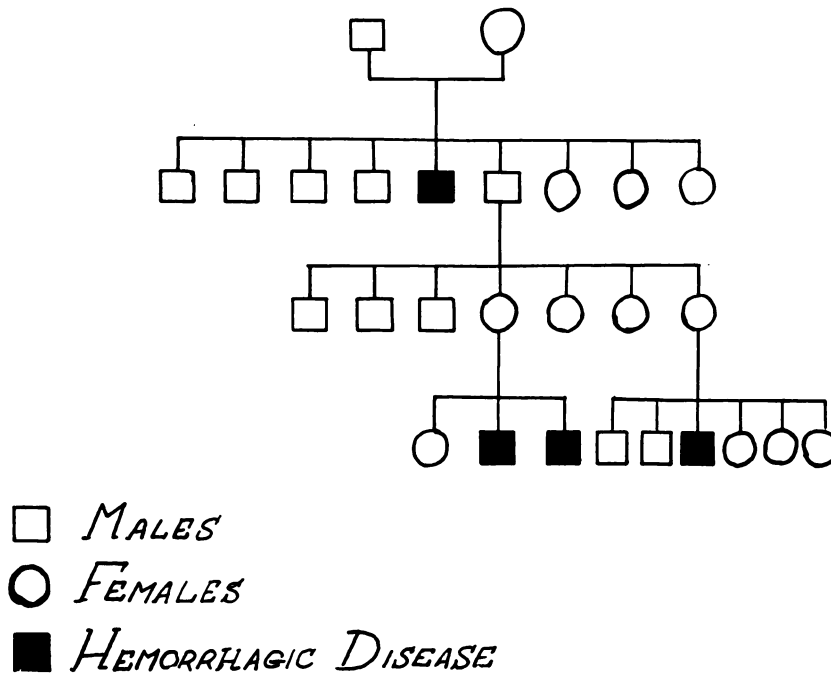


FIG. 1. Family history of the patient.

two additional factors termed stable and labile factors, to yield thrombin. In the third phase thrombin and fibrinogen react together to form fibrin which is the actual clot.

The investigation of the patient's bleeding disorder includes the application of certain tests which may detect difficulties in the individual phases of coagulation. Difficulties in the third phase can be due only to fibrinogen deficiency. This can be detected by an actual fibrinogen determination, but even more simply by the fact that, if the clotting time is normal, the fibrinogen is usually adequate. A deficiency in the second phase is determined by the one-

stage prothrombin time. In this test one adds thromboplastin and calcium in excess, and thus measures the adequacy of the components of the prothrombin complex (prothrombin, labile factor and stable factor). In the first phase, only extreme deficiency of any of the thromboplastin precursors will cause a prolonged clotting time. In the minor or moderate deficiencies, the clotting time will be normal, and it becomes necessary to use other tests to establish the deficiency in the first phase. Under normal circumstances, sufficient thromboplastin is formed in the first phase to utilize almost all the prothrombin available for forma-

TABLE I
COAGULATION TESTS ON THE PATIENT'S BLOOD (PRIOR TO ADMISSION)

| Test | Age | | | | |
|------------------------|--------|---------|---------|----------|---------|
| | 3 days | 1 year | 3 years | 3½ years | 4 years |
| Bleeding time (min) | 1½ | 2½ | 5 | 3 | 3 |
| Clotting time (min) | 6 | 5 | 7 | 6½ | 10 |
| Platelets | — | 162,000 | 294,000 | 160,000 | 265,000 |
| Prothrombin time (sec) | — | — | — | 11 | 16 |
| Fibrinogen (mg/100 ml) | — | — | 250 | 250 | 235 |
| Calcium (mg/100 ml) | — | — | — | — | 11.1 |
| Clot retraction | N | N | N | N | N |
| Tourniquet test | — | — | N | N | N |

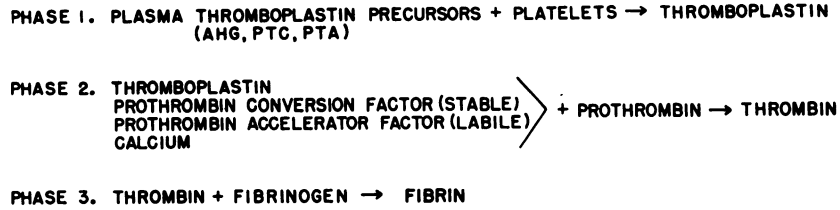


FIG. 2. The normal coagulation cycle.

tion of the clot. Therefore, the serum contains little or no prothrombin. If a defect exists in phase 1, however, insufficient thromboplastin is formed, inadequate amounts of prothrombin are utilized, and therefore the serum will contain abnormal amounts of prothrombin. This constitutes the basis for the prothrombin-consumption test. The prothrombin-consumption test will detect moderate deficiencies, but may be normal in mild deficiencies in phase 1. The most sensitive test available today is the thromboplastin-generation test.

In this test the following materials are used: 1) Patient's barium-sulfate-adsorbed plasma (which normally should contain AHG

and PTA); 2) Patient's serum (which normally should contain PTC and PTA); 3) Platelets; 4) Calcium chloride. It will be noted that these reagents should supply all of the factors necessary for thromboplastin formation. In the actual test the reagents are incubated together, and at periodic intervals aliquots are removed and added to normal plasma. The induced speed of clotting of the normal plasma is then a measure of the thromboplastin formed. Figure 3 demonstrates the normal range for the thromboplastin-generation test, with more than 80% activity demonstrated within 7 minutes of incubation.

The laboratory studies in this patient as

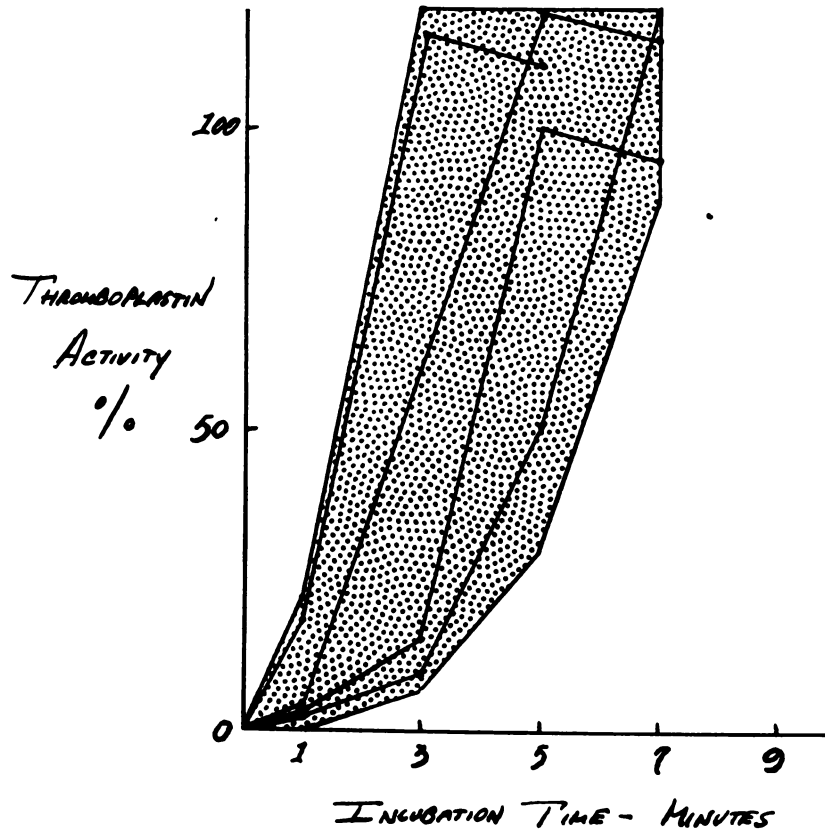


FIG. 3. Range of normal for thromboplastin-generation test in children.

TABLE II
COAGULATION TESTS ON THE PATIENT'S BLOOD
(THE NEW YORK HOSPITAL)

| | |
|-------------------------|----------------------|
| Bleeding time | 4.5 min |
| Clotting time | 9.5 min |
| Clot retraction | Normal |
| Prothrombin time | 14 secs—100% |
| Prothrombin consumption | 17 secs (Normal >20) |

determined in this hospital are indicated in Table II. The bleeding time was confirmed as normal. The clotting time, clot retraction, and the prothrombin time were normal; thus defi-

ciencies in phase 3 and phase 2 have been eliminated. Prothrombin consumption was 17 seconds, the normal being greater than 20 seconds. Here is the first indication that this patient does indeed have a defect in coagulation, and that it resides in the first phase of coagulation. Proof of the defect in phase 1 is shown in Figure 4 which demonstrates the thromboplastin-generation test obtained with the patient's plasma and serum as compared to that obtained using normal plasma and serum. As mentioned earlier, the defect in phase 1 could result from deficiency of any one of three different factors. We would like to identify the

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INCUBATION MIXTURE
 A — ALL NORMAL REAGENTS
 B □ 50% PT. PLASMA SUBSTITUTED
 C ○ 50% HEMOPHILIC PLASMA "
 D ■ 50% PT. } PLASMA "
 50% HEM. }
 E x 100% PATIENT

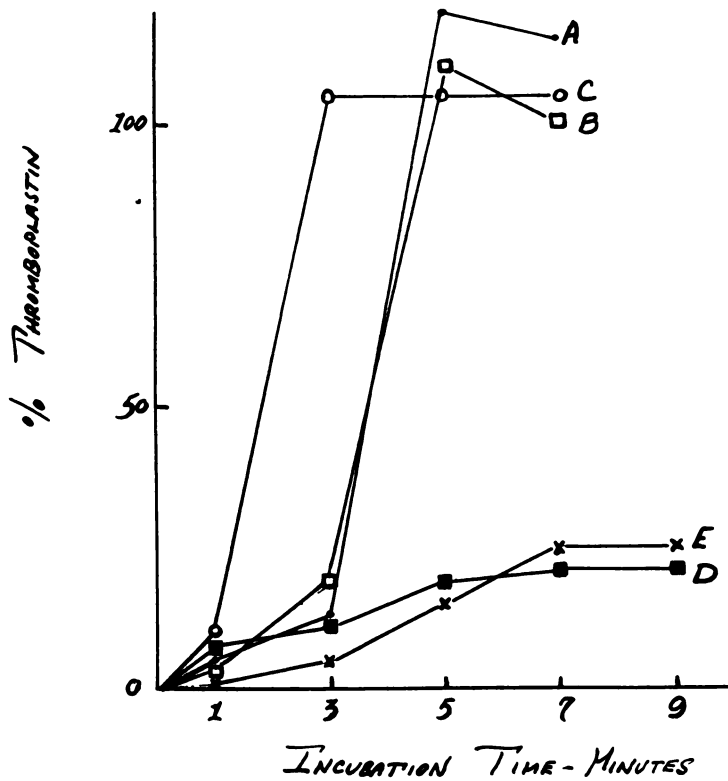


FIG. 4. Thromboplastin-generation test in patient. Results demonstrate phase 1 defect and indicate AHG deficiency.

exact defect. A modification of the thromboplastin-generation test, in which mixtures of patient's reagents are incubated with normal reagents, permits this identification, as follows:

(a) If patient's adsorbed plasma incubated with normal serum results in abnormal generation, the patient must have AHG deficiency (since normal serum supplies PTC and PTA).

(b) If patient's serum incubated with normal adsorbed plasma results in abnormal generation, the patient must have PTC deficiency (since normal adsorbed plasma supplies AHG and PTA).

(c) If abnormality results only when patient's plasma and patient's serum are present together, with correction by *either* normal plasma or normal serum, the patient must have PTA deficiency. The results of these tests in this patient are shown in Figure 4. It will be seen that a mixture of patient's adsorbed plasma plus normal serum results in abnormal thromboplastin generation, thus indicating AHG deficiency. Further proof of this may be obtained by testing the ability of the patient's plasma to correct the abnormal thromboplastin generation of a patient with *known* classic hemophilia. It will be seen in Figure 5 that

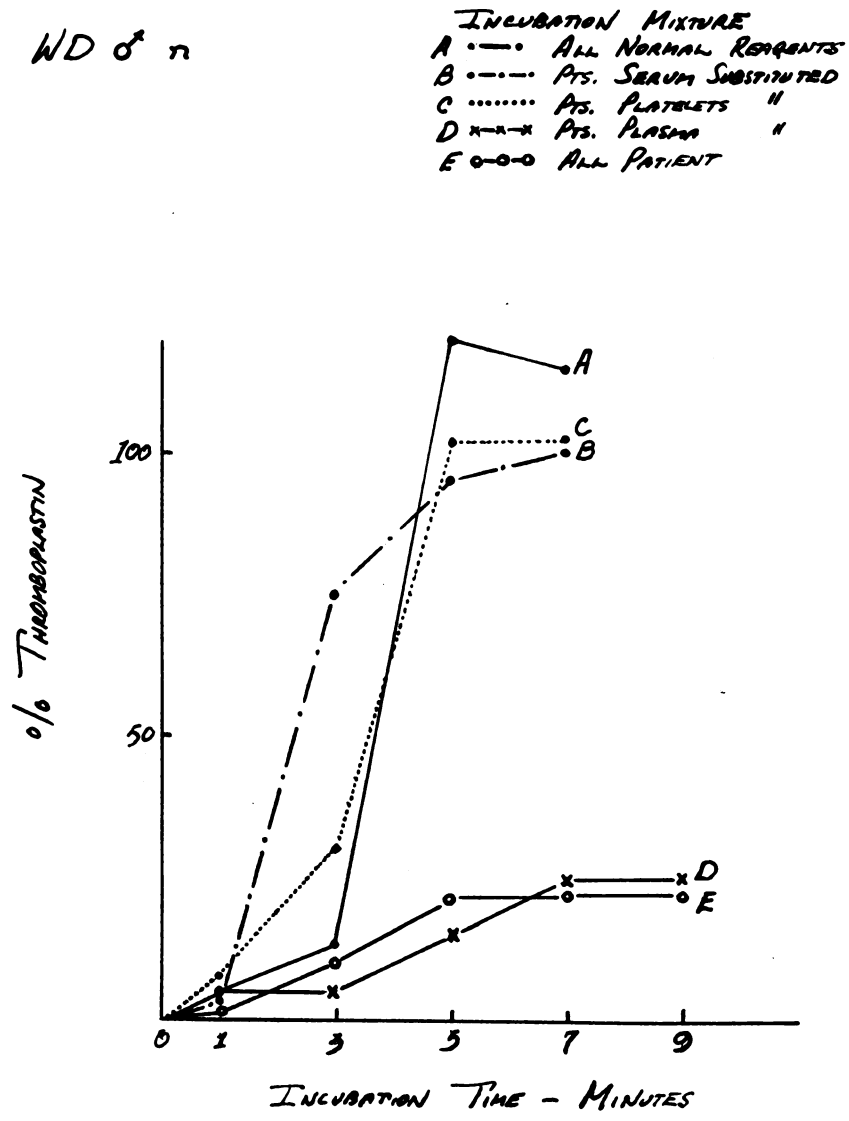


FIG. 5. Thromboplastin-generation test modified to demonstrate failure of mutual correction between patient's plasma and normal plasma.

whereas normal plasma completely corrects the defect, the plasma of the present patient fails to do so. Thus the patient and a true hemophiliac have identical deficiencies.

Therefore, this patient who had a history of bleeding and a positive family history, but completely normal routine coagulation studies, does indeed have hemophilia of the type due to AHG deficiency of a moderate degree.

This little boy had shown sufficient hemorrhagic manifestations to give ample warning to the doctor that something was going on, and the doctor was concerned enough to do repeated and satisfactory studies. However, a much more serious current problem concerns the patients with mild deficiencies, because these patients may not manifest hemorrhagic tendencies until something happens to them; bleeding may appear only after trauma or after such common surgical procedures as tonsillectomy or dental extraction. Most of the patients we have observed with the mild hemophilic syndromes have been admitted here for severe bleeding after one of the aforementioned procedures.

The detection of these cases, their identification, and the exact description of the factors which are missing is of more than academic interest, and has very important implications in therapy. For instance, the PTC and PTA components are very stable on storage. Therefore, if one has to treat such a patient one is quite justified in giving stored blood, bank blood or old plasma. Antihemophilic globulin, however, is quite labile on storage; consequently, fresh blood or fresh plasma is indicated in the treatment of this deficiency. In addition, antihemophilic globulin is dissipated very rapidly in the body, being completely utilized within 24 hours. Therefore, in treating such a patient fresh plasma may be required at frequent intervals. PTC and PTA have a greater longevity in the body than AHG, and in these deficiencies plasma may be required only at intervals of 24 to 48 hours or longer.

I think the most valuable result, however, lies in the realm of preventive medicine. By giving the appropriate plasma before a surgical procedure, we can prevent trouble. With adequate pre-treatment, excessive bleeding following dental extraction or any type of necessary surgery can be avoided. Bleeding can be more easily prevented than stopped once it has started.

Many of you have probably been thinking of your next patient who requires a tonsillectomy. I can assure you we have been giving this matter considerable thought too. Unfortunately, the routine screening tests which are now performed are only of value if they are positive, because they will indicate that something is wrong, even though they may not exactly define the deficiency. If they are negative, as exemplified by this child, there is absolutely no assurance that the child is normal.

Now, it is ludicrous to consider doing a prothrombin-consumption or thromboplastin-generation test on every patient admitted for tonsillectomy. At the present time we believe the best screening procedure available is a complete history, and as complete a family history as possible. Evidence of bleeding from any source, of hematoma after injections, of bleeding upon eruption or loss of deciduous teeth or following tonsillectomy, in the event it has been performed, should be sought. If the patient has sustained a major dental extraction or tonsillectomy without difficulty, you can be practically certain that he does not have one of the congenital hemorrhagic diseases.

At the present time there remains the task of developing a screening test which will be readily available and will enable the doctor to determine whether or not the patient has a disorder which predisposes to hemorrhage.

QUESTION: How fresh does the blood or plasma used in treatment have to be to be effective?

DR. SCHULMAN: This important question has been re-examined in several laboratories in recent years and it has become apparent that antihemophilic globulin is appreciably more stable on storage under blood-bank conditions than previously thought. The earlier views were based on tests using oxalate as the anticoagulant, and it is now known that citrate leads to much greater stability of AHG on storage. With modern blood-bank technique as much as 30 to 40% of the AHG may disappear within 6 hours after the blood is drawn. Thereafter the rate of loss is much slower and as much as 50% of the original content of AHG may still be found after 1 week. Difficulty arises from the fact that the range of normal values for AHG in the original donor blood varies from 60 to 180% and also the rate of subsequent fall is highly variable. Therefore if one chooses blood or plasma which has been stored for 1 week, it is impossible to tell in

advance whether or not it has significant anti-hemophilic activity. We prefer to use blood as plasma which is less than 24 hours old, whenever possible. Probably the best method available today for preserving AHG activity is freezing the plasma within a few hours after it is obtained. We maintain a bank of fresh frozen plasma, here, and many other institutions do likewise.

QUESTION: What is the value of ordinary lyophilized plasma?

DR. SCHULMAN: Lyophilization appears to be a fairly good method of maintaining anti-hemorrhagic activity providing it is carried out soon after blood is obtained, when adequate AHG is present. The ordinary lyophilized plasma does not contain significant amounts of AHG because the pools of plasma used as a source are not very fresh. There is, however, one good commercial preparation of lyophilized plasma which is prepared with the specific intent of maintaining AHG activity. This is available from the Hyland Laboratories and is

called "Anti-Hemophilic Plasma." In the preparation of this product, the donor plasma is frozen within hours after it is obtained and is lyophilized from the frozen state. We have assayed several lots of this plasma and have found an average AHG activity of 70%. The preparation is extremely stable and many patients carry it with them when they travel. We find it a useful preparation to have available.

QUESTION: What is the relative incidence of deficiency of these major factors?

DR. SCHULMAN: The only adequate data we have pertains to the relative frequency of PTC deficiency. It is thought to constitute about 15% of the total number of patients with "hemophilia." We have the impression here that in all probability PTA is going to be more common than the other two combined.

There is one important point that I neglected to stress earlier. PTC and AHG deficiencies are recessive traits and occur in males, whereas PTA is a dominant trait, and it can therefore be found in both boys and girls.

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Pediatrics 1958;21;155

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