Symposium: What Is Hemophilia?

Hemophilic Syndromes and Hemophilia

By LEANDRO M. TOCANTINS, M.D.

FOR SOME TIME, to most of us, the term hemophilia meant a clinical disorder characterized by a tendency to bleed, strongly familial, almost exclusively present in males and characterized by a prolongation of the clotting time of the blood. As with other diseases, additional clinical experience and expanding knowledge of the mechanisms of blood coagulation has made it necessary to revise this definition. We must now recognize the existence of hemophilic syndromes almost indistinguishable from hemophilia on clinical grounds alone, but amenable to differentiation and characterization by special studies.

A patient may be said to have a hemophilic syndrome when he displays an abnormal tendency to bleed (inherited, congenital, or acquired) because of a delay in the rate of coagulation of his blood. Fundamentally, this delay may result from a slow or insufficient elaboration of (1) plasma thromboplastin, (2) thrombin, or (3) fibrin. Though any of these defects may give rise to a hemophilic syndrome, the one for which we believe the term hemophilia (classic hemophilia, hemophilia A) should be reserved, is that resulting from a slow or insufficient elaboration of plasma thromboplastin, because of a defective platelet cofactor/lipid inhibitor conjugate in the plasma.

Components and Evolution of Plasma Thromboplastin

In table 1 are listed the components that enter into the generation of plasma thromboplastin. According to this schema, a cephalin-like lipid factor contained within the platelets, which in themselves have little immediate thromboplastin activity, forms one component. The other, in the plasma, is in the form of a conjugate, made up of the platelet cofactor associated with a lipid inhibitor. In the undissociated form, this platelet cofactor/lipid inhibitor conjugate resists activation by the platelet cephalin-like lipid. The latter, on the other hand, is unavailable for the reaction, so long as the platelet remains intact, as in unshed blood. The normal cofactor inhibitor conjugate is represented diagrammatically in figure 1 as a large sphere (the plasma cofactor) covered by a number of smaller spheres (the lipid inhibitor).

Plasma thromboplastin is formed by the interaction of the platelet lipid with its cofactor in the plasma. Two events precede this interaction: (1) Disruption of platelets; (2) dissociation of the plasma cofactor conjugate. Contact with certain surfaces may produce both of these changes. It follows that a slower than normal elaboration of plasma thromboplastin may result from one of three causes:

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TABLE 1.—Components and Evolution of Plasma Thromboplastin

<table>
<thead>
<tr>
<th>A. Components:</th>
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<tbody>
<tr>
<td>1. Platelet lipid factor (in platelets)</td>
<td></td>
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<tr>
<td>2. Platelet cofactor/lipid inhibitor* conjugate (in plasma)</td>
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<td>B. Evolution:</td>
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<tr>
<td>1. Contact with injuring surfaces:</td>
<td></td>
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<tr>
<td>a) Disruption of platelets, freeing of platelet lipid surfaces</td>
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<tr>
<td>b) Dissociation of plasma cofactor/inhibitor conjugate</td>
<td></td>
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<tr>
<td>2. Platelet + (cofactor/inhibitor) [\rightarrow] Platelet lipid/cofactor + free lipid lipid conjugate [\rightarrow] inhibitor</td>
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</table>

* Lipid antithromboplastin.  
† Plasma thromboplastin.

1. Pronounced Diminution or Absence of Platelets

A simple diminution in the number of platelets will slow the rate of conversion of prothrombin, but since a great excess normally exists in the blood, even 10,000 platelets per cu.mm. will provide sufficient platelet material for thromboplastin generation; moreover, since only a small amount of thrombin is needed to start coagulation, thrombocytopenia, per se, will seldom delay significantly the rate of blood coagulation, especially in glass. When platelets are virtually absent, however, (as after acute total body irradiation) elaboration of plasma thromboplastin is negligible and plasma antithromboplastin becomes relatively and, sometimes, absolutely increased. In acutely irradiated dogs, this leads to a hemophilia-like disorder which responds readily to platelet-rich plasma transfusions.

2. Disproportionate Increase in the Lipid Inhibitor (Antithromboplastin) Conjugated with the Plasma Cofactor of Platelets

This is shown schematically by the large complexes in figure 1. When such are present, the amount of platelet material available is insufficient to overcome the excess of inhibitor and the interaction of platelet lipid and its plasma cofactor is prevented or greatly slowed. Little or no plasma thromboplastin therefore is

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**Fig. 1**—Diagramatic representation of the theoretic relationships between the platelet cofactor of the plasma and lipid antithromboplastin in normal and hemophilia A and B blood.
formed. We consider this to be the fundamental defect in hemophilia A blood. Various degrees of excess of antithromboplastin activity above normal account for the different degrees of severity of hemophilia, and the corresponding variations in the rate of coagulation and prothrombin conversion of hemophilic blood. Individuals whose blood coagulation has been normal may develop an excess of this anticoagulant; their blood will then behave essentially like hemophilic (A) blood. Hemophiliacs themselves have, perhaps, as a reaction to repeated transfusions, been known to develop even greater excesses of this inhibitor than they had previously. In our judgement, these represent instances of more or less transient increases in a naturally occurring blood anticoagulant and not the appearance of new anticoagulants, or antibodies against certain blood coagulants. The same state may be produced experimentally by the simple intravenous injection of lipid antithromboplastin.

3. Disproportionate Decrease in the Platelet Plasma Cofactor with which the Lipid Inhibitor is Conjugated

This may constitute the fundamental defect in certain patients thought to have had hemophilia A, but whose blood coagulation is said to be corrected by addition of plasma from other hemophilic patients with a blood coagulation time sometimes even longer than their own. The platelet cofactor of plasma corresponds probably to the “plasma thromboplastin component” (PTC). We may expect that various degrees of insufficiency of this factor may be found. The defect is represented by the small complexes on the extreme right of figure 1.

We have now observed two examples of this disorder. To this group the designation hemophilia B would seem appropriate. When a small portion of hemophilia A plasma is added to hemophilia B blood or plasma, the rate of coagulation is rendered normal or even shorter than normal. Listing of other points necessary for the characterization of this form of hemophilia is here deferred at this time, in view of the incompleteness of our knowledge concerning it.

WHAT SHOULD AND SHOULD NOT BE EXPECTED FROM THE BLOOD IN HEMOPHILIA A

The blood of a patient with uncomplicated hemophilia of this type should almost always display a delay in its rate of coagulation when the test is properly performed in glass tubes, and always when silicone surfaces are used. The bleeding time of shallow cuts of the skin should be normal, but that of deep (5 mm. or greater) cuts should be prolonged. The delayed clotting time of venous blood and plasma should be markedly shortened by dilution (down to a 10 per cent blood concentration) with physiologic salt solution. There should be, during clotting, a slow and insufficient elaboration of plasma thromboplastin, which can be corrected by an excess of platelets or cephalin. The formation of thrombin, serum accelerator globulin, and fibrin should also be slow or insufficient, but can be rendered normal by adequate amounts of thromboplastin. The concentration of platelets, prothrombin, Ca, Ac-globulin, and fibrinogen in the blood should be normal. The conversion of prothrombin to thrombin in blood or plasma should be slower than normal, especially when platelets, cephalin, or diluted thromboplastin are used as activating agents. This slower response should be rendered
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essentially normal by appropriate dilution of the blood or plasma or by adding an excess of these activating agents. Platelet-poor hemophilic plasma should delay the rate of clotting of an equal amount of platelet-poor normal plasma in a clotting mixture of near 100 per cent plasma concentration, in silicone coated tubes, and sometimes even in glass tubes. There should be no increase in anti-thrombin or profibrinolysin. The addition of protamine to the blood should not shorten its rate of coagulation. The antithromboplastin (antiepiphelin) activity of the plasma when tested by one-stage or two-stage methods should be several times greater than that of normal plasma. The euglobulin separated by a 1 to 10 dilution of hemophilic plasma, followed by acidification and centrifugation, should have much less clot promoting activity on hemophilic plasma than a similarly prepared euglobulin obtained from normal plasma; if the euglobulins are prepared from a greater than 1 to 100 dilution of the plasma, their activities should be alike. The plasma cofactor activity (for the elaboration of plasma thromboplastin) of hemophilic plasma should be less than that of normal plasma; after suitable extraction with ether, the two plasmas should behave alike. Addition of a well adjusted amount of purified lipid antithromboplastin to stable normal plasma should make it behave, with respect to the functions named above, essentially as hemophilic plasma. The transfusion of normal blood or plasma (500 ml.) collected without special precautions, by supplying partly dissociated normal platelet cofactor conjugates, should transiently shorten the rate of blood coagulation of mild or moderate hemophiliacs, but have little or no effect on the blood of severe hemophiliacs.

SUMMARIO IN INTERLINGUA

Le termino synsdromc hemophihic c-s proponite pro qualcunque tendentia hemorrhagic (hereditate, congenite, o acquirite) in tanto que illo resulta de un relenstamensto del coagulation del sansguinse. Iste relenstamento pote esser causate per uins elaboration insufficicente de (1) thromboplastina dcl plasma, (2) throm-

bina, o (3) fibrina. Le termino hemophilia (hemophilia classic, hemophilia A) deberea esser restringite a casos de insufficienste elaborations de thromboplastinsa del plasma debite a un excesso de antithromboplastina. Es presentate un schema del evoluzione de thromboplastina del plasma sequite per un discussion del factores que pote relientar lo. Le presentation es un summario de vinti articulos previemente publicate.

REFERENCES*


* Because of the limited scope of the presentation, the supporting evidence for the statements and hypothesis above is being deliberately omitted, but may be found in these papers.
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