Symposium: What Is Hemophilia?

Hemophilia and the Hemophilioid States

By K. M. Brinkhous, M.D. and John B. Graham, M.D.

HEMOPHILIA has been studied with increasing intensity in both man and animals in recent years. The biochemical derangement appears to be due to a genetically determined deficiency of a specific plasma protein, the antihemophilic factor (AHF), which is required for effective conversion of prothrombin to thrombin. Also, certain bleeders appear to have inherited as a sex-linked recessive character a disease with severe hemorrhagic manifestations, including hemarthroses, which is not true hemophilia.1, 2, 7, 16 Contrariwise, certain bleeders who suffer only from easy bruising or excessive postoperative bleeding, often without a family history of a hemorrhagic tendency, prove to have hemophilia after determination of plasma AHF.5, 11 These observations have led to the recognition of hemophilia as an inherited disease in which AHF activity may be almost absent (classic hemophilia) or present in amounts inadequate to provide effective hemostasis under severe stress (mild hemophilia and subhemophilia). These forms of hemophilia have been distinguished from several clinically similar diseases, also genetically determined, which may be referred to as the “hemophilioid states” (Ac-globulin deficiency, SPCA deficiency, PTC deficiency, PTA deficiency). In each of the hemophilioid diseases, as in true hemophilia, there appears to be a deficiency of a plasma protein which is needed for effective thrombin formation and hemostasis.

The basic defect in all of these diseases appears to be failure of the body to synthesize certain plasma proteins necessary for the clotting process. A widely held theory of biochemical genetics is that protein synthesis is due to the action of specific enzyme systems on appropriate substrates, the specific synthesizing enzymes being controlled by hereditary units, the genes. A one-to-one relationship between gene and enzyme is believed to exist, a given gene controlling the production of a single enzyme. This hypothesis implies that there are at least two ways in which the mutant gene might express itself:

1. The mutant gene might be responsible, through impaired enzymatic synthesis, for an alteration in the molecular structure of a clotting protein, rendering it functionally inadequate. On the other hand, the mutant gene might operate to limit the rate of formation of the enzyme so that only trace quantities of a protein with normal functional activity could be produced. Perhaps both mechanisms are operative in hemophilia and the hemophilioid states, as has been postulated in hemoglobin synthesis.14

2. A simpler and therefore, perhaps, less likely relationship between the mutant genes and the clotting factors is the possibility that each factor is itself a proenzyme or enzyme whose chemical structure is based directly on a gene.
model. Mutation, or stereoisomeric rearrangement, of the gene itself might result directly in a similar rearrangement of the enzyme molecule (clotting factor), causing it to lose specificity for its substrate, thus introducing a block into the complex reactions leading to the conversion of prothrombin to thrombin.

In view of the many similarities between hemophilia and the hemophiloid states, hemophilia needs to be clearly distinguished from the other diseases. It is a genetic disease of blood clotting which is transmitted as a completely sex-linked characteristic, and is characterized by slow conversion of prothrombin to thrombin without added thromboplastin. Furthermore, AHF, the clotting factor defective in hemophilia, is not adsorbed from normal plasma by the usual alkaline earth adsorbents (BaSO₄, BaCO₃, etc.), requires platelets for its action, and disappears during the clotting of normal blood. This factor is precipitated from plasma, along with fibrinogen on salt fractionation, but is dissociated by cautious heat denaturation of the fibrinogen. It is possible that at some future date another disease possessing the above characteristics will be discovered. In such case, perhaps the strain of Irish setter dogs, which appears to be deficient in the same factor as human hemophiliacs, could become the standard of reference for hemophilia.

During the past several years, much effort in this laboratory has been devoted to developing methods for the accurate measurement of the antihemophilic factor. From this work two assay procedures have evolved. The earlier one is based on the corrective effect of AHF on the defective prothrombin utilization of hemophilic whole blood. The more recent method, simpler but no less accurate, is based on the ability of AHF to shorten the clotting time of hemophilic plasma in the presence of partial thromboplastins. Observations made while assaying human plasmas by these techniques have led us to postulate that the mutant for classic hemophilia and the normal dominant gene are members of a larger allelomorphic series. The milder forms of hemophilia appear due to the presence of still other members of the allelic series. With the AHF assay, it has been found that patients with diminished AHF can be placed in one of four categories, each of which is characterized by bleeding symptoms of a different degree of severity. The severity of the symptoms, of course, increases with decreasing AHF titer. The proposed names for the grades of hemophilia, their characteristic AHF levels, and suggested genic notations are shown in table 1.

The fact that the normal range of AHF is quite large suggests that there are other alleles responsible for characteristic AHF levels among normal individuals. We have proposed that the hemophilia locus on the X-chromosome is capable of occupancy by any one of a number of alleles ranging from the

<table>
<thead>
<tr>
<th>Grade of Hemophilia</th>
<th>AHF Levels</th>
<th>Suggested Gene Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic hemophilia</td>
<td>0-trace</td>
<td>h</td>
</tr>
<tr>
<td>Intermediate hemophilia</td>
<td>±5%</td>
<td>h_i</td>
</tr>
<tr>
<td>Mild hemophilia</td>
<td>±15%</td>
<td>h_m</td>
</tr>
<tr>
<td>Subhemophilia</td>
<td>±35%</td>
<td>h_s</td>
</tr>
<tr>
<td>Normal</td>
<td>70-180%</td>
<td>H, H', H''...</td>
</tr>
</tbody>
</table>

* 100 per cent AHF = mean of twenty eight randomly selected normal individuals.
normal dominant $H \ldots$ through the mild hemophilia gene $h^m \ldots$ to the classic hemophilia gene $h$. The exact order of dominance in this series remains to be determined.

Recently, it has been suggested that one of the hemophilioid diseases, "PTC deficiency" (Christmas disease), be called hemophilia B or II$^{22, 24}$ because of its similarity to classical hemophilia. This designation will probably prove popular because of its simplicity. However, this terminology implies that hemophilia and PTC deficiency are allelic in the same sense as mild and classic hemophilia.$^{24}$ This appears to us a highly unlikely possibility.$^{22}$ Although both hemophilia and PTC deficiency appear transmitted as sex-linked mutations and have similar clotting defects and clinical courses, the clotting anomalies are due to factors with entirely different properties. The genes are almost certainly located at different loci on the X-chromosome because there is normal AHF in PTC deficiency and normal PTC in hemophilia, this in men whose cells contain only one X-chromosome, and thus only one allele at the $H-h$ locus. Linkage studies with colorblindness or some other sex-linked gene might settle this important point.

Table 2 contains our suggestion for nomenclature for this group of bleeding diseases. It will be observed that the method of designation is elastic, avoids eponyms and implies no special insights into the poorly understood intricacies of blood coagulation. It might be noted that the hemoglobin chemists have recently adopted a comparable nomenclature as the solution for a somewhat similar problem.$^6$

Plasmas from affected individuals have been widely used as substrates in clotting tests for the diagnosis of these clotting disorders.$^1, 5, 17, 18, 20$ The validity of this diagnostic technic obviously depends upon the specificity of action of the mutant genes. Most of the available data suggest that the effect of each mutant is highly specific, as the known effects are limited to the blood, and the clotting defects are constant in a single pedigree. Plasmas from any one of the five better-known anomalies correct the clotting defect in all of the others.$^5$ The only published exception to this generalization has been reported recently.$^{21, 22}$ This patient appears to have both hemophilia and hemophilioid state C. If he has a double defect, it remains to be seen whether a single or multiple mutants are being transmitted.

**SUMMARIO IN INTERLINGUA**

Es postulate que le factor antihemophilic e su deficiencia in hemophilia es regulate per un gen dominante e un correspondente serie allelomorphe de muta-
tiones. De acordo con isto on propone un classification del hemophilia in (1) hemophilia classic, (2) hemophilia intermediari, (3) hemophilia benigne, e (4) subhemophilia. Es postulate in plus que le morbos hemophilioide non pertine in le mesme serie allelomorphe. On propone classificar los como statuses hemophilioide A, B, C, D, e presenta lor symptomas e probable modos de transmission genetic.

REFERENCES
Symposium: What Is Hemophilia?: Hemophilia and the Hemophilioid States

K. M. BRINKHOUS and JOHN B. GRAHAM