Symposium: What Is Hemophilia?

Is Hemophilia a Nosologic Entity?

By F. Koller, M.D.

Hemophilia has, until recently, been considered an apparently well-defined clinical entity, characterized by a general bleeding tendency, with special emphasis on the following points: frequent joint bleeding, various skin hemorrhages (with the exception of petechiae), a markedly prolonged clotting time and—last but not least—a sex-linked recessive hereditary transmission.

Hemophilia A and B

In 1950 we observed a family with a mild form of hemorrhagic diathesis, inherited as a recessive sex-linked characteristic, the clotting defect of which was entirely corrected by blood of a “typical” hemophiliac. We concluded at that time that a sex-linked hemorrhagic diathesis (i.e., hemophilia) might be produced by the deficiency of two different clotting factors.*

Similar observations have been made by Aggeler, et al., Biggs, Macfarlane, et al., and Schulman, et al. in 1952. The differentiation of the two clotting factors involved in hemophilia was especially furthered by the thromboplastin generation test of Biggs, which showed that one of the two factors disappears during the clotting process whereas the other maintains its activity in serum.

The following designations have been proposed:

<table>
<thead>
<tr>
<th>Factor disappearing during coagulation</th>
<th>Factor present in serum</th>
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<tbody>
<tr>
<td>Antihemophilic globulin of Cohn et al.</td>
<td>Christmas factor of Biggs and Macfarlane</td>
</tr>
<tr>
<td>Factor VIII*</td>
<td>Plasma thromboplastin component (PTC) of Aggeler, et al.</td>
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<td>Factor IX†</td>
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</table>

Deficiency: hemophilia A

Deficiency: hemophilia B

The hemorrhagic diatheses corresponding to a deficiency of these factors cannot be differentiated clinically. Both show a sex-linked hereditary transmission. In our opinion the time honored designation “hemophilia” has, therefore, to be applied to both. In order to differentiate the two forms we propose to call the deficiency of Factor VIII: “hemophilia A”, the defect of Factor IX, “hemophilia B”. In both instances the pathologic gene has to be localized in the X-chromosome (fig. 1).

Until now we have examined nineteen cases of Swiss hemophiliacs with a modified thromboplastin generation test. Ten proved to have hemophilia A,

* Pavlovsky had already, in 1947, reported in this journal on matching experiments with blood samples of hemophiliacs—showing mutual normalization of the clotting defect. He interpreted these results as being due to the neutralisation of an inhibiting factor.
nine hemophilia B. The Swiss bleeder family with the most extensively studied pedigree, the bleeders of Tenna, are affected with hemophilia B. We had the opportunity of examining four representatives of this family; all of them showed the characteristics of hemophilia B. This observation favors the assumption that in the same family the same form of hemophilia is found. In the genealogic tree of the bleeders of Zurich Oberland we found, however, one case of hemophilia A as well as one of hemophilia B. As these two hemophiliacs are only distantly related, their pedigrees joining in the sixteenth century, the existence of two independent genetic abnormalities can be presumed.

**Allelic Form of Hemophilia**

The Moëna family, already mentioned, is characterised by a mild form of hemophilia, which never produces joint hemorrhages. The typical hemophiliac, whom we used as test person and whose plasma was able to normalise the clotting defect of this family, proved to have hemophilia B. The anomaly of the Moëna family is, therefore, hemophilia A, but the analysis of the clotting defect showed that there is no complete absence but only a reduction of antihemophilic globulin (factor VIII). Its concentration in one typical member of the family was estimated to be 25 per cent of normal.

These findings are in complete agreement with those of Graham, McLendon, and Brinkhous, who postulated that the mild gene is an allelic mutant occurring at the same locus of the x-chromosome as the classical hemophilia gene. It is probable that both hemophilia A and B can occur in this allelic form. This mild hemophilia is probably much more frequent than hitherto assumed.

**Genuine and Concomitant Hemophilia**

The cases referred to so far may be considered as genuine hemophilia. They are not—as far as we know—associated with any other anomaly; the only pathologic finding is the absence or reduction of one clotting factor. Recent observations have shown, however, that not only in acquired but also in hereditary or congenital coagulopathies more than one clotting factor may be involved.
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In two brothers with congenital factor V* (Ac globulin) deficiency, we were able to demonstrate a concomitant factor VIII (antihemophilic globulin) defect; mixture of this plasma with plasma of typical hemophilia A (factor VIII deficiency) had no influence on the delayed thromboplastin generation, although Quick's prothrombin time was entirely normalised. This observation proves that hemophilia A plasma contains factor V in normal amount, but corrects the clotting defect of factor V deficient plasma only partially, the latter being combined with factor VIII deficiency. If this combination applies to all cases of factor V deficiency one may speculate that factor V or its precursor is necessary for the production of antihemophilic globulin (factor VIII). This would explain the fact that factor V deficiency is characterised by a markedly prolonged clotting time (Lee-White method) although factor V alone has only a minor influence, if any, on the production of blood thromboplastin. The latter is, however, decisive for the Lee-White clotting time.

We suggest calling a deficiency of one of the antihemophilic factors (factor VIII and factor IX), associated with a lack of another clotting factor, concomitant hemophilia. The cases just presented justify the designation "concomitant hemophilia A".

Is there any evidence for the existence of concomitant hemophilia B?

If sera of different cases considered as hemophilia B (on the basis of the thromboplastin generation test) are mixed, usually no normalization of the clotting defect occurs. This is also true if serum samples of Swiss bleeders (of the B type) are mixed with those of English hemophiliacs, showing that an identical clotting defect is present.† However, in rare instances, a partial normalization may be found. The analysis of the coagulation defect of these cases (we have observed two until now) shows that it cannot be explained by the assumption of an allelic form of hemophilia B alone. Another clotting factor must be involved for which the designation factor X has been proposed. The existence of this latter clotting factor has been demonstrated by matching experiments of serum of various acquired hemorrhagic diatheses with serum of genuine hemophilia B. Factor X is decreased during dicoumarol treatment, in K avitaminosis, in hepatitis, in the newborn, etc. It disappears slowly during storage. In the rare cases mentioned above, a deficiency of factor X (hemophilia C?) with concomitant hemophilia B (factor IX deficiency) might be assumed. Mixture of serum of these cases with dicoumarol or hepatitis serum always produces only partial normalization of thromboplastin generation. Both the deficiency of factor IX and that of factor X appear to be incomplete. In one of our two cases a sex-linked hereditary transmission seems most probable. Further experiments are necessary to elucidate the manifold problems raised by these observations.

The analysis of the clotting defect in hemophilia has contributed greatly to the understanding of the normal coagulation mechanism. Ten plasmatic clotting factors have been differentiated at the present time. In table 1 they are numbered

* We are indebted to Dr. Hauser Basel for having sent us blood samples of a family with factor V deficiency. A complete report of these findings will be published in Acta haematologica.
† We are indebted to Drs. Biggs and Macfarlane who supplied us with serum of a case of Christmas disease (hemophilia B).
TABLE 1.—Hemorrhagic Diatheses with Deficiency of Clot Promoting Factors

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Acquired</th>
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<tr>
<td>Factor I: Fibrinogen</td>
<td>Afibrinogenemia</td>
</tr>
<tr>
<td>Factor II: Prothrombin</td>
<td>“Essential” hypoprothrombinemia</td>
</tr>
<tr>
<td>Factor III: Thromboplastin</td>
<td>(see factors VIII to X)</td>
</tr>
<tr>
<td>Factor IV: Calcium</td>
<td>no hemorrhagic diathesis</td>
</tr>
<tr>
<td>Factor V (VI): Parahemophilia</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Factor VII: Familial factor VII deficiency</td>
<td>Purpura fulminans</td>
</tr>
<tr>
<td>Factor VIII: Antihemophilic globulin</td>
<td>Vitamin K deficiency</td>
</tr>
<tr>
<td>Factor IX: Christmas factor, PTC</td>
<td>Dicoumarol effect</td>
</tr>
<tr>
<td>Factor X:</td>
<td>Hemophiloid of the newborn?</td>
</tr>
<tr>
<td></td>
<td>Liver disease</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>Dicoumarol effect</td>
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</tbody>
</table>

According to their discovery in chronologic order with the exception of factor VIII which was discovered before factor VII but has close clinical connections with factor IX. As a rule a congenital or hereditary as well as an acquired hemorrhagic diathesis corresponds to each. The deficiency of an isolated factor is found only in hereditary hemorrhagic diatheses. As already mentioned there are, however, congenital or hereditary bleeding tendencies characterized by a lack of two factors (factors V and VIII for instance). In acquired hemorrhagic diatheses several factors are always involved (prothrombin, factors VII and X in dicoumarol treatment, in K avitaminosis, and in the newborn; almost every factor in severe liver disease, etc.).

The exact mode of action of these different clotting factors is still unknown. Biggs and Macfarlane presented evidence that the majority act in the gener-
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ation of a potent blood thromboplastin. Table 1 summarizes our present knowledge of the clot promoting mechanism.* It is clear that the classical coagulation scheme of Schmidt, Hammarsten, Arthus, Morawitz, and others is still valid and needs only to be completed by the series of factors necessary for the production of blood thromboplastin.

In conclusion, genuine hemophilia may be defined as a bleeding tendency with a sex-linked recessive inheritance. Its clotting defect is not uniform: hemophilia A is characterized by a deficiency of factor VIII (antihemophilic globulin), hemophilia B by a lack of factor IX (Christmas factor, PTC). A deficiency of these antihemophilic factors may be associated with other clotting defects (congenital factor V deficiency for instance). For these conditions the designation concomitant hemophilia is proposed.

SUMMARIO IN INTERLINGUA

Usque recentemente hemophilia poteva esser considerate como un ben-definite entitate clinic. Nove studios e recercas (hic sunmmarisate) require un conception minus rigide. Es proponite le sequente definition: Le termino hemophilia designa qualunque tendentia hemorrhagic characterisate per un deficiencia partial o complete de ille factores coagulative que manca in le varie formas de diathese hemorrhagic hereditabile como character recessive a specificitate sexual. Le deficiencia pote esser o genuin o accessorii.

REFERENCES


* The points of interrogation below factor V & VII signify that the rôle of these factors in the generation of blood thromboplastin is still open to question (in opposition to their unequivocal effect in the activation of tissue thromboplastin).
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F. KOLLER

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