Symposium: What Is Hemophilia?

Hemophilia, Christmas Disease, and Matters of Terminology

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The sudden posing of the question “What is hemophilia?” is slightly dismaying to anyone familiar with the confusion of the subject, and before attempting to give an answer, it might be helpful to review the evolution of ideas associated with the name “hemophilia” because it is the repeated change of meaning which has led to present difficulties. Actually, the pattern of this evolution is not unusual; it has, among many others, a close parallel in the growth of ideas on pernicious anemia, which has been admirably described by Robb-Smith. We can take comfort, therefore, in the fact that the problem set by the question “What is hemophilia?” is no worse than those raised by other questions of this sort. What, for example, is Hodgkin’s disease, or acholic jaundice?

The birth and development of a clinical entity seems to follow a consistent pattern. Out of a heterogeneous mass of clinical observations there crystallizes an apparently homogeneous condition which can be defined by certain characteristics not previously appreciated. With this emergence from the background the newly recognised condition develops both forward and, paradoxically, backward in time. Thus, in the light of a new definition, past observations take on a new significance. Fresh cases conforming to the definition are found in old records and at any time the earliest discovered may earn for its recorder an unforeseen distinction, one which may soon be lost as historical research pushes further back. Simultaneously there is the more important evolution of the contemporary view of the disease. As methods of investigation improve and multiply, so the essential process of recognition is widened and made more precise. The accepted characteristics of the disease can be perceived or measured more accurately and new ones become apparent. As a result, it often happens that what was taken to be a single entity is found to consist of a group of entities now distinguishable from each other, and sub-division of the original condition becomes inevitable. Thus the old definition has to be changed and with it, incidentally, much of the history of the disease. In fact the general concept of a condition such as hemophilia is not static. All contemporary views of the condition, and of its past, change continuously. I cannot do more now, therefore, than to present my view of hemophilia as it is at this time.

The realization that conditions existed in which the patient might bleed uncontrollably, even fatally, from slight injuries began and grew rapidly during the first half of the nineteenth century. Accounts of individuals and families affected in this way appeared with increasing frequency during this time, but there was no uniformity of nomenclature. The condition was variously referred to as “the hemorrhagic disposition”, “hemorrhagy”, “hemorrhea”, “pernicious hemor-
rhage”, “idiosyncrasy hemorrhagica”, “hemorrhagic diathesis” and “hemorrhaphilia”. It was not until about 1850 that the term “hemophilia” began to establish itself. It had apparently been first used in 1828 by Hopff, and was resuscitated by Steiner. It is clear from the exhaustive historical review of Bulloch and Fildes that many of these cases of abnormal bleeding to which the term “hemophilia” was applied would not be accepted as such today. Among them were examples of purpura hemorrhagica, scurvy, and probably of telangiectasia and many cases in which the hemorrhage was secondary to some other disease process.

The concept of hemophilia as we now know it probably arose from the work of Nasse who recognized among the many available descriptions of “bleeders” a definite syndrome consisting of a liability for males to bleed abnormally, this liability being transmitted by apparently normal females through their marriage to normal males. This peculiar mode of inheritance, known for some time as “Nasse’s law”, provided a clear distinction from other hemorrhagic states. It was to cases so distinguished that the name “hemophilia” became more and more frequently applied, and early descriptions of such a condition were recognized in the writings of Otto, Consbruch, and Alsatavius, and in the Talmud. But the process of definition was by no means rapid. For many years cases of hemophilia were described under other names and the same “hemophilia” was (and still is) applied to other conditions.

With increasing knowledge of the disease there came an increasing precision of diagnosis. The swelling of the joints noted by the earliest writers was later recognised as a characteristic hemorrhagic manifestation and regarded by many authorities as pathognomonic of hemophilia. An important advance was provided by the work of Wright, who introduced a method for measuring the clotting time of blood and showed that this time was prolonged in hemophilia. Thus a number of well-defined criteria were available by the beginning of the present century: the history of an abnormal liability to hemorrhage existing from early childhood; the limitation of this hemorrhagic state to males; its inheritance through apparently normal females; the joint hemorrhages and a demonstrable delay in the clotting of the blood. With the aid of these criteria, Bulloch and Fildes produced, in 1911, their critical review of the whole of the available literature concerned with hemophilia, a monumental work which is the foundation of the modern concept of the condition. From a mass of descriptions of hemorrhagic states these authors were able to select those cases which conformed to their definition of hemophilia. It is now evident that, invaluable as this definition was, it is not completely satisfactory today, being at once too narrow, excluding cases now acceptable, and too wide, thus including cases that should now be excluded. Bulloch and Fildes considered that hemophilia was not transmitted in any way by the affected male. They criticized or rejected the diagnosis of hemophilia in families in which males had transmitted the condition, even through their daughters to their grandsons. They also rejected the possibility that hemophilia could occur in females, and they were suspicious of any case in which a positive family history was not obtained. Our present view of the sex-linked inheritance in hemophilia insists that all the daughters of an affected male are transmitters and
that the homozygous female will herself show hemorrhagic tendencies, a theory substantiated by human experience and by experimental breeding of "hemophilic" dogs. It is now recognised that there is a high mutation rate in hemophilia with a correspondingly high proportion of patients who have no family history.

The most recent advances in the recognition of hemophilia have sprung from investigation of the mechanism of coagulation. Addis,11 in 1911, showed that a small proportion of the globulin fraction of normal plasma would, when mixed with hemophilic blood, correct its clotting defect. This observation, misinterpreted at the time, was confirmed and extended many years later by Govaerts and Gratia,12 Patek and Stetson,13 and Pohle and Taylor.14 From this work there grew the concept of a previously unrecognised factor known as antihemophilic factor or antihemophilic globulin which is present in normal plasma but deficient or inactive in hemophilic plasma. Thus the emphasis in the definition of hemophilia shifted from clinical and genetic observations to the demonstration of the deficiency of a specific plasma factor. One could define hemophilia at that stage as an "inborn deficiency of antihemophilic globulin, this defect being inherited as a sex-linked (x-borne) recessive character." Such a definition at once raises the necessity of defining what one means by "antihemophilic globulin". To state that "antihemophilic globulin is the factor which is deficient in hemophilia" does not advance the matter to any marked degree. Yet this circular definition has been the basis of much diagnostic work on hemophilia and is typical of serologic work in general. One determines if a particular patient has a deficiency of antihemophilic globulin by testing the ability of his plasma to correct the clotting defect of known hemophilic plasma, that is, of plasma from a patient conforming to one's preconceived idea of hemophilia. This sort of testing was used by Joules and Macfarlane15 in 1938 to show that a female patient had a deficiency of antihemophilic factor, though she was not suffering from hereditary hemophilia. Similar testing was extensively used by Merskey16 in his study of the laboratory diagnosis of hemophilia. This work demonstrated that the whole blood clotting time is not a sensitive test of a deficiency of antihemophilic globulin. More sensitive, but also nonspecific, are the prothrombin consumption and thrombin generation tests, which reveal deficiencies not detected by determinations of coagulation time, but the specific identification of the deficiency depended, until the introduction of the thromboplastin generation test, on the use of a standard hemophilic blood sample with an attendant danger that the patient then regarded as a standard hemophilic might subsequently be considered to have some other condition.

The idea of mixing blood samples from established and supposed hemophilic patients has had interesting results. Pavlovsky,17 Koller, et al.,18 Aggeler, et al.,19 Schulman and Smith,20 and Poole21 all reported that blood from certain cases resembling hemophilia had the ability to correct the clotting defect of known hemophilic blood. Thus it appeared that the condition usually referred to as hemophilia might be heterogeneous or at least contain sub-varieties. This was confirmed by the observations of Biggs, et al.,22 who studied seven cases clinically indistinguishable from hemophilia, although the blood from them corrected known hemophilic blood. Since there was evidence that these seven patients were all suffering from the same defect it was considered that they were examples
of a hemorrhagic state distinct from hemophilia, which was called Christmas disease from the name of the first patient.

Thus, by mixing blood samples, one can separate what might be called the pre-1950 variety of hemophilia into at least two categories. The first consists of a larger group of patients with severe symptoms and a clear cut sex-linked recessive inheritance; the second is a smaller group in which the symptoms may be in general less severe and the inheritance, though predominantly sex-linked, may be less definite. This second group, which itself may not be homogeneous, includes the condition we have called Christmas disease. The distinction between these two groups is of clinical importance, since cases in the second will not respond to the therapeutic administration of antihemophilic globulin preparations.

Information obtained from mixture experiments is restricted, merely indicating that the clotting defect in the two groups is different in origin. More positive information can be obtained by an independent definition of antihemophilic globulin and of any other factors which by their deficiency may produce a hemophilia-like condition. Antihemophilic factor is present in normal plasma, associated with the globulin and fibrinogen fractions, or more specifically with Fractions I, III, and III2 of Cohn. There are indications that further electrophoretic definition may be possible. Active antihemophilic globulin is consumed during clotting and is therefore not present in serum; it is not adsorbed by BaSO4 or Al(OH)3. Its function for many years defied elucidation, but in 1947 Quick24 and Brinkhous25 independently showed that it was concerned with the platelets and after contact with a foreign surface, in the production of active thromboplastin. It has now been shown by experiments in Oxford26 that antihemophilic factor is an essential part of a system consisting of at least five factors which, following contact with a foreign surface, normally produces a thromboplastic activity capable of causing the coagulation of plasma in 8 seconds or less. It has also been shown that Christmas disease is due to the deficiency of another factor concerned in this thromboplastin-producing mechanism. This factor, which has been called the Christmas factor, is not consumed during coagulation, is present in serum, and is adsorbed by Al(OH)3. It is thus sharply differentiated from antihemophilic factor. In making the distinction between antihemophilic globulin and Christmas factor, or, indeed, between any of the recognised factors concerned in the early stages of coagulation, the thromboplastin generation test, developed by Biggs and Douglas,27 has proved valuable. This test allows each of the components of the thromboplastin-producing system to be assayed separately, so that it is no longer necessary to rely on blood samples from standard cases of deficiency of these factors in order to identify and measure their deficiency in unknown cases.

Aggeler, et al.19 had previously shown that a patient with a hemorrhagic condition resembling hemophilia lacked, not antihemophilic globulin, but a factor normally present in serum and adsorbed by BaSO4, which is probably identical with Christmas factor. They have called this factor “plasma thromboplastin component” or P.T.C., not a very satisfactory name since there are several known plasma thromboplastin components. There are indications that further division of the hemophilia-like conditions is impending since observa-
SYMPOSIUM: WHAT IS HEMOPHILIA?

tions by Rosenthal, et al. suggest that another factor, called by them "plasma thromboplastin antecedent", or P.T.A., may be distinct from those already described and cause a hemorrhagic condition by its deficiency.

What then is hemophilia? It is reasonable to suggest that the name, honored by long usage, should be applied exclusively and without qualification to what is still the most important hemorrhagic condition, the hereditary deficiency of antihemophilic globulin. This latter factor can be defined in terms of the properties already mentioned, and identified and assayed by means of the thromboplastin generation test. Conditions clinically similar to hemophilia, but due to the deficiency or inhibition of other factors, or to an acquired deficiency or inhibition of antihemophilic globulin should not be called hemophilia. Hemophilia and the conditions most likely to be mistaken for it all belong to the group of clotting defects in which hypothyromboplastinemia is the common result of different faults in the thromboplastin generating system. Included in this group are Christmas disease, quantitative or qualitative platelet-factor deficiency, and a number of conditions in which inhibitors of thromboplastin generation are present in the plasma. If one defines thromboplastin as the direct activator of prothrombin, then one must also include factor V and factor VII deficiencies among the hypothyromboplastinemas. All these deficiencies may be inherited or acquired, and all may have a similar symptomatology, but can readily be distinguished by means of the thromboplastin generation test. Hemophilia is usually considered peculiar among the hemorrhagic states in its mode of inheritance, but, from preliminary observations on Christmas disease, it would seem that this condition also may be inherited as an X-borne defect, though probably less recessive than hemophilia, since there are instances of affected heterozygous females. Though Christmas factor and antihemophilic globulin are apparently quite different entities, the similarity of their rare mode of inheritance suggests that they may be more closely related than in vitro studies have indicated. The inheritance of factor V, factor VII, and platelet-factor deficiencies appear from the scanty records available to be mainly of the simple dominant type.

There has been an understandable tendency to introduce the name "hemophilia", qualified in various ways, into the nomenclature of these conditions. Owen named factor V deficiency "parahemophilia"; Joules and Macfarlane applied the term "pseudohemophilia" to a case of acquired antihemophilic globulin deficiency; Graham and Brinkhous have suggested the names "hemophiloid state A, B, C, and D" for factor V deficiency, factor VII deficiency, Christmas disease, and P.T.A. deficiency respectively. Wiener considers that hemophilia and Christmas disease should be called hemophilia I (or A)" and "Hemophilia II (or B)" respectively. Such variants of the word "hemophilia" are confusing, and difficult to remember, and for these and other reasons given previously it would seem preferable to avoid them, and, when no established name like "hemophilia" is available, to refer to deficiencies in terms of the missing factor. As to the nomenclature of the factors themselves some agreement will have to be reached, and soon, if inextricable confusion is to be avoided. Meanwhile, it would be wise to use in each case an unassuming name, with a careful definition of the factor to which it refers, until it is clear that the factor
concerned actually exists, and its chemical or functional identification is established. It would be premature, for example, to use such terms as “thrombo-cytolysin”, “accelerin”, or “converting” until it is established that the factors concerned have the specific function of lysing, accelerating and converting respectively.

SUMMARIO IN INTERLINGUA

Historicamentemente un serie de reportos de varie casos de hereditari tendencias hemorrhagie in patientes masculine se crystallisava in le prime medietate del decenove seculo in le recognition de un specific syndrome designate circa 1850 como hemophilia. Iste termino esseva seligite inter varie candidatos. Depost 1911, investigaciones del mechanismo de coagulation permitteva le definition del syndrome hemophilic como un morbo causate per un deficiencia de globulina anti-hemophilic, occasionate per un character recessive a specificitate sexual. Recentie effortos a identificar le factor denominate globulina antihemophilic resultava in un differentiation inter illo e pure altere factores cuje deficiencia esseva recognoscite como causa de conditiones hemophiliode, inter illos le morbo Christmas (nominate assi secundo le nomine del patiente in qui illo esseva discoperite). Il es proponite qu3 le termino hemophilia sia usate exclusivemente pro casos de hemophilia classic e que omne conditiones hemophiliode sia identificate non per un modification del mesme termino sed per un locution que indica le specific factor deficiente in illos.

REFERENCES

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