The Diagnosis of Von Willebrand’s Disease

The definition of a disease by precise chemical criteria is an ideal we cannot expect to achieve easily. It has been attained in some rare instances; the hemoglobinopathies are the outstanding example but for the most part current nosology is in a much more primitive state. However much it is recognized in theory, there has been too little recognition, in practice, of the difficulty in pursuing this objective. Because the correspondence between a fundamental defect and its clinical manifestation is imperfect, a clinical nosology is necessarily tentative and subject to repeated reformulation. The problem of identifying the basic defect is to find what is common to all members of the group, but if the membership of the group is itself subject to errors, both of inclusion and exclusion, then the solution must be iterative, i.e., attained by trial and error and not by any straightforward course of action. To the geneticist, the problem is a familiar and a vexed one.

Von Willebrand originally described three extensive pedigrees on the Aland Islands in the Baltic and adjacent Finland, of which the members exhibited prolonged bleeding from a small cut. Analysis of the pedigree suggested an autosomal dominant pattern of inheritance somewhat perturbed by greater severity in female patients and by variation with age. The conscientious geneticist is made uneasy by a characteristic which is not qualitatively different from normal but merely an exaggeration of some normal state. He would require that on some scale of measurement there be evidence of unambiguous (though not necessarily perfect) grouping before considering whether or not a Mendelian pattern of inheritance obtains. If a specific chemical defect can be shown that will resolve the matter beyond doubt, so much the better, but genetics would make very slow progress if this were a requirement.

The problem of reducing “prolonged hemorrhage” to a metrical characteristic is met by measuring, under standard conditions, the bleeding time of an iatrogenic cut. Considering the complexity of the processes involved in the response to injury and the large number of genetic loci that must contribute to them, it is altogether too much to expect much specificity from bleeding time. While its primacy in the diagnosis of the disease should not be lightly set aside, it would be idle to pretend (from a nosological standpoint at least) that it enjoys any great security, even aside from the question of its reproducibility.

The Factor VIII assay, the major corroborative test, is hardly in a better position. The determination of Factor VIII in skilled hands is probably subject to less experimental error than the bleeding time, but the depression of the Factor seen in hemophiliacs and carriers of hemophilia disqualifies its reduction as a unique feature peculiar to von Willebrand’s disease.

A third hematologic abnormality identified with the diagnosis of von Willebrand’s disease is defective platelet function. Faulty platelet behavior was claimed in early descriptions of the disease, although later workers chal-
More recently, abnormal retention of platelets in columns of glass beads (platelet adhesiveness) has been described. Studies derived from these reports have raised doubts concerning the traditional view that von Willebrand’s disease is transmitted as an autosomal dominant trait. Strauss and Bloom and Meyer et al. have suggested that normal sibs of persons with this disorder have platelets less adhesive than average, and, while the study of Papayannis et al. is less conclusive, it shows a similar trend. These findings are difficult to reconcile with the pattern of an autosomal dominant Mendelian (i.e., unilocal) disorder. Thus, there seems, at the present time, no very secure basis for classifying cases.

In 1967 an ad hoc subcommittee on platelet function of the International Committee on Haemostasis and Thrombosis organized a cooperative study on the value of one such test, the glass bead method of measuring the platelet adhesive index (PAI) of Salzman. The study was set up in full awareness of the foregoing difficulties. It seemed best to design the study as if the assumption of an autosomal dominant pattern of inheritance were correct. The hypothesis could be tested when both cases and controls were collected from within the same sibships. In this way, many extraneous sources of variation would be kept low, and the ages would be more or less comparable. Such a scheme would not solve all the problems; deciding which cases were affected was difficult at times. How is a person to be classified who has sibs, undoubtedly affected, if he himself has a striking bleeding history but more or less normal bleeding time or Factor VIII level or both? Such cases did occur from time to time among the 277 subjects collected from the 15 participating laboratories.

The subcommittee did not lay down hard and fast criteria in advance, but it adopted two measures: one was to require of the investigator at least a tentative diagnosis; the other was to request particulars of the findings, anamnestic, genealogical, and hematological, which would allow separate assessment. The weaknesses of the former are all too obvious. If the investigator is to define his cases according to bleeding time and factor VIII level, then no criterion, not even the specific chemical defect itself, could improve on them. Any discrepancies would (by definition) be ascribed to the new test. Such circularities of logic are hard to avoid in empirical science, but they should be recognized as defects, not glorified as principles. The weakness of not grouping but merely comparing the PAI with the other measurements is that nothing can be said about the discriminating value of the test.

Despite these problems some interesting conclusions emerged. The details of the analysis, which are somewhat complex, are to be published elsewhere, and preliminary reports have already appeared. (1) The platelet adhesiveness shows a clear relationship to the bleeding history when subjects are grouped without regard to diagnosis. (2) Patients with a provisional diagnosis of von Willebrand’s disease are found to have, on the average, lower platelet adhesiveness values than unaffected normal subjects. This finding confirms previous claims in the literature. (3) Despite the diagnostic primacy accorded to the bleeding time and the
Factor VIII level, the percentage misclassifications of both normal and abnormal cases by either test are much the same as those for the PAI. Moreover, the mean values in normal subjects are more constant from one laboratory to another for the PAI than for either of the other two tests.

(4) Analysis confirms the previous findings that “normal” relatives of affected cases have less adhesive platelets than controls, even after adjustment for age and factor VIII levels.

(5) The PAI level has, in a patient population, no demonstrable contribution to make to diagnosis of this condition over and above that made by factor VIII and bleeding time: i.e., there is redundancy in these data. Three qualifying comments are called for. (1) The classification of cases reflects, to some extent at least, these other measures so that, as before, there is some circularity in the reasoning. (2) Much of the redundancy seems to be between bleeding time and the PAI. Of the two, the PAI is quicker to perform, less unpleasant for the patient and (especially in inexpert hands) less capricious. (3) The test may occasionally be decisive in an individual patient when other tests are equivocal.

As to the broader implications of this study, they are encouraging in that they have thrown some light on the location of the defect. Whether or not it lies in the platelet or the plasma, the fact that there is an anomaly in platelet function demonstrable in vitro suggests that an abnormality in the vessel wall is not the cause of the prolonged bleeding. The term “vascular hemophilia” is no longer of even historic interest. Secondly, a test is established which is much simpler than and as discriminating as either Factor VIII or bleeding time. It should at least have adjunctive value.

On the other hand, the prospect of using genetic analysis as a direct route to the fundamental defect seems to be much further away than it was 10 years ago. The common claim that von Willebrand’s disease is a single locus disorder calls for some serious amendment. It may be possible to salvage this hypothesis by invoking incomplete penetrance or epistasis, but these will complicate genetic analysis and make conclusions much less secure.

Perhaps recent evidence of a plasma antigen present in hemophilia (but absent in von Willebrand’s disease) apparently related in some way to Factor VIII and also to platelet activity, will point the way to a more pertinent definition of the disorder based on understanding of the molecular defect and will permit a rigorously testable statement concerning its inheritance that can at present only be hinted at.

EDMUND A. MURPHY, M.D.
Johns Hopkins Medical School
Baltimore, Md.

EDWIN W. SALZMAN, M.D.
Harvard Medical School
Boston, Mass.

REFERENCES

Editorial: The Diagnosis of Von Willebrand's Disease

EDMUND A. MURPHY and EDWIN W. SALZMAN