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THE HEREDITARY HAEMORRHAGIC DISEASES: THEIR CLASSIFICATION AND DIAGNOSIS*

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We in America take great pride in William Beaumont's outstanding contribution to scientific medicine. He, an Army surgeon—untrained in research and stationed in a frontier wilderness—advanced knowledge concerning gastric physiology more than any other individual before him because he had the unique opportunity to look directly into the human stomach. The advantage of exploring the machinery of the body by visual means is easily comprehended, but its limitations become evident when one attempts to look into the body to learn, for example, how blood accomplishes its haemostatic function. For this purpose a physical instrument comparable to the bronchoscope would be valueless. A more subtle approach with what might be described as physiological haematoscopes is far more promising. These hypothetical instruments are the blood-clotting tests, most of which have been developed only during the past two and a half decades. These alone would hardly suffice were it not for the fortuitous existence of at least twelve or more hereditary haemorrhagic diseases in each of which there is usually only one particular factor of the haemostatic mechanism that is defective.

Much can be learned concerning the probable mechanism of haemostasis by correlating the data that have been obtained recently from the study of the hereditary haemorrhagic diseases by means of the modern laboratory methods. It is the objective of this presentation not merely to present a classification of these diseases and to discuss their diagnosis, but also to utilize some of the salient observations made on the coagulation defects of the various bleeding conditions to formulate a more critical concept of the stanching process.

In the clotting of blood an undetermined number of co-ordinated reactions occur between factors from the plasma and platelets; two recognizable end-products are formed—namely, thrombin and fibrin. For convenience the process can be divided into three major steps. The first consists in the generation of thromboplastin from the interaction of a platelet factor and several agents of the plasma. Of the latter, thromboplastinogen (antithaemophilic globulin or factor VIII) and P.T.C. (plasma thromboplastin component, Christmas disease, or factor IX) are the two which have

been most clearly established. The second step is the conversion of prothrombin to thrombin by the action of thromboplastin and several plasma agents such as labile factor (ac-globulin, proaccelerin, or factor V), stable factor (proconvertin or factor VII), and perhaps other agents like the Stuart-Prower factor. The third step is the formation of fibrin by the action of thrombin on fibrinogen.

For ease and clarity of presentation, the clotting mechanism may be summarized in the form of a relatively simple scheme (see Diagram). It will be observed that thrombin has two important functions: it converts fibrinogen to fibrin and it catalyses in some manner the production of intrinsic thromboplastin. The control of this autocatalysis appears to reside in the fibrin reticulum, which has a great affinity for thrombin, and therefore removes it promptly from the reaction

mixture. Particularly noteworthy is the existence of two types of thromboplastin. One is widely distributed in the various tissues of the body in a preformed state but is absent in the blood. The other is formed from the interaction of platelets and several plasma constituents. Whether or not tissue thromboplastin has a primary function in haemostasis is unknown, and knowledge concerning its relationship to intrinsic or

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plasma thromboplastin has not advanced beyond the stage of speculation. Since even a severe haemophilic has a normal concentration of thromboplastin in his tissues, it seems likely that it may be only the intrinsic thromboplastin which is primarily concerned with haemostasis.

Classification of the Hereditary Haemorrhagic Diseases

The hereditary haemorrhagic diseases fall into three classes (Table I). In the first, the defect is entirely in the clotting reaction. The term "haematostaxis" is proposed for this group. In the second class, a vascular dysfunction in addition to a coagulation defect is present. A suitable name for this class is haematostaxis with

TABLE I.—Classification of the Hereditary Haemorrhagic Diseases

	Key Diagnostic Tests	Type of Heredity
I. Due to Clotting Dysfunction (Haematostaxis):		
A. Hypoprothrombinaemic states:		
a. Hypoprothrombinaemia vera, Type I	Prothrombin time	Autosomal, recessive
b. Hypoprothrombinaemia, Type II	" "	Autosomal, dominant
c. Labile factor deficiency	" "	Autosomal, recessive
d. Stable factor deficiency	" "	" "
B. Hypothromboplastinaemias:		
a. Haemophilia vera	Prothrombin consumption time, and thromboplastin generation test	Sex-linked recessive
b. Haemophilia B (P.T.C. deficiency, Christmas disease)	" "	" "
C. Combined hypoprothrombinaemic states and hypothromboplastinaemias (Stuart-Prower factor deficiency)		
	Prothrombin time and prothrombin consumption time	Autosomal, recessive
D. Hyperheparinaemia		
	Thrombin time	" "
E. Hypofibrinogenaemia		
	Clotting time and fibrinogen determinations	" "
II. Due to Clotting Defect Combined with Vascular Dysfunction (Haematostaxis and Angiostaxis):		
A. Pseudohaemophilia A (von Willebrand's disease)	Bleeding time	Autosomal, dominant
B. Pseudohaemophilia B	Bleeding time and prothrombin consumption time	Autosomal, recessive
C. Thrombasthenia	Bleeding time, platelet count, and prothrombin consumption time	Autosomal, dominant
III. Due to Vascular Abnormality (Angiostaxis):		
A. Telangiectasia	Detection of spider naevi	" "

angiostaxis; the latter term was first proposed by Lethaby Tidy (1926). In only one known bleeding disease—namely, telangiectasia—is there evidence that the defect is solely in the vascular structure.

Only a few key diagnostic tests are needed to characterize and diagnose most of the bleeding diseases. The prothrombin time and the prothrombin consumption time have the widest application, but the thromboplastin generation test is particularly valuable for studying the haemophilic group. In addition to the laboratory tests, information supplied by the clinical picture and by the hereditary pattern may often be very helpful in the differential diagnosis.

The Hypoprothrombinaemic States

Since the one-stage prothrombin time was developed on the basis of the classical theory of coagulation, it was natural to assume that the test determined prothrombin specifically. I became one of the staunch defenders of this view; yet, paradoxically, I was the first to cast doubt unwittingly on the correctness of this assumption when I discovered that the prolonged prothrombin time

of stored plasma and of plasma from a dicoumarolized subject, when mixed, mutually corrected each other (Quick, 1943). Somewhat later, Owren (1947) found a patient who lacked the factor that disappears in stored normal plasma. From the studies of Mann *et al.* (1947), MacMillan (1948), and particularly Alexander *et al.* (1949), a third factor was established which has been given various names: co-thromboplastin, S.P.C.A., proconvertin, factor VII, and stable factor. Alexander *et al.* (1951) were the first to report a bleeding case due to a deficiency of this clotting agent. During this development I had the good fortune to find a true hypoprothrombinaemic state in two brothers (Quick, 1947). Thus it became obvious that three types of bleeding diseases exist which are hereditary and have in common a markedly prolonged prothrombin time.

A comparison of the three states can best be made by selecting a representative case of each. A girl now 8 years old who has a deficiency of prothrombin and a second girl who is 7 years old serve as typical cases of the first two states. For labile factor deficiency I have chosen the patient (aged 27) who was reported by Brink and Kingsley (1952). In Table II the important laboratory findings are given. The differential diagnosis is simple. Serum rich in stable factor corrects only plasma deficient in this agent. Rabbit plasma, which has an exceedingly high concentration of labile factor when treated with an adsorbent such as $\text{Ca}_3(\text{PO}_4)_2$ or BaSO_4 to remove prothrombin and stable factor, becomes a diagnostic reagent which corrects only plasma lacking labile factor. True hypoprothrombinaemia is corrected by neither reagent nor by a mixture of the two.

On inspecting the data of Table II, the finding which stands as if it were in bold relief is the normal clotting time in both labile and stable factor deficiencies, in contrast to the markedly prolonged value in true hypoprothrombinaemia. Terms such as accelerators and convertins have been used rather loosely, and many investigators maintain that both labile factor and stable factor act as accelerators. Oddly, in the two conditions in which they are lacking the clotting time is normal; whereas in true hypoprothrombinaemia, in which both are normal in concentration, the clotting time is very prolonged. Since the three patients selected may be

TABLE II.—Laboratory Findings in the Hypoprothrombinaemic States

	Deficiency of			Normal
	Pro-thrombin	Stable Factor	Labile Factor (Brink-Kingsley)	
Prothrombin time:				
Basic (seconds)	73	60	41½	12
With added S.F.* (seconds)	60	13	—	12
" " L.F.† (seconds)	51	60	10½	12
Clotting time (minutes)	60+	7	7	5-10

* Stable factor = aged normal serum. † Labile factor = deprothrombinized rabbit plasma. Data were obtained from case histories.

regarded as severe bleeders, the unreliability of the clotting time as a measure of haemostasis is clearly brought out.

The true significance of the prothrombin time is still poorly understood, as shown by the following observations. The girl who lacks prothrombin and also the one who is deficient in stable factor were suffering from severe intramuscular haemorrhages at

the time when each received 250 ml. of fresh frozen plasma. In the first patient the prothrombin time dropped from 73 to 19 seconds, and in the second from 60 to 22 seconds. In both, the haemorrhages were promptly arrested, and the absorption of blood began after 24 hours. In the first girl the beneficial effect lasted five weeks, even though the prothrombin time was already increased within 24 hours after the transfusion. In the second a transfusion was again required in two weeks. It seems likely that the prothrombin time in these instances did not accurately measure the haemorrhagic state. In the first girl the spontaneous haemorrhage was controlled at a prothrombin time level of 19 seconds, yet in two other subjects who also have true hypoprothrombinaemia (Quick, 1947) bleeding often occurs from trauma at this level.

To explain this apparent paradox it may perhaps be necessary to distinguish between spontaneous and traumatic bleeding. Such an idea has recently been expressed by Jacobson (1958): "Other factors than trauma or the penetration of vessels must be the cause of spontaneous bleeding. These factors must arise from a systemic disorder which, in my opinion, lies somewhere in the endocrine balance. The problem of hemostasis in spontaneous bleeding has been either ignored or neglected or managed as if it were traumatic hemorrhage. The literature makes no distinction between the two and thus the fallacies of this approach have been perpetuated." The prompt clinical response of both girls to the transfusions suggests that the plasma supplied something that their organism needed for vascular integrity and normal function, which includes the reabsorption of extravasated blood. Whether this factor is supplied directly by the plasma or is the resultant of precursors such as prothrombin and stable factor is entirely speculative.

It may be significant that various clotting factors have a relatively high metabolic turnover. When, for instance, thromboplastinogen is supplied by means of a fresh plasma transfusion to a severe haemophilic, its disappearance from the blood stream is fairly rapid. Likewise, when the subject whose prothrombin activity is depressed by dicoumarol is given a transfusion of normal plasma the resulting elevation is of short duration and little remains after 24 hours. It is not known why certain clotting factors seem to be consumed metabolically at a rapid rate. There may be a possibility that this is in some manner related to the maintenance of the normal function of the blood vessel and the prevention of spontaneous haemorrhages. The widely held concept that the clotting mechanism is kept in readiness to bring about stanching immediately after a blood vessel is injured may not be sufficiently inclusive.

The hereditary pattern of the known types of hypoprothrombinaemic states are alike. All are transmitted as non-sex-linked or autosomal, recessive traits. Since a bleeder can result only if both parents carry the defective gene (and, even then, only one out of four should theoretically inherit both defective genes and be a bleeder), it is understandable why these hypoprothrombinaemic states are rare.

The Haemophilias

One of the more interesting developments in the study of hereditary haemorrhagic diseases was the discovery that two distinct types of haemophilia exist. The

thromboplastin generation test developed by Biggs and Douglas (1953) played an important part in establishing the existence of the second type of haemophilia and in its differentiation from the classical type (Biggs *et al.*, 1952). Interestingly, these two are the only bleeding diseases known to be transmitted as sex-linked recessives. Both follow the rule that the degree of the severity of the defect remains constant from generation to generation. Interestingly, the famous bleeding disease of Tenna, Switzerland, is mild haemophilia B or Christmas disease. The two descendants of this family whom I have studied have only a slightly prolonged clotting time and a relatively mild clinical bleeding state. It is likely that all the affected members of this pedigree have been mild bleeders, which would explain why many lived beyond the adolescent period despite lack of adequate medical care.

In regard to a name for the new type of haemophilia, I prefer the term "haemophilia B," in agreement with the French and Swiss workers, because the two diseases are clinically very similar and both have the characteristic hereditary pattern. The observation, made first by Biggs *et al.* (1952), that the ratio of classical haemophilia to the new type is roughly 5 or 4 to 1, appears to hold throughout the whole population of the world. Whether the reason for this is a different rate of mutation presents a provocative genetic problem.

While the thromboplastin generation test has been invaluable in establishing haemophilia B as a distinct clinical entity, the prothrombin consumption test, especially the modification in which an extract of erythrocytes is used, has proved to be an important tool for obtaining further information concerning the basic defect. In Table III the application of the prothrombin

TABLE III.—*Differentiation of Haemophilia B from True Haemophilia by the Prothrombin Consumption Test, Using Haemolysate, Normal Aged Serum, and Plasma*

	ml.	Prothrombin Consumption Time		
		Normal (sec.)	True Haemophilia (sec.)	Haemophilia B (sec.)
Native platelet-poor plasma ..	1.0	8	8	11
With: Haemolysate ..	0.1	55	8	11
Serum, aged normal ..	0.03	8½	8	11
Haemolysate ..	0.1	135	8	70
Serum ..	0.03			
Haemolysate ..	0.1	55	30	11*
Fresh normal plasma ..	0.005			

* Even 0.1 ml. of plasma did not increase the prothrombin consumption.

consumption test to true haemophilic and haemophilia B blood is shown. Native plasma from which the platelets are removed is the test medium. When platelet-poor plasma is clotted, almost no prothrombin is consumed; consequently, the prothrombin time of the resulting serum is short. The addition of aged serum to the plasma does not improve the prothrombin consumption, as is to be expected, since serum lacks the platelet factor. The addition of haemolysate, which has platelet activity, causes a high consumption of prothrombin in normal plasma, but not in either type of haemophilia. The addition of both haemolysate and serum to haemophilia B plasma brings about a very high utilization of prothrombin, but not when added to true haemophilic plasma. When, however, haemolysate and fresh normal plasma are added to true haemophilic plasma a striking consumption of prothrombin occurs;

but on adding it to haemophilia B plasma no significant conversion of prothrombin is effected.

The results recorded in Table III are in accord with the studies of other investigators, showing that the production of intrinsic thromboplastin requires at least three factors: a phospholipid, thromboplastinogen, and P.T.C. or Christmas factor. While it appears certain that the first is supplied by platelets, erythrocytin (the factor isolated from erythrocytes) may actually be the immediate reagent that reacts with the plasma components, since it is much more active than platelet extract. It is interesting to speculate whether the platelet factor is converted to erythrocytin before it brings about the production of thromboplastin. The factor lacking in haemophilia B does not appear to be in the active state in fresh plasma but is present abundantly in normal serum, suggesting that it becomes activated during coagulation. Nothing is known of how this activation is effected. The possibility is presented that a condition may perhaps occur in which lack of activation rather than a true deficiency of Christmas factor is the basic defect.

The Haematostatic-Angiostatic Group

Attention should be called to the group of hereditary haemorrhagic diseases in which the bleeding time is prolonged. A discussion of these conditions is beyond the scope of this paper, but a few comments should be made. In the past these diseases were all grouped under the general class of thrombopathies, implying that the defect was specifically in the platelets. While it is well established that a prolonged bleeding time is found in severe thrombocytopenia and also when the platelets are qualitatively defective, it is now recognized that the bleeding time may be abnormally long in conditions in which the platelets are quantitatively and qualitatively normal but the plasma lacks a factor which is identical or at least very similar to the agent that is lacking in true haemophilia. The latter diseases are hereditary but not sex-linked and therefore occur in both males and females. Apparently a normal bleeding time requires both a platelet and plasma factor.

Hyperheparinaemia

Particularly devastating to my own rather smug concept of haemostasis have been the observations made on a young woman with pronounced hyperheparinaemia which is probably of congenital origin (Quick and Hussey, 1957). Though her clotting time is usually 40 minutes or more, and at times infinity, her bleeding tendency is surprisingly mild. Only after surgical operations and after the birth of her two babies has she encountered real difficulties. In fact, she had to have over 30 transfusions to control the bleeding after each of her two deliveries. Even when her blood is incoagulable she does not bruise easily, has no epistaxis, no haemarthroses, no deep intramuscular bleeding, no haematuria or any other type of haemorrhage. Since her blood does not clot in a glass test-tube at 37° C., it seems unlikely that intracorporeal clotting could take place. Any amount of thrombin that could be conceivably formed would be promptly neutralized by the excess of heparin in her blood.

The bleeding state caused by hyperheparinaemia is especially interesting in that heparin probably does not have a physiological role in coagulation. It is likely

that the hypocoagulable state is only incidental. In preparing this patient for dental surgery, the hyperheparinaemia was reduced significantly with cortisone and fresh frozen plasma transfusions. No abnormal bleeding occurred, but the hyperheparinaemia again increased immediately after treatment was stopped. In this patient the difference between the control of spontaneous and traumatic haemorrhage is clearly illustrated.

Conclusions

Even from this rather cursory consideration of a few of the hereditary haemorrhagic diseases, it becomes clear that the commonly held concepts of haemostasis need re-evaluation. The view that the fibrin clot serves as a mechanical seal and that the speed with which it is formed is significant in haemostasis is not only unsound but is also hampering progress. Perhaps too much attention is being given to so-called accelerators and inhibitors. While it is still largely pure speculation, one must not overlook the possibility that the first stages of haemostasis are carried out by the vessel itself. Even in severe hyperheparinaemia when the formation of thrombin is almost completely suppressed, haemostasis is remarkably effective and breaks down only when the injury is very severe. The generation of thrombin and the formation of a fibrin clot may perhaps function only as third-line measures of defence against excessive loss of blood. It is not improbable that some of the recognized clotting factors may have as their primary function the maintenance of the integrity of the vessel and its normal physiological function. Thus, in acute thrombocytopenic purpura the bleeding is essentially angiostatic in type. The clotting time in this disease is never prolonged and often is shorter than normal.

The development of the newer clotting tests has made it possible to diagnose and classify satisfactorily the hereditary haemorrhagic diseases. Their treatment, however, has not reached such a successful stage, because the mechanism of haemostasis is still imperfectly understood. To obtain the required information to solve the enigma of stanching, the haemorrhagic diseases themselves may serve as the most promising source. When sufficient data have been gathered it may perhaps be necessary to revise drastically our present concepts. It may be well to remember the classical advice of Descartes: "Pour atteindre la vérité, il faut, une fois dans sa vie, se défaire de toutes les opinions qu'on a reçues et reconstruire de nouveau et dès le fondement, tout le système de ses connaissances."

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