A CLASSIFICATION OF DISEASES OR CONDITIONS CHARACTERIZED BY HEMORRHAGE

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The hemorrhagic studies which are of greatest value in the diagnosis of diseases characterized by abnormal bleeding are skin bleeding time, test tube coagulation time, measurement of the amount of serum expressed from the clot, platelet count, capillary fragility test, and the estimation of prothrombin concentration. Tests of occasional value are the coagulation time of recalcified oxalated plasma after rapid and slow centrifugation, the estimation of fibrinogen concentration, and the demonstration of the presence of anticoagulant substances. The methods used in the hematology laboratory of Cleveland Clinic and the range of normal values for these laboratory procedures are given in table 1.

A classification of hemorrhagic diseases based upon the principal coagulation and hemostatic components involved, as revealed by standard laboratory tests, is given in table 2. The grouping of diseases with hemorrhagic manifestations on the basis of pathologic physiology is a modification of classifications by Quick,[1] Lucia and Aggeler,[2] Wintrobe,[3] and others.

Local vascular abnormality is suggested when the patient is bleeding from a single focus and no abnormalities are revealed when hemorrhagic studies are made. Generalized vascular abnormality is suggested when there are multiple purpuric manifestations, a prolonged skin bleeding time, and a positive capillary fragility test. If the platelets are normal the purpura is of the nonthrombopenic type. If the number of platelets is decreased, the purpura is of the thrombopenic type. Platelet deficiency is revealed by a low platelet count, defective clot retraction, and a wet and flabby clot. A prolonged coagulation time is indicative of abnormalities in the circulating blood of such factors as fibrinogen, prothrombin, and anticoagulants.

The coagulation time of recalcified oxalated plasma after rapid and slow centrifugation is of use in the diagnosis and differential diagnosis of hemophilia. In hemophilia the platelets do not disintegrate and liberate their thromboplastin as readily as they do in normal blood. On centrifugation at rapid speed the more resistant platelets are separated more effectively than in nonhemophilic conditions; the coagulation time of recalcified plasma of hemophilic blood which is rapidly centrifuged is therefore appreciably greater than recalcified plasma which is slowly centrifuged.

Table 1

TESTS ROUTINELY USED IN HEMORRHAGIC STUDY

Test	Method	Normal Value
Skin bleeding time	Ivy	2-6 minutes
Coagulation time	4 tube method using venous blood	5-15 minutes
Clot retraction	3-5 cc. venous blood in graduated tube	40-60 ml. serum/100 ml. expressed from clot in 4 hours, room temperature
Platelet count	Reese-Ecker	200,000 to 400,000 per cu.mm.
Capillary fragility	Blood pressure cuff above elbow; 40 mm. Hg for 5 minutes. If no petechiae, 100 mm. for 5 minutes.	No petechiae
Prothrombin concentration	Quick	80-120 per cent
TESTS OF OCCASIONAL VALUE		
Coagulation time of recalcified oxalated plasma	Quick	2-4 minutes. Less than 15 seconds difference between rapid and slow centrifugation
Fibrinogen concentration	Cullen and Van Slyke	0.3-0.5 Gm./100 ml.
Test for anticoagulants	Coagulation time of recalcified normal plasma to which plasma of patient is added	No increase in clotting time of normal plasma

Table 2

CLASSIFICATION OF DISEASES OR CONDITIONS CHARACTERIZED BY HEMORRHAGE

Principal Factor	Laboratory Findings	Diseases or Conditions
I. VASCULAR ABNORMALITY A. LOCAL	Hemorrhagic studies reveal no abnormality	Trauma Ulceration, necrosis Thrombosis, embolism (embolic purpura) Defects in vascular wall Increased intravascular pressure Tumors Hereditary hemorrhagic telangiectasia Certain skin diseases Purpura annularis telangiectoides Progressive pigmentary dermatosis Hyperelasticity of the skin Functional uterine bleeding
B. GENERAL 1. Without decrease in platelets (Nonthrombopenic vascular purpuras)	Tourniquet test usually positive Bleeding time variable Clotting time and other tests usually negative	Nonthrombopenic purpuras secondary to: Infections Chemicals Toxemias Nephritis Cushing's syndrome Allergic (anaphylactoid) purpuras Vitamin C deficiency (scurvy) Purpura simplex (easy bruisability)

	Bleeding time prolonged Tourniquet test variable Other tests usually negative	Hereditary purpura with prolonged bleeding time (pseudohemophilia)
2. With decrease in platelets (Thrombopenic purpuras)	Platelets decreased Bleeding time prolonged Tourniquet test usually positive Defective clot retraction Clotting time normal or only slightly prolonged Other tests usually negative	Thrombopenic purpuras secondary to: Infections Chemicals (sedormid, quinine, sulfa drugs, organic arsenicals, gold salts, colchicine, salicylates, etc.) Sensitivity to foods or inhalants Physical agents Artificially induced fever Radioactive substances Diseases characterized by hypoplasia of bone marrow Diseases characterized by splenomegaly Neoplasia Leukemias Carcinoma Myeloma, etc. Miscellaneous diseases Cirrhosis of liver Nephritis Hodgkin's disease Lupus erythematosus Idiopathic hemorrhagic purpura (Essential thrombopenic purpura) Congenital thrombopenic purpura
II. PROTHROMBIN DEFICIENCY	Plasma prothrombin decreased (prolonged prothrombin time)	Vitamin K deficiency Obstructive jaundice

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Table 2—(Continued)

CLASSIFICATION OF DISEASES OR CONDITIONS CHARACTERIZED BY HEMORRHAGE

Principal Factor	Laboratory Findings	Diseases or Conditions
	Prolonged coagulation time of recalcified oxalated plasma If moderate prothrombin deficiency, no alteration in bleeding time, coagulation time, or other tests If severe prothrombin deficiency, may have prolonged bleeding time, prolonged clotting time, and defective clot	Biliary fistula Intestinal disease Sulfa drugs Hemorrhagic disease of the newborn Liver disease, severe Drugs Dicumarol Salicylates Congenital (essential) hypoprothrombinemia
III. FIBRINOGEN DEFICIENCY	Plasma fibrinogen reduced below 0.1 Gm. per 100 ml. Coagulation time prolonged Clot defective Bleeding time variable	Liver disease, severe Diseases involving bone marrow Congenital fibrinogenopenia
IV. THROMBOPLASTIN DEFICIENCY		Hemophilia ? (See VII)
V. CALCIUM DEFICIENCY		(No well defined hemorrhagic disease)
VI. EXCESS ANTICOAGULANTS	Coagulation time prolonged Increased coagulation time of recalcified normal plasma to which plasma of patient is added Other tests usually negative	Hemorrhage, unknown cause with demonstrable excess anticoagulant Excess heparin Heparin therapy Anaphylactic shock
VII. UNCLASSIFIED	Coagulation time prolonged Coagulation time of recalcified oxalated plasma prolonged. Longer after rapid than after slow centrifugation Bleeding time and other tests usually normal	Hemophilia Hemophilia-like syndrome in female

Schönlein's purpura, Henoch's purpura, Osler's erythemas, Frank's capillary toxicosis, David's disease, and Glanzmann's hereditary thrombasthenia are not included in the classification, for the clinical syndromes described by these authors are ill defined in terms of etiology, pathology, or laboratory findings by modern methods. Terms such as "purpura fulminans", "purpura senilis", "orthostatic purpura", and "mechanical purpura" are likewise not considered, for these terms are obviously descriptive and nonspecific.

In practice it is not always possible to fit all diseases characterized by hemorrhage snugly into one or the other pigeonholes of classifications, for there are combinations and varying degrees of abnormality of coagulation components, and there may be more than one etiologic agent. Also, the laboratory tests are subject to variations depending upon the exact technic used and the manner of interpreting results.

In making the final diagnosis, the family and personal history, the physical examination, and other laboratory and radiologic studies are to be evaluated along with tests for hemorrhagic abnormality. The response to therapy, the course of the disease, and the changes that occur when possible etiologic agents are eliminated are also of value. No diagnosis of primary or hereditary hemorrhagic disease should be made until all other possibilities have been excluded, for hemorrhage is usually secondary to and a manifestation of disease entities, the etiology of which can be demonstrated.

Summary

A classification of disease or conditions characterized by hemorrhage based upon laboratory tests and essential coagulation and hemostatic components involved is presented.

References

1. Quick, A. J.: Classification of hemorrhagic diseases due to defects in coagulation mechanism of blood based on recently published studies. Am. J. M. Sc. **199**:118-132 (Jan.) 1940.
2. Lucia, S. P., and Aggeler, P. M.: A clinical evaluation of bleeding tendency. Clinics **1**:414-432 (Aug.) 1942.
3. Wintrobe, M. M.: Clinical Hematology, ed. 2 (Philadelphia: Lea and Febiger, 1946).