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Coagulation of Blood

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BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
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MINNESOTA MEDICAL FOUNDATION

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I. THE MECHANISM OF COAGULATION OF BLOOD

Paul G. Frick, M.D.

In 1904 Morawitz[1] postulated that the coagulation of blood occurs in two successive stages:

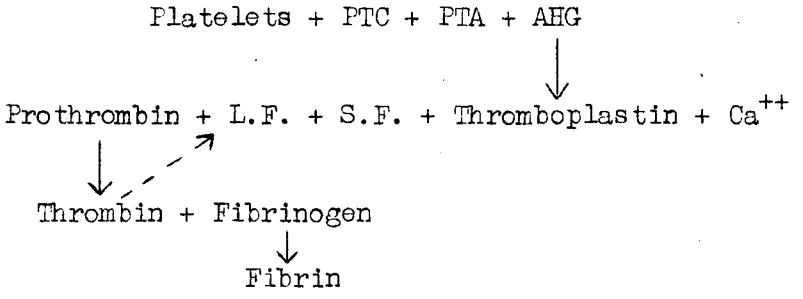
1. Prothrombin + Calcium + Thrombokinase = Thrombin

2. Thrombin + Fibrinogen = Fibrin.

This theory remained unaltered until 1934. During the last 19 years the application of new technical methods to the study of blood clotting in normal individuals and in congenital and acquired hemorrhagic diseases led to the discovery of several new clotting factors. The rapid development in this field has taken place simultaneously in different laboratories working independently from each other, and the great variation of terms applied to the new factors has unfortunately led to some confusion and makes it quite difficult to follow the literature pertaining to blood coagulation. Despite a crying need for a unified nomenclature, no agreement has been reached thus far among the leading investigators. Laurell[2] has recently published a list of synonyms for each clotting component which can be used as a practical guide through the labyrinth of the literature on coagulation.

The scheme of coagulation most widely accepted at the present time is illustrated in Figure 1.

Fig. 1. Scheme of Coagulation 1953



PTC	Plasma Thromboplastin Component
PTA	Plasma Thromboplastin Antecedent
AHG	Anti-Hemophilic Globulin
L.F.	Labile Prothrombin Conversion Factor
S.F.	Stable Prothrombin Conversion Factor

From a practical standpoint it is best divided into 3 stages:

1. The formation of thromboplastin.

2. The formation of thrombin.

3. The formation of fibrin.

1. Formation of Thromboplastin. The careful study of the various congenital hemorrhagic diseases grouped under the diagnosis of hemophilia has shown that thromboplastin is the result of the interaction between the platelets and three nonformed plasma components. Besides the typical hemophilia caused by a deficiency of Antihemophilic Globulin (AHG), there are two other types of hemophilia-like diseases which are undistinguishable clinically from the original form. One is caused by a deficiency of Plasma Thromboplastin Component (PTC),[3] the other by a deficiency of Plasma Thromboplastin Antecedent (PTA).[4] The differentiation between the three types by laboratory tests will be discussed later. The mechanism of interaction be-

tween platelets, AHG, PTC and PTA is not known exactly. Quick[5] postulates that the platelets supply an enzyme (thromboplastinogenase) which converts the inactive thromboplastinogen (=AHG) to active thromboplastin.

2. Formation of Thrombin. Prothrombin, a sulfar containing glycoprotein, is the precursor of thrombin. The conversion of prothrombin occurs with the aid of thromboplastin, calcium ions, and two conversion factors named Labile Factor (L.F.) and Stable Factor (S.F.)[6]. The adjectives Labile and Stable define stability during storage. The inactive L.F. is changed to an active component under the influence of thrombin during the process of normal coagulation. This explains, at least in part, the autocatalytic action of thrombin. It has not been conclusively established if the S.F. has an inactive precursor as well. The S.F. definitely appears to be an accelerator of prothrombin conversion;[7] it is not well known if the L.F. acts by the same mechanism or if it enters the reaction in stoichiometric proportions. A deficiency of either L.F. or S.F. results in a delayed conversion of prothrombin to thrombin. From a clinical standpoint it is of interest that Dicumarol and other Coumarin compounds used as anticoagulants inhibit the formation of prothrombin and S.F., hence inducing hypoprothrombinemia and a retarded prothrombin conversion at the same time. Both factors can be promptly restored to normal with vitamin K_1. The antagonistic effect between vitamin K_1 and Dicumarol is probably due to competitive inhibition of the same enzyme system. Quick[8] believes that vitamin K_1 is the coenzyme of an apoenzyme essential for prothrombin synthesis.

3. Formation of Fibrin. The last and only visible phase of coagulation is the result of the enzymatic conversion of fibrinogen to fibrin by thrombin. Recent studies of Sherry have firmly established the proteolytic action of thrombin.[9]

Methods of Investigation of Hemorrhagic Diatheses

The main handicap in the study of hemorrhagic diatheses has been the lack of exact quantitative methods for the determination of each clotting factor. At present it is only possible to quantitate platelets, fibrinogen, prothrombin (2-stage method)[10] and calcium. The determination of calcium can be omitted for practical purposes because a bleeding tendency due to hypocalcemia is not known in men. The other clotting tests are only semi-quantitave and not absolutely specific for a single clotting factor. For this reason the investigation of hemorrhagic diseases has to be carried out with a whole battery of tests and conclusions can only be drawn by inference.

Table I. Tests of Hemostasis

Bleeding time (Ivy)
Clotting time (Lee-White)
1-stage prothrombin time (Quick)
Capillary fragility (Rumpel-Leede)
Platelet count
Clot retraction
Fibrinogen determination
2-stage prothrombin determination (Ware-Seegers)
Prothrombin consumption (1-stage and 2-stage method)
Thrombin titration.

The tests listed on Table I were routinely carried out on most of the patients studied at the University of Minnesota Hospitals during the last 4 years. Some of these tests had to be modified depending on the type of hemorrhagic disease under investigation. A more detailed discussion of the single methods will be presented with the case reports.

Because most of the progress in eliciting the basic mechanism of coagulation was made through the systematic study of congenital hemorrhagic diseases, the present report is restricted to this group of abnormalities. It is of special interest that each of them represents a deficiency of an isolated clotting factor. The medical literature contains reports of congenital hemorrhagic diseases due to isolated deficiencies of each clotting component known up to the present time.

Classification of Congenital Hemorrhagic Diatheses

The most practical and reasonable classification is based on the scheme of coagulation (Table II).

Table II. Classification of Congenital Hemorrhagic Diseases

1. Thrombocytopenia
2. AHG deficiency } Hemophilia group
3. PTC deficiency } Hemophilia group
4. PTA deficiency } Hemophilia group
5. Hypoprothrombinemia
6. L.F. deficiency (Parahemophilia)
7. S.F. deficiency
8. Afibrinogenemia
9. v. Willebrand's disease (Pseudohemophilia)

Laboratory Features of Congenital Hemorrhagic Diatheses

Congenital Thrombocytopenia. Judging from the literature congenital thrombocytopenia is a rare condition[11]. It is mandatory to restrict such a diagnosis to congenital thrombocytopenia occurring in infants born from normal mothers. The temporary thrombocytopenia occurring in children from mothers with essential thrombocytopenia does not belong to this category. Thrombocytopenia is characterized by a long bleeding time, positive tourniquet test, and decreased prothrombin consumption. No such cases have been studied at the University of Minnesota Hospitals during the last 3 years.

AHG, PTC and PTA Deficiency:

Up to 1952, hereditary hemophilia was considered a single disease entity due to a deficiency of a plasma component called Anti Hemophilic Globulin (AHG). Evidence has been recently presented for two additional plasma thromboplastic factors. White et al.[3] studied a patient with clinical symptoms and coagulation abnormalities similar to hemophilia whose blood corrected the clotting defect of true hemophilia (= AHG deficiency). These authors concluded that their patient had a deficiency in a clotting factor different from AHG. The new clotting factor was called Plasma Thromboplastin Component (PTC). More recently Rosenthal[4] reported three members of a family with a coagulation defect similar to hemophilia whose blood not only corrected the defect of true hemophilia but also the defect of PTC deficiency. The second group of investigators postulated the existence of a third plasma precursor of thromboplastin designated Plasma Thromboplastin Antecedent (PTA). It is obvious that all cases thus far diagnosed as hemophilia will have to be reclassified in three different categories. The difference in physico-chemical characteristics and in utilization of the three thromboplastin components during spontaneous coagulation of normal blood has been applied to devise differential diagnostic tests for the reclassification of this group of diseases (Table III).

Table III. Occurrence of AHG, PTC, PTA, L.F., S.F., and Prothrombin in Normal $BaSO_4$ Treated Plasma and 48-hr. Old Serum

	Normal $BaSO_4$ treated plasma	Normal 48-hr. old serum
AHG	present	absent
PTC	absent	present
PTA	present	present
L.F.	present	absent
S.F.	absent	present
Prothrombin	absent	absent

AHG is utilized during normal coagulation and is practically absent in 48-hour old serum. AHG cannot be absorbed on barium sulfate from normal plasma. PTC is utilized very little if at all during normal coagulation and is fully active in 48-hour old serum. It can be absorbed with barium sulfate, however. PTA is neither used during spontaneous coagulation nor adsorbed on barium sulfate, hence it is present in both serum and barium sulfate treated plasma. The ability or failure of normal serum and normal barium sulfate treated plasma to correct the coagulation defects which are

common to all diseases grouped under the name hemophilia (prolonged clotting time and impaired prothrombin consumption) has been used in the study of 35 hemophilic patients (Table IV).

Table IV. Effect of Normal $BaSO_4$ Plasma and 48-hr. Old Serum on the Clotting Defect in AHG, PTC, PTA, L.F., S.F., and Prothrombin Deficiency.

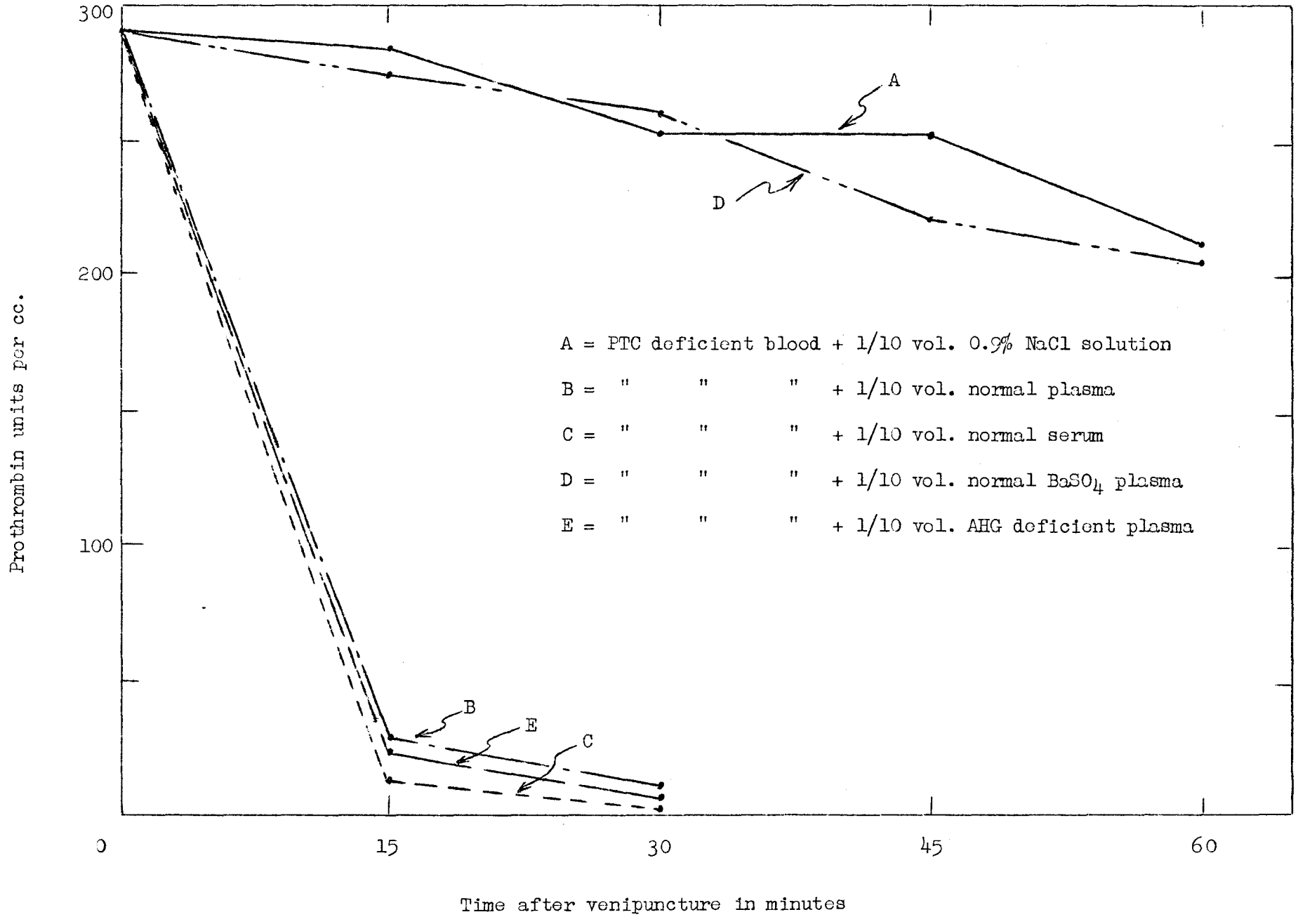
Disease entity	Normal $BaSO_4$ treated plasma	Normal 48-hr. old serum
AHG deficiency	corrective	ineffective
PTC deficiency	ineffective	corrective
PTA deficiency	corrective	corrective
L.F. deficiency	corrective	ineffective
S.F. deficiency	ineffective	corrective
Hypoprothrombinemia	ineffective	ineffective

An example of the typical results obtained in a case of PTC deficiency is represented in Table V and Figure 2.

Table V

PTC deficient blood	cc.	1.0	1.0	1.0	1.0	1.0
0.9% NaCl solution	cc.	0.1				
Normal plasma	cc.		0.1			
Normal $BaSo_4$ plasma	cc.			0.1		
Normal 48-hr. serum	cc.				0.1	
AHG deficient plasma	cc.					0.1
Clotting time in min.		120	10	119	18	20

Fig. 2. Prothrombin Consumption in PTC Deficiency



The relative incidence of AHG, PTC and PTA deficiency is given in Table VI.

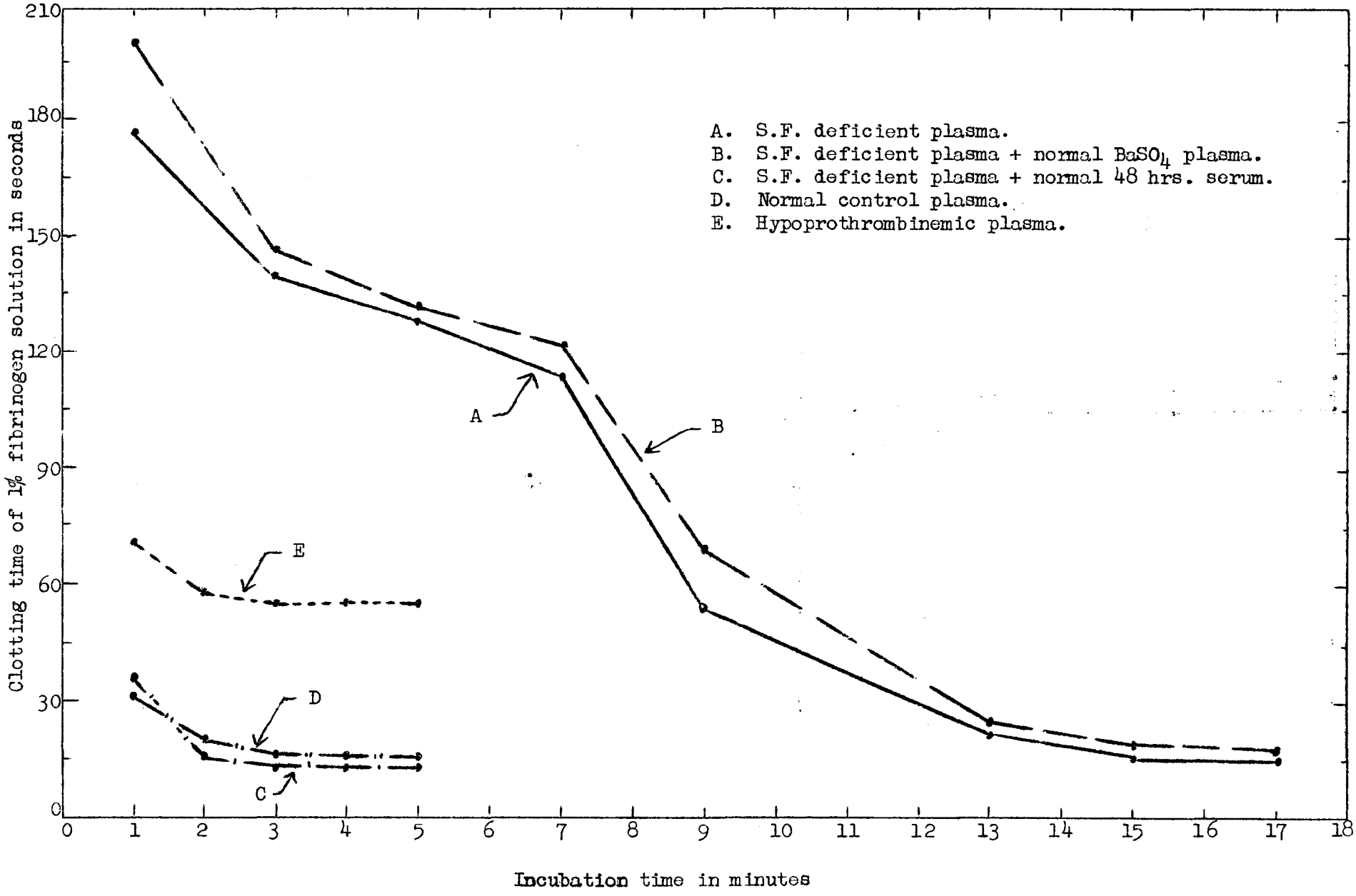
Table VI. Relative Incidence of AHG, PTC and PTA Deficiency

Disease entity	Number of cases	Percent case incidence	Number of families	Percent family incidence
AHG Deficiency	27	77.2	24	85.7
PTC Deficiency	4	11.4	3	10.7
PTA Deficiency	4	11.4	1	3.6
Total	35	100	28	100

It appears that the so-called true hemophilia (a term reserved to AHG deficiency) is the most frequent type.

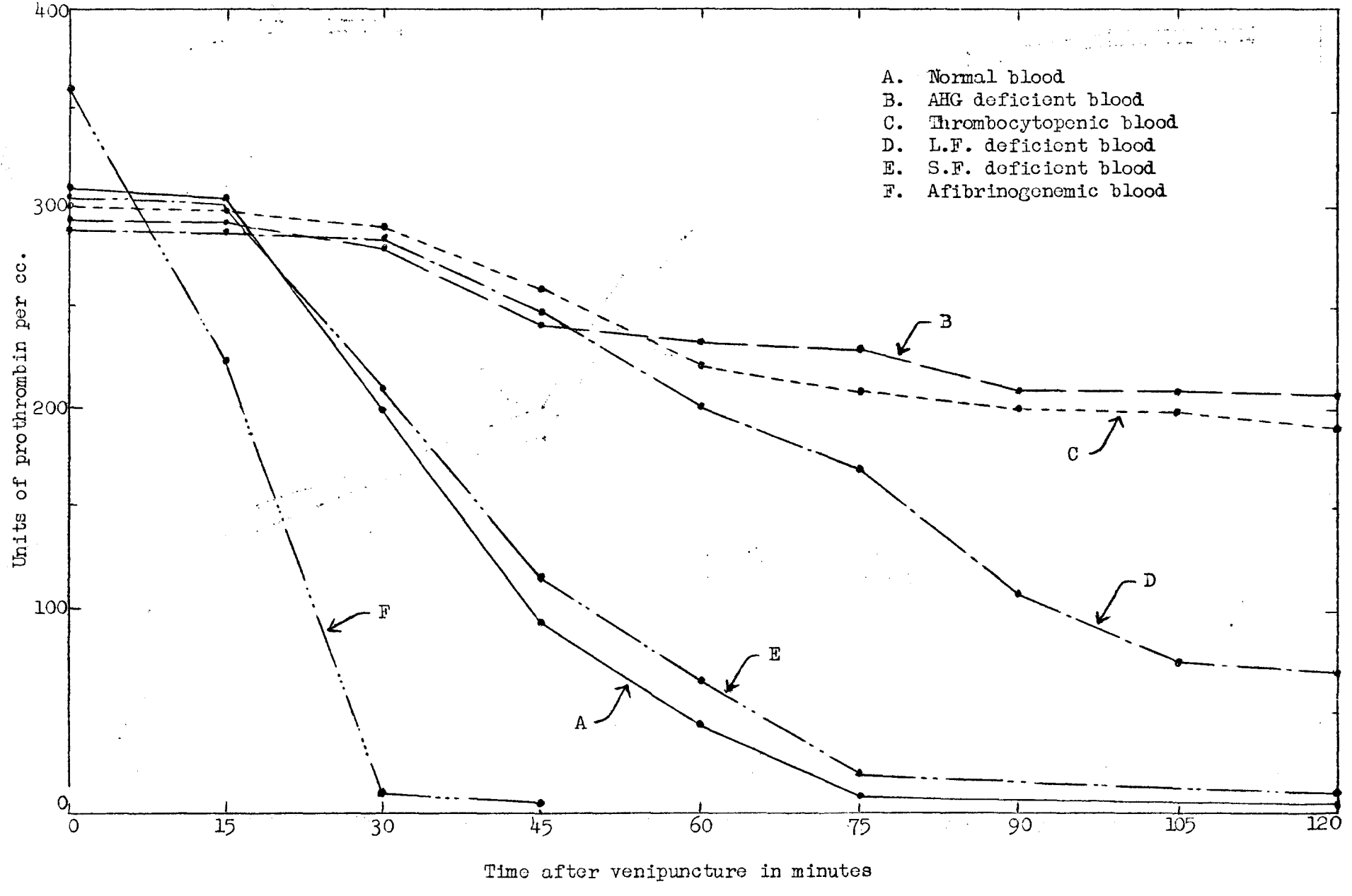
Congenital Deficiency of Prothrombin and Prothrombin Conversion Factors (L.F. & S.F.) These three types of congenital hemorrhagic diseases have been grouped together because their common laboratory denominator is a prolonged one-stage prothrombin time. The separation of the three conditions can only be made by using a modified two-stage method for prothrombin determination whereby one can determine the concentration of prothrombin in units and, at the same time, obtain detailed information about the rate of prothrombin conversion. In analyzing data obtained with the two-stage method one should remember that the slope of the curve is an index of prothrombin conversion rate, which in turn depends upon the concentration of L.F. or S.F. The shortest time recorded on the ordinate is the index of prothrombin concentration. The correcting effect of one or the other conversion factors added to a plasma with abnormal prothrombin conversion differentiates S.F. from L.F. deficiency. The unavailability of purified L.F. and S.F. was circumvented in this laboratory by using plasma or serum preparations which contained only one of the two conversion factors. Fresh normal barium sulfate treated plasma which is free of prothrombin and S.F., can be used as a source of L.F. Forty-eight-hour old normal serum which is practically free of prothrombin and L.F. was used as a source of S.F. The delayed conversion rate of L.F. deficient plasma can be corrected with fresh normal barium sulfate plasma; it is unaffected by normal serum. On the other hand, normal serum corrects the defect of S.F. deficiency which is refractory to barium sulfate treated plasma. The results obtained in a case of S.F. deficiency are presented in Figure 3.

Fig. 3. Concentration and Conversion Rate of Prothrombin. (Two-Stage Method)



The consumption of prothrombin in S.F. deficiency is normal (Fig. 4).

Fig. 4. Two-Stage Prothrombin Consumption



In order to avoid confusion a timely definition of the term "conversion" and "consumption" of prothrombin will be included in the text. Conversion is used to indicate the changes in prothrombin concentration against time as measured by the two-stage method. In this test three clotting factors (calcium, thromboplastin and fibrinogen) are kept constant by adding the appropriate reagents. The only variants are prothrombin, L.F. and S.F. Consumption of prothrombin is used to describe the changes in prothrombin concentration occurring during spontaneous coagulation in glass tubes at 37° C. This test is obviously less specific because all clotting factors are variants; the study of the different types of congenital hemorrhagic diseases has shown, however, that it is mainly influenced by the four precursors of thromboplastin (platelets, AHG, PTC & PTA) and by the L.F., i.e. any condition with a deficiency of one of these clotting factors will have a decreased prothrombin consumption. The normal consumption of prothrombin in S.F. deficiency was unexpected, especially if one considers the decreased rate of prothrombin conversion encountered in such plasma. An attempt to explain this paradoxical situation was made by Alexander[12], who felt that the influence of S.F. is limited to the very early phase of clotting, a range of time which cannot be analyzed with the prothrombin consumption test. In contrast to S.F. deficiency, parahemophilic plasma (L.F. deficient) has a poor prothrombin consumption. Another interesting abnormality, which is common to L.F. and S.F. deficiency, is the prolongation of the bleeding time. Hemostasis following a lancet stab applied when carrying out the bleeding time, is afforded by vasoconstriction and a platelet thrombus; hence prolongation of the bleeding time is encountered in congenital increased capillary fragility (von Willebrand's disease) and in thrombocytopenia. It is also known that adequate platelet agglutination occurs only in the presence of thrombin. It is probable, therefore, that the retarded formation of thrombin in S.F. and L.F. deficiency is responsible for a delayed agglutination of platelets. Why then is the bleeding time normal in hemophilia where there is also a delay in thrombin evolution? This paradox may be explained by postulating that tissue thromboplastin replaces the deficiency of nonformed plasma thromboplastin precursors and induces a rapid conversion of prothrombin to thrombin which in turn will agglutinate platelets. In L.F. and S.F. deficiency even an excess of tissue thromboplastin cannot accelerate the formation of thrombin. The results recorded in this report were obtained from the study of two patients who respectively had S.F. and L.F. deficiency. We have had no opportunity to study a case of pure hypoprothrombinemia.

Literature reports of cases of so-called "idiopathic hypoprothrombinemia" whose diagnosis was based on a prolonged one-staged prothrombin time, should be studied with modern methods in order to determine if the prolonged one-stage prothrombin time is caused by a low concentration of prothrombin, L.F. or S.F.

Congenital Afibrinogenemia

During the last year we had the unusual opportunity to study a case of congenital afibrinogenemia[13]. The patient was a 7-year old boy who was referred with the diagnosis of hemophilia. His blood, however, was found completely incoagulable after the effects of transfusions had worn off. Several methods were applied in a vain attempt to demonstrate the presence of fibrinogen; the addition of thrombin, calcium chloride, or calcium chloride and thromboplastin combined failed to induce a clot formation in the patient's plasma. Heating of the patient's plasma to 53-56° C (zone of fibrinogen precipitation) did not reveal any turbidity or flocculation. The first sign of increased viscosity followed by turbidity and heat coagulation became manifest at 71° C as a result of physical changes of serum albumin. Electrophoresis failed to reveal a fibrinogen peak.

The patient's plasma was systematically studied to determine the concentration of all other known coagulation factors which were all found to be present in

normal concentration. The clotting and prothrombin time were infinite. The bleeding time was always normal. The normality of this test in afibrinogenemia is the best proof that platelet agglutination occurs under the influence of thrombin without the presence of fibrin. The fibrin-free platelet thrombus is sufficient to seal the open capillaries severed by the lancet stab. The consumption of prothrombin was more rapid than in normal blood. This is presumably due to the fact that in afibrinogenemic blood the adsorbing and neutralizing effect of fibrin on the thrombin is missing and the thrombin evolving during coagulation remains uninhibited in its autocatalytic action on the conversion of prothrombin.

The complete absence of fibrinogen in the patient's circulation offered an excellent opportunity to study the turnover rate of fibrinogen. In order to exclude any source of errors due to losses of fibrinogen secondary to lysis, the patient's plasma and serum were tested for fibrinogenolytic and fibrinolytic activity; no lytic effect could be detected. After an infusion of 4.0 gms. of Cohn's Fraction I (mainly purified fibrinogen), the fibrinogen level rose to 161 mgm%, which corresponds to approximately half the concentration in normals. There was a fall during a period of 12 days at the end of which no fibrinogen could be detected with any of the methods listed above. The turnover rate of fibrinogen is slower than the values reported for AHG, S.F., prothrombin and L.F. This probably explains, at least in part, the longer lasting effect of therapeutic plasma transfusions in afibrinogenemia when compared with other types of congenital hemorrhagic diseases, especially hemophilia.

Pseudohemophilia or von Willebrand's Disease

No progress has been made in the study of the pathogenesis of this disease since its original description. This entity is considered a congenital defect of capillary fragility without any evidence of clotting disturbance.

Clinical Features of Differential Diagnostic Importance in Congenital Hemorrhagic Diatheses

Congenital thrombocytopenia is frequently associated with other congenital defects such as microcephaly, cardiac defects, kidney abnormalities, etc. The prognosis is very poor; most children die during their first month of life. Thrombocytopenia is the only condition with frank purpura. Patients with other types of hemorrhagic diatheses usually show only ecchymoses and hematomas. While deficiencies of L.F., S.F., and prothrombin may not be symptomatic in the first days or weeks of life, afibrinogenemia invariably manifests itself with hemorrhage from the umbilical cord. The onset of hemorrhagic manifestations in the hemophilia group depends on the severity of the disease. In this connection it has recently been recognized that a certain number of hemophilics may have a normal clotting time and the only diagnostic abnormality is a decreased consumption of prothrombin. We had an opportunity to study two such patients. In one of them the diagnosis was unfortunately only made after severe hemorrhage following surgical evacuation of a traumatic hematoma. The symptom of hemathrosis which may lead to severe crippling occurs only in hemophilia. Despite the absolute incoagulability of afibrinogenemic blood this symptom does not occur in congenital afibrinogenemia. Thus far there has been no adequate explanation for this paradox.

Hereditary Pattern of Congenital Hemorrhagic Diatheses

Congenital Thrombocytopenia

This disease is not hereditary in type.

Hemophilia Group

The classical hereditary pattern of AHG deficiency is recessive sex-linked in type. It was originally felt that hemophilia occurred in males only. Recent reports[14] have refuted this assumption: hemophilia can occur in females as a result of intermarriage between a male

hemophilic and a female carrier of the hemophilic trait. In this connection it appears appropriate to mention the study carried out by Brinkhous and Graham[15] in a strain of hemophilic dogs. These investigators have been able to produce hemophilic female dogs by breeding a hemophilic male with a known female carrier. The number of affected male and female puppies confirmed the theory that hemophilia is transmitted as a recessive sex-linked character. The extremely rare occurrence in the human female is due to the unlikeliness of the union of a hemophilic male with a heterozygous female carrier, which usually involves the intermarriage of cousins.

Our most recent studies have shown that PTC deficiency has the same hereditary pattern as AHG deficiency. No adequate studies are available thus far in this respect for PTA deficiency.

Hypoprothrombinemia, L.F. and S.F. Deficiency

The paucity of cases with a hemorrhagic diathesis due to deficiency of prothrombin or its conversion factors and the necessity of reclassifying previously reported cases of so-called "idiopathic hypoprothrombinemia" have made it impossible to establish the definite hereditary pattern of such conditions. Our studies of the family with one member showing hemorrhagic symptoms due to S.F. deficiency revealed a decreased concentration of S.F. in the mother and in 2 of 4 siblings. The only other report of a familial incidence of this disease has been published by Owren[16]. Congenital S.F. deficiency is probably transmitted as a dominant character with various degrees of penetration.

Not having had a chance to study the family of our patient with L.F. deficiency, we have to rely on literature reports[17]. So far it is only known that L.F. deficiency occurs in siblings and there is no report of the disease in more than one generation. Hence any statement regarding the hereditary pattern would be mere speculation.

Afibrinogenemia.

The large and cooperative family of our case offered an excellent opportunity to study the hereditary pattern in afibrinogenemia. The patient's parents were first cousins. Both showed a diminished fibrinogen level. This was also the case in most of the tested aunts and uncles. In addition, 2 siblings were hypofibrinogenemic while the third one had a normal fibrinogen level. It is indeed remarkable that the four children happened to follow the classical pattern of a recessive non-sex-linked Mendelian character. A review of the literature on congenital afibrinogenemia reveals that intermarriage between progenitors was present in 6 out of 11 cases where parental data were reported. Several cases of low fibrinogen levels in consanguinous relatives have been published. In addition six siblings were either proven or suspected cases of afibrinogenemia because they bled to death from umbilical hemorrhage. The male:female ratio of reported cases of afibrinogenemia, including our own patient, is 13:7. It is reasonable to conclude that afibrinogenemia is transmitted as a non-sex-linked recessive character.

Summary:

1. The present status of the mechanism of blood coagulation has been presented.

2. The congenital hemorrhagic diseases have been reclassified by using the scheme of blood clotting as basic reference.

3. The diagnostic methods, clinical symptoms and the hereditary pattern of each single type of congenital hemorrhagic diathesis have been presented and illustrated with cases studied at the University of Minnesota Hospitals.

Table VII. Results of "routine clotting tests" in the various types of hemorrhagic diseases.

	Clotting time	Bleeding time	Prothrombin time	Clot retraction	Platelets	Cuff test	Fibrinogen	Prothrombin consumption
Hypoprothrombinemia	0+	0	+	0	0	-	0	0
Stable Factor Deficiency	0+	0+	+	0	0	-	0	0
Parahemophilia, Labile Factor Deficiency	0+	0+	+	0	0	-	0	-
Thrombocytopenia	0	+	0	-	-	+	0	-
Hemophilia Group	+	0	0	0	0	-	0	-
Hypo- & Afibrinogenemia	+	0	+	0-	0	-	-	0
Pseudohemophilia (v. Willebrand)	0	+	0	0	0	+-	0	0

- negative or decreased.
+ positive, increased or prolonged
0 normal

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II. MEDICAL SCHOOL NEWS

Coming Events

December 3 - 5	Continuation Course in Obstetrics for General Physicians
January 7	Phi Delta Epsilon Lecture; "Present Concepts in the Management of Intussusception;" Dr. Mark R. Ravitch, Director of Surgery, Mt. Sinai Hospital, New York City; Owre Amphitheater; 8:00 p.m.
January 7 - 9	Continuation Course in Pediatrics for General Physicians
January 25 - 30	Continuation Course in Neurology for General Physicians and Specialists
January 27	J. B. Johnston Lecture; "Recent Advances in the Morphology and Significance of the Cerebral Cortex;" Dr. Andrew T. Rasmussen, Professor Emeritus of Anatomy, University of Minnesota; Museum of Natural History Auditorium; 8:00 p.m.

* * *

Faculty News

Dr. C. J. Watson, Professor and Head, Department of Medicine, attended the American Clinical and Climatological Association Meeting in Hot Springs, Virginia, on November 2, 3, and 4. He and Dr. F. W. Hoffbauer, Associate Professor of Medicine, attended the meetings of the Commission on Liver Disease in Washington, D. C., on November 5 and 6. On November 20 and 21, Dr. Watson also attended the meetings of the National Institute of Arthritis and Metabolic Diseases in Washington, D. C.

A paper entitled, "Routine Chest Films in the Detection of Early Lung Cancer with Particular Attention to the Importance of Comparative Studies" was presented by Dr. Leo G. Rigler, Professor and Head, Department of Radiology, at the scientific program of the American Cancer Society in New York City on November 4. Dr. Rigler presented the Alpha Omega Alpha Convocation Lecture to the graduate and undergraduate students at Wayne University College of Medicine, Detroit, Michigan, entitled, "Bronchostenosis," on November 21.

Dr. Roy G. Holly, Associate Professor, Department of Obstetrics and Gynecology, recently spoke to general practitioners in Eau Claire, Wausau, and Appleton, Wisconsin, in a series of cancer seminars sponsored by the American Cancer Society.

* * *

Publications of the Medical School Faculty

Brown, E. B., Jr.: Physiological Effects of Hyperventilation. Physiol. Rev., 33: 445, 1953.

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III

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
WEEKLY CALENDAR OF EVENTS

Physicians Welcome

November 30 to December 5, 1953

Monday, November 30

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; W-612, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:30 - Tumor Conference; Doctors Kremen, Moore, and Stenstrom; Todd Amphitheater, U. H.

11:30 - 12:30 Physical Medicine Seminar; Cerebral Hypoxia in Poliomyelitis; A. B. Baker; Heart Hospital Auditorium.

12:15 - Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:30 Physiology Seminar 201; The Effect of Diet on Serum Cholesterol in Man; Joseph T. Anderson; 214 Millard Hall.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

1:30 - 3:30 Dermatology Hospital Rounds; H. E. Michelson and Staff; Dermatology Histopathology Room, M-434, U. H.

4:00 - 5:00 Residents Conference; Presentation of Cases from Mt. Sinai Hospital; Heart Hospital Theater.

4:30 - ECG Reading Conference; Staff Room, Heart Hospital.

4:30 - Infectious Disease Rounds; Sta. 43, U. H.

4:30 - Public Health Seminar; 15 Owre Hall.

5:00 - 6:00 Physiology-Surgery Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; C. D. Creevy, O. J. Baggenstoss, and Staff; Eustis Amphitheater

Ancker Hospital

8:30 - 10:00 Tuberculosis and Chest Conference; Auditorium.

2:00 - 3:00 Surgery Journal Club; Classroom.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Eldon Berglund; Newborn Nursery, Station C.

10:30 - 12:00 Medicine Rounds; Thomas Lowry; Sta. F.

11:00 - Orthopedic and Fracture Rounds; Drs. John Moe and Arthur Zierold; Sta. A.

11:00 - Pediatric Rounds; Erling Platou; Station K.

12:30 - Surgery Grand Rounds; Dr. Zierold; Sta. E.

1:30 - 2:30 Tuberculosis Conference; J. A. Myers; Sta. M.

2:00 - Pediatric Rounds; Robert A. Ulstrom; Stations I and J.

Monday, November 30 (Cont.)

Veterans Administration Hospital

1:30 - Cardiac Conference; Drs. Berman, Weisbart, and Smith; Rounds Immediately following conference.

Tuesday, December 1

Medical School and University Hospitals

9:00 - 9:50 Roentgenology-Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Cardiovascular Rounds; Station 30, U. H.

12:30 - 1:30 Physiology 114C -- Respiration; E. B. Brown; 129 Millard Hall.

12:30 - 1:20 Pathology Conference; Autopsies; J. R. Dawson and Staff; 102 I. A.

12:30 - 1:30 Bacteriology Seminar; The 80 Per Cent Law in Virus Neutralization; William Murphy; The Phenomenon of Virus Interference; Richard Crowell; 214 Millard Hall.

3:30 - Pediatric Seminar; Chalasia; Wilmer Pew; Sixth Floor, U. H.

3:30 - General Physiology-Biophysics Seminar; 323 Zoology Building.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

4:30 - 5:30 Clinical-Medical-Pathological Conference; Todd Amphitheater, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 X-ray Conference; Presentation of Cases from Minneapolis General Hospital; Drs. Lipschultz and Conklin; Eustis Amphitheater, U. H.

Ancker Hospital

9:00 - 10:00 Medical X-ray Conference; Auditorium.

Minneapolis General Hospital

10:00 - Pediatric Rounds; Spencer F. Brown; Stations I and J.

11:30 - 12:30 Neurology-Neurosurgery Conference; Classroom, Sta. M.

12:30 - 2:30 Dermatology Rounds and Clinic; Carl W. Laymon and Staff.

12:30 - ECG Conference; Boyd Thomes and Staff; 302 Harrington Hall.

1:00 - Tumor Clinic; Drs. Eder, Coe, and Lipschultz; Classroom.

1:00 - Psychiatry Grand Rounds; J. C. Michael and Staff.

Veterans Administration Hospital

7:30 - Anesthesiology Conference; Conference Room, Bldg. I.

8:45 - Surgery Journal Club; Conference Room, Bldg. I.

9:30 - Infectious Disease Rounds; Drs. Hall, Zinneman, and Brown.

9:30 - Surgery-Pathology Conference; Conference Room, Bldg. I.

10:30 - Surgery-Tumor Conference; L. J. Hay, J. Jorgens and Donn Mosser; Conference Room, Bldg. I.

1:00 - Review of Pathology, Pulmonary Tuberculosis; Conference Room, Bldg. I.

1:30 - Combined Medical-Surgical Chest Conference; Conference Room, Bldg. I.

Tuesday, December 1 (Cont.)

Veterans Administration Hospital (Cont.)

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III.

4:00 - Thoracic Surgery Problems; Conference Room, Bldg. I.

Wednesday, December 2

Medical School and University Hospitals

8:00 - 9:00 Roentgenology Surgical-Pathological Conference; Paul Lober and L. G. Rigler; Todd Amphitheater, U. H.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Pediatrics Case; O. H. Wangensteen, C. J. Watson, and Staffs; Todd Amphitheater, U. H.

12:30 - 1:30 Physiology 114B -- Transport Seminar; Nathan Lifson and M. B. Visscher; 214 Millard Hall.

12:30 - 1:30 Radioisotope Seminar; Clinical Use of Radioactive Colloidal Gold for for Control of Effusions; Richard Johnson; Underground Cobalt Unit, Hospital.

1:00 - 2:00 Dermatology Clinical Seminar; 300 North Clinic.

1:30 - 3:00 Pediatric Allergy Clinic; Albert V. Stoesser and Lloyd Nelson; W-211, U. H.

3:30 - 4:30 Dermatology Pharmacology Seminar; J. D. Krafchuk; 3rd Floor Conference Room, Heart Hospital.

4:00 - Medicine-Physiology Cardiovascular Conference; Medicine and Physiology Staffs; Heart Hospital Theater.

4:30 - 5:50 Dermatology Infectious Disease Seminar; J. D. Krafchuk; 3rd Floor Conference Room, Heart Hospital.

4:30 - ECG Reading Conference; Staff Room, Heart Hospital.

5:00 - 6:00 Residents Lecture; Gastric Surgery; F. John Lewis; Todd Amphithoater, U. H.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Eustis Amphitheater, U. H.

5:30 - 7:30 Dermatology Journal Club and Discussion Group; Hospital Dining Room.

7:30 - 9:30 Dermatology Pathology Seminar; Review of Interesting Slides of the Week; Robert W. Goltz; Todd Amphitheater, U. H.

Ancker Hospital

8:30 - 9:30 Clinico-Pathological Conference; Auditorium.

12:30 - 1:30 Medical Journal Club; Library.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Max Seham; Stations I and J.

10:30 - 12:00 Medicine Rounds; Thomas Lowry and Staff; Station D.

11:00 - Pediatric Seminar; Arnold Anderson; Classroom, Station I.

11:00 - Pediatric Rounds; Erling S. Platou; Station K.

12:00 - Surgery Seminar; Arthur Zierold; Classroom.

12:15 - Pediatric Staff Meeting; Classroom, Station I.

Wednesday, December 2 (Cont.)

Minneapolis General Hospital (Cont.)

1:30 - Visiting Pediatric Staff Case Presentation; Classroom, Station I.

Veterans Administration Hospital

8:30 - 10:00 Orthopedic X-ray Conference; E. T. Evans and Staff; Conference Room; Bldg. I.

8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker.

9:00 - Gastro-Intestinal Rounds; Drs. Wilson, Zieve, Hay, Brakel and Nesbitt.

12:30 - X-ray Conference; J. Jorgens; Conference Room, Bldg. I.

1:30 - 2:30 Infectious Disease Conference; Wesley W. Spink; Conference Room, Bldg. I.

2:30 - 4:00 Infectious Disease Rounds; Main Conference Room, Bldg. I.

5:00 - Medical Journal Club; Conference Room, Bldg. I.

7:00 p.m. Lectures in Basic Science of Orthopedics; Conference Room, Bldg. I.

Thursday, December 3

Medical School and University Hospitals

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

12:00 - 1:00 Medical Journal Club; Folic Acid and Vitamin B_{12}; Elsa Proehl; 116 Millard Hall.

12:30 - Physiological Chemistry Seminar; Liver Changes Induced by Insulin in Alloxan Diabetic Rats; Joseph Eusterman; 214 Millard Hall.

1:30 - 4:00 Cardiology X-ray Conference; Heart Hospital Theatre.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - 6:00 Radiology Seminar; Thoracic Surgery Conference; Dr. Varco, et al; Eustis Amphitheater, U. H.

7:30 - 9:30 Pediatric Cardiology Conference and Journal Club; Review of Current Literature 1st hour and Review of Patients 2nd hour; 206 Temporary West Hospital.

Ancker Hospital

8:00 - 10:00 Medical Grand Rounds; Auditorium.

Minneapolis General Hospital

9:30 - Neurology Rounds; Heinz Bruhl; Station I.

10:00 - Pediatric Rounds; Spencer F. Brown; Station K.

10:00 - Psychiatry Grand Rounds; J. C. Michael and Staff; Sta. H.

11:30 - 12:30 Clinical Pathological Conference; John I. Coe; Classroom.

12:30 - 2:30 Dermatology Rounds and Clinic; Carl W. Laymon and Staff.

1:00 - Fracture - X-ray Conference; Dr. Zierold; Classroom.

1:00 - House Staff Conference; Station I.

Thursday, December 3 (Cont.)

Veterans Administration Hospital

8:00 - Surgery Grand Rounds; Conference Room, Bldg. I.

8:00 - Surgery Ward Rounds; Lyle Hay and Staff; Ward 11.

11:00 - Surgery-Roentgen Conference; J. Jorgens; Conference Room, Bldg. I.

1:00 - 3:00 Metabolic Disease Conference; Drs. Flink, Heller and Hoseth.

Friday, December 4

Medical School and University Hospitals

8:00 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Medicine Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:30 - 1:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Vascular Rounds; Davitt Felder and Staff Members from the Departments of Medicine, Surgery, Physical Medicine, and Dermatology; Out-Patient Department, Heart Hospital.

11:45 - 12:50 University of Minnesota Hospitals Staff Meeting; The Bone Marrow in Pregnancy; Roy G. Holly; Powell Hall Amphitheater.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

1:30 - 2:30 Dermatology Grand Rounds; Presentation of Cases from Grouped Hospitals (University, Ancker, General and Veterans) and Private Offices; H. E. Michelson and Staff; Skin Clinic; W-312, U. H.

2:30 - 4:00 Dermatology Hospital Rounds; H. E. Michelson and Staff; Begin at Dermatology Histopathology Room, M-434, U. H.

3:00 - 4:00 Neuropathological Conference; F. Tichy; Todd Amphitheater, U. H.

4:00 - 5:00 124 Advanced Neurophysiology Lecture; Werner Koella and Ernst Gellhorn; 111 Owre Hall.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

4:30 - ECG Reading Conference; James C. Dahl, et al; Staff Room, Heart Hospital.

5:00 - Urology Seminar and X-ray Conference; Eustis Amphitheater, U. H.

Ancker Hospital

1:00 - 3:00 Pathology-Surgery Conference; Auditorium.

Minneapolis General Hospital

9:30 - Pediatric Rounds; Wallace Lueck; Station J.

10:30 - Pediatric Surgery Conference; Oswald Wyatt; Tague Chisholm; Station I, Classroom.

12:00 - Surgery-Pathology Conference; Dr. Zierold, Dr. Coe; Classroom.

1:00 - 3:00 Clinical Medical Conference; Thomas Lowry; Classroom, Station M.

1:15 - Pediatric X-ray Conference; Oscar Lipschultz; Classroom, Main Bldg.

2:00 - Pediatric Rounds; Robert Ulstrom; Stations I and J.

Friday, December 4 (Cont.)

Veterans Administration Hospital

10:30 - 11:20 Medicine Grand Rounds; Conference Room, Bldg. I.

1:00 - Pathology Slide Conference; E. T. Bell; Conference Room, Bldg. I.

2:00 - Autopsy Conference; E. T. Bell and Donald Gleason, Conference Room, Bldg. I.

Saturday, December 5

Medical School and University Hospitals

7:45 - 8:50 Orthopedic X-ray Conference; W. H. Cole and Staff; M-109, U. H.

9:00 - 10:00 Infertility Conference; Louis L. Friedman, David I. Seibel, and Obstetrics Staff; Eustis Amphitheater, U. H.

9:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; Heart Hospital Amphitheater.

9:15 - 10:00 Surgery-Roentgenology Conference; L. G. Rigler, J. Friedman, Owen H. Wangensteen and Staff; Todd Amphitheater, U. H.

10:00 - 11:30 Surgery Conference; Todd Amphitheater, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:30 - Anatomy Seminar; The Medical School of Bologna as Illustrated by the Life and Times of Gaspare Tagliacozzi (1534-1599); S. P. Miller; 226 Institute of Anatomy.

Ancker Hospital

8:30 - 9:30 Surgery Conference; Auditorium.

Minneapolis General Hospital

8:00 - Urology Staff Conference; T. H. Sweetser; Main Classroom.

11:00 - 12:00 Medical - X-ray Conference; O. Lipschultz, Thomas Lowry and Staff; Main Classroom.

Veterans Administration Hospital

8:00 - Proctology Rounds; W. C. Bernstein and Staff; Bldg. III.

8:30 - 11:15 Hematology Rounds; Drs. Hagen and Sherman.

11:15 - 12:00 Morphology . . . . Dr. Aufderheide; Conference Room.