REPORT

of

COMMITTEE ON EXAMINATION

This is to certify that we the undersigned, as a Committee of the Graduate School, have given Dorothy Foster Pettibone final oral examination for the degree of Master of Science. We recommend that the degree of Master of Science be conferred upon the candidate.

Minneapolis, Minnesota
May 28 1917

H Z Gifford
Chairman
A. H. Sanford
F. C. Mann

REPORT

of

Committee on Thesis

The undersigned, acting as a Committee of the Graduate School, have read the accompanying thesis submitted by Dorothy Foster Pettibone for the degree of Master of Science. They approve it as a thesis meeting the requirements of the Graduate School of the University of Minnesota, and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science.

H. J. Griffin

O. H. Sanford Chairman

Frank C. Mann

May 28 1917

Statement Concerning Life of Candidate for Master's Degree.

1. Name of candidate.

Dorothy Foster Pettibone.

2. Place and date of birth.

Burlington, Wis., March 30, 1894.

3. Preliminary education, secondary and collegiate.

1911-1913, Beloit College.
1913-1915, University of Wisconsin.

4. Degrees obtained, with date and name of institution.

A.B., 1915, University of Wisconsin.

5. Language examination passed.

French,

6. Minor line of work.

Pathology. No written examination required.

7. Major line of work, with date of final written examination.

Bacteriology. May 24, 1917.

8. Thesis subject, with date of final approval.

The factors in Coagulation in Certain Pathologic Conditions.

9. Degree applied for.

Master of Science.

Factors in Coagulation in Certain Pathologic Conditions

A Thesis

Submitted to the Faculty

of the

Graduate School

of

The University of Minnesota

by

Dorothy Foster Pettibone

In partial fulfillment of the requirements for

the degree

of

Master of Science

1917

FACTORS IN COAGULATION IN CERTAIN PATHOLOGIC CONDITIONS

A Thesis offered

by

Dorothy Foster Pettibone, B.A.,

In Partial Fulfillment of the Requirement for the Degree of

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1917.

FACTORS IN COAGULATION IN CERTAIN PATHOLOGIC CONDITIONS.

Dorothy Foster Pettibone, M.D.

Elaborate studies have been made on the various factors which concern the coagulation of blood. Howell[1] has outlined minutely the individual constituents and their respective functions in normal blood. According to him, there are five factors in coagulation, viz., prothrombin, fibrinogen, calcium salts, thromboplastin and antithrombin, all of which may show variations in disease. These are all normally present in the circulating blood except thromboplastin, which is contained in all tissue juices as well as in the formed elements of the blood. Upon injury of the vessel then, thromboplastin is liberated from the surrounding tissue and the platelets and frees the blood of antithrombin, allowing prothrombin to act with calcium and the thrombin unites with fibrinogen and forms fibrin. According to Morawitz (quoted by Brinker and Hurwitz[15]), thrombokinase transforms thrombogen, which normally circulates in the blood, to prothrombin. Prothrombin is then changed to thrombin by calcium salts. Thrombin reacts with fibrinogen and produces fibrin. Thrombogen has not been differentiated in any way from prothrombin.

Since the common acceptance of these underlying principles, much work has been done on these same factors in various pathological conditions with special reference to hemorrhagic disturbances. Methods have been devised whereby these separate factors may be isolated and quantitatively estimated. I have studied a group of cases with special emphasis upon prothrombin, calcium salts, and platelets. Among these forty seven cases, I present 2 hemophiliacs, 7 myelogenous leukemias, 2 purpura, 10

epilepsy, 17 jaundice cases (7 obstructive and 10 hemolytic) and 8 of a miscellaneous group.

HEMOPHILIA

Many workers have reported observations on bloods of hemophiliacs, and the facts they note have agreed for the most part. Howell[2] in his prothrombin tests proved that one may by this comparative method readily distinguish between hemophilic and normal bloods. Addis believes that the condition is due to deficient thromboplastic material, but there has been suggested as yet no satisfactory method for determining the amount of this substance. The method used for determining prothrombin time is that of Howell[3], viz., Draw 5 cc. of blood into sterile syringe previously rinsed out with normal salt solution and express into tube containing 1 cc. of 1% potassium oxalate. Invert tube once to mix thoroughly and centrifuge for fifteen minutes. In a series of small tubes place graduated amounts of 0.5% calcium chloride, beginning with 2 gtts. and stopping at 8 gtt. Add to each tube 8 gtt. of the plasma and take time of coagulation.

	Tube 1.	Tube 2.	Tube 3.	Tube 4.	Tube 5.	Tube 6.	Tube 7.
Calcium chloride	2 gtt.	3 gtt.	4 gtt.	5 gtt.	6 gtt.	7 gtt.	8 gtt.
Plasma	8 gtt.	8 gtt.	8 gtt.	8 gtt.	8 gtt.	8 gtt.	8 gtt.
Normal Prothrombin time	4 min.	6 min.	8 min.	10 min.	10 min.	12 min.	14 min.

We know by this test that in hemophiliacs the prothrombin-antithrombin balance is upset, but it is not certainly proved that it is the actual amount of prothrombin that is altered. Addis[4] believes the prothrombin to be present in normal amounts in these cases, but is so altered as to require longer time for activation to the thrombin present. An excess of antithrombin is present only as a result of decreased prothrombin.

The coagulation time of hemophilia is always long. In estimating this time accurately there are many difficulties to consider. The method used is that described by Lee and White[8], viz.: One cc. of blood is drawn from the vein into a sterile syringe previously washed with normal salt solution, and expressed into Wassermann tube which has also been rinsed with normal salt solution. Care must be taken to leave the salt solution in the needle before puncture as the admission of air bubbles greatly hastens the coagulation of the blood. The needle is removed so as not to break up the platelets in expressing the blood, and the tube is rotated sublime every thirty seconds till the clot adheres to the tube when inverted. H. B. Cohen[6] has shown how necessary is absolute cleanliness, uniformity of apparatus used, exact amount of blood, and constant temperature[7]. The time of coagulation greatly depends on the extent of contact to the glass; it can be greatly hastened by any shaking of the tube. The hemophilic blood may become gelatinous in comparatively short time, but it is easily noted that the clot is not firm and that its disturbance results in its breaking down. Minot and Lee[9] found that the clots often formed as quickly as normal but never became as firm. If this first clot is removed, a second clot will form; this is also an imperfect clot and can be removed. It has been observed recently by Lee, but not as yet published, that 5 and 6 clots can be removed in succession from hemophilian blood while that of a normal blood will seldom form a second clot. It was able to remove four clots from the blood of one case, while in normal controls I have never removed more than two.

Case No. 1[illegible]2 is worthy of special attention. This case had a definite history of family hemophilia; his coagulation time was exceedingly long but his prothrombin time was within normal limits and his platelet count was 118,000 per c.m.m. His mother's blood was then examined and found to

have an exceedingly long prothrombin time, though a normal coagulation time. When the prothrombin time was determined, the material was invertable though not as solid and set as in normal sera. Workers who are interested in this type of case have been looking for just such findings, but have not made the actual observations.

Case No. 12555 had a coagulation time of 72 minutes, and after transfusion the coagulation time was reduced to 34 minutes.

Wright[9] has attributed the hemophilic condition to a calcium deficiency. Hurwitz and Lucas[10] in studying five cases in detail observed the characteristic delay in coagulation and a constant deficiency in prothrombin: other factors of coagulation, however, were present in normal amounts. In the following cases no appreciable differences in amount or activity of calcium were observed.

(Table - Hemophilias)

EPILEPSY.

Results of numerous observations on the blood of epileptic patients have been fairly uniform with the exception of the coagulation time, and these results have been most varied. It has been found by several workers to be greatly shortened, while Dr. John Turner believes the time to be greater in cases of epilepsy. Dr. H. A. Thorn[11] reports a series of 203 cases of epilepsy whose coagulation time he determined in the method outlined by Lee and White.[5] 92 per cent of these cases fell within normal limits, 5.5 per cent fell under the minimum and 2.5 per cent were over the maximum. Two and one-half to fourteen minutes marked the extremes of this series. Using the same method for determining coagulation time, I studied a series of ten cases presenting a range of from four to fifteen minutes, while controls of normal individuals ranged from four to twelve minutes.

HEMOPHILIAS.

Calcium chloride	Prothrombin time 2 gtt.	3 gtt.	4 gtt.	5 gtt.	6 gtt.	7 gtt.	8 gtt.	Coagulation time	Calcium time	Platelet per c.m.m.
183593	0	0	12 min.	10.5 min.	10.5 min.	10 min.		93 min.	3 hrs. (imperfect clot)	115,000
	24 hours after transfusion: 0	0	75 min.	25 min.	38 min.	39 min.		10 min.	12 min.	171,000
Mother	99 min.	99 min.	Lost	-	-	87 min. (imperfect clot thruout)		8 min.	11.5 min.	202,000
182535	Not done because of difficulty in procuring blood							73 min.		
	After transfusion:							34 min.		

It seems reasonable to conclude that there is no change in the coagulation time in cases of epilepsy. Variations in coagulation time are to be expected and with much greater leaway for error than with the morphological characteristics, for instance. A great deal depends on the technic of this method and the differences occurring among normal indiviiduals vary in the same manner.

It is believed that epileptic patients can be benefited by calcium lactate treatment and many of these cases have greatly improved, since these tests were made, under that treatment. Two cases have returned after a period of six weeks or two months and found to have enough calcium present in the blood to produce coagulation in less time than by the addition of calcium chloride.

(Table - Epilepsy)

Retraction.

It has been noted by many that the normal retractability of the blood clot depends upon the presence of platelets. Duke[12] proved experimentally that platelets can leave behind them the power to clot but must be present to produce retraction of the clot. I have noted two cases in which the platelet count was 14,000 per c.m.m. and no retraction of the clot occurred in eighteen hours. These are typical cases in all respects:

	Prothrombin Time.							Coagulation Time	Calcium Time	Platelet per c.m.m.
Calcium Chloride.	2 gtt.	3 gtt.	4 gtt.	5 gtt.	6 gtt.	7 gtt.	8 gtt.			
1	5 min.	5 min.	6 min.	6 min.	8 min.	10min.	10 min.	5 min.	5 min.	14,000
	With 1 cc. oxalate:									
	3 min.	3 min.	5 min.	8 min.	10min.	10min.	10 min.			
2	Not taken.							3 min.	3 min.	14,000
	After transfusion:									139,000

Morawitz and Lucas[13] are convinced that chronic purpuras do at times present abnormalities other than platelet deficiency. In two cases they observed over a period of six months, they noted fluctuations in the amount of circulating antithrombin. I have made estimation of antithrombin in none of my series.

JAUNDICE

It has long been an established fact that in certain types of jaundice there is a definite delay in coagulation time. Morawitz and Bierich believed that the altered coagulation time was independent of the intensity of the jaundice. Lee and Vincent[14] note that this delayed coagulation does not show up until five or six weeks after the onset of jaundice. The good effects of calcium treatment are felt after several days and the case is deemed operable when the calcium time reaches seven minutes. This time is estimated according to Lee and Vincent's technic, viz.: One cc. of patient's blood is drawn into sterile syringe previously rinsed with salt solution and expressed, without the needle, into a small tube containing 6 gtt. of a 0.5 per cent calcium chloride solution. The tube is inverted every thirty seconds and the calcium time is taken at the point of coagulation. The test is the same as for coagulation time with the addition of calcium chloride. It has been found that too much as well as too little calcium will serve to delay the process of coagulation.

Blood platelets were isolated in these cases by Lee and Vincent and found to act normally both in the formation and retraction of the clot.

It has been found experimentally that bile has an inhibitory effect on the formation of thrombin. Bile will entirely prevent coagulation in vitro even in the presence of the optimum amount of calcium. It is probably however that bile never becomes so concentrated in the blood of jaundice patients.

(Table -- Obstructive Jaundice)

(Table -- Hemolytic Jaundice)

Obstruction jaundice.

Calcium chloride.	Prothrombin time							Coagulation time.	Calcium time.	Platelet count.
	2 gtt.	3 gtt.	4 gtt.	5 gtt.	6 gtt.	7 gtt.	8 gtt.			
1	8 min.	10 min.	10 min.	10 min.	10 min.	13 min.	13 min.	8 min.	5 min.	212,000 per c.m.m.
		One-half cc. oxalate:								
	6 min.	6 min.	8 min.	8 min.	8 min.	11 min.	11 min.			
2	19 min.	20 min.	20 min.	21 min.	34 min.	15 min.		15 min.	11 min.	200,000 per c.m.m.
								After cal. treatment.		
								12 min.	20 min.	
3	30 min.	16 min.	15 min.	16 min.	16 min.			4 min.	6 min.	253,000 per c.m.m.
4	13 min.	11 min.	11 min.	11 min.	9 min.	10 min.	11 min.	10 min.	6 min.	212,000 per c.m.m.
		With one-half cc. oxalate:								
	5 min.	5 min.	5 min.	5 min.	5 min.	5 min.	5 min.			
5	5 min.	5 min.	5 min.	6 min.	6 min.	7 min.	8 min.	5 min.	5 min.	194,000 per c.m.m.
6	6 min.	6 min.	6 min.	9 min.	9 min.	9 min.	9 min.	8 min.	8 min.	262,000 per c.m.m.
		With one-half cc. oxalate:								
	3 min.	3 min.	3 min.	3 min.	3 min.	3 min.	4 min.			
7	21 min.	19 min.	18 min.	16 min.	18 min.	20 min.	24 min.	21min.(2 clots)	14 min.	209,000 per c.m.m.

Hemolytic jaundice.

Calcium chloride.	Prothrombin time 2gtt.	3 gtt.	4 gtt.	5 gtt.	6 gtt.	7 gtt.	8 gtt.	Coagulation time.	Calcium time.	Platelet count.
1	9 min.	9 min.	10 min.	13 min.	14 min.	14 min.	15 min.	14 min.(1 clot)	17 min.	131,000 treatment excess
	One-half cc. clot spinning.									
2	0	36 min.	25 min.	18 min.	19 min.	20 min.		20 min.	8 min.	208,000.
	One-half cc. clot spinning.									
3	6 min.	5 min.	4 min.	5 min.	5 min.			11 min.	10 min.	198,000.
	One-half cc. clot spinning.									
4	8 min.	8 min.	8 min.	7 min.	8 min.	9 min.	9 min.	7 min.	9 min.	208,000 (treatment?)
	One-half cc. clot spinning.									
5	5 min.	7 min.	7 min.	7 min.	7 min.	9 min.	9 min.	9 min.	5 min.	200,000.
	One-half cc. clot spinning.									
6	17 min.	17 min.	16 min.	16 min.	16 min.	16 min.	16 min.	15 min.	10 min.	223,000.
	One-half cc. :									
	10 min.	10 min.	10 min.	10 min.	10 min.	11 cc.	11 min.			
7	9 min.	8 min.	7 min.	7 min.	7 min.	9 min.	9 min.	4 min.	6 min.	210,000 (treatment?)
	One-half cc.:									
	4 min.	4 min.	4 min.	4 min.	4 min.	4 min.	4 min.			
8	5 min.	5 min.	5 min.	5 min.	5 min.	6 min.	6 min.	7 min.	8 min.	255,000 (treatment?)
	One-half cc.:									
	4 min.	4 min.	4 min.	4 min.	4 min.	5 min.	5 min.			
9	10 min.	10 min.	13 min.	15 min.	15 min.	16 min.	18 min.	9 min.	12 min.	228,000 (treatment?)
	One-half cc.:									
	10 min.	12 min.	14 min.	15 min.	15 min.	15 min.	16 min.			
10	6 min.	6 min.	7 min.	8 min.	8 min.	10 min.	10 min.	9 min.	8 min.	200,000.
	One-half cc.:									
	Clot while spinning.									

Myelocytic leukemia.

Calcium chloride.	Prothrombin time. 2 gtt.	3 gtt.	4 gtt.	5 gtt.	6 gtt.	7 gtt.	8 gtt.	Coagulation time.	Platelet count.
1	7 min.	7 min.	8 min.	9 min.	9 min.	9 min.	10 min.	8 min.	196,000 with hemorrhage.
	One-half cc. oxalate: 6 min.	7 min.	7 min.	8 min.	8 min.	8 min.	8 min.	12 min.calcium.	
2	16 min.	13 min.	12 min.	12 min.	12 min.	14 min.	14 min.	8 min.calcium	194,000.
	One-halfcc. oxalate: 7 min.	7 min.	8 min.	8 min.	8 min.	8 min.	8 min.	8 calcium time.	
3								12 cal.time. 14 cal.time.	270,000.
4	17 min.	13 min.	15 min.	120 min.	120 min.			8 cal.time. 9 cal.time.	185,000.
5	14 min.	12 min.	13 min.	15 min.	15 min.			8 cal.time.	Impossible too many myelocytes.
	One-half cc. oxalate: 15 min.	14 min.	12 min.	13 min.	13 min.			11 cal.time.	
6	Not done.							10 cal.time. 12 cal.time.	280,000.
7	15 min.	15.min.	20 min.	20 min.	20 min.	21 min.	25 min.	7 min.	188,000.
	One-half cc. oxalate: 15 min.	16 min.	19 min.	20 min.	24 min.	24 min.	24 min.	6 min.cal. time.	

MISCELLANEOUS.

		Prothrombin time.							Coagulation time.	Calcium time.	Platelet count.
Calcium chloride.		2 gtt.	3 gtt.	4 gtt.	5 gtt.	6 gtt.	7 gtt.	8 gtt.			
Diabetes		30 min.	23 min.	16 min.	17 min.	11 min.	15 min.		4 min.		
Splenomegaly	(1)	0		40 min.	25 min.	25 min.	23 min.		16 min.	22 min.	288,000 c.m.m.
	(2)	11 min.	13 min.	14 min.	15 min.	15 min.	17 min.	19 min.	9 " (1 clot)	10 min.	177,000 c.m.m.
		With one-half cc. oxalate:									
		16 min.	16 min.	16 min.	16 min.	16 min.	16 min.	16 min.			
	(3)	7 min.	9 min.	9 min.	12 min.	14 min.	18 min.	18 min.	10 min. (2clots)	13 min.	
		With one-half cc. oxalate:									
		8 min.	10 min.	14 min.	14 min.	18 min.	19 min.	19 min.			
T. B. Spleen.	(1)	9 min.	8 min.	7 min.	7 min.	7 min.	7 min.	8 min.	7 min.	6 min.	197,000 c.m.m.
		With one-half cc. oxalate:									
		4 min.	4 min.	4 min.	4 min.	4 min.	4 min.	4 min.			
Pernicious Anemia.	(1)	14 min.	20 min.	22 min.	24 min.	30 min.	30 min.	30 min.	5 min. (1 clot).	4 min.	204,000 c.m.m.
		With one-half cc. oxalate:									
		22 min.	20 min.	24 min.	30 min.	30 min.	30 min.	30 min.			
	(2)	Not done.							6 min.	Not done.	157,000 c.m.m.
	(3)	Not done.							Not done.	Not done.	269,000 c.m.m.
Polycythemia	(1)	8 min.	8 min.	7 min.	6 min.	6 min.	6 min.	6 min.	8 min. (1 clot)	9 min.	115,000 c.m.m.
		With one-half cc. oxalate:									
		5 min.	8 min.	7 min.	6 min.	6 min.	6 min.	6 min.			

Epilepsy.

	Prothrombin time							Coagulation time.	Calcium time.	Platelet count.
Calcium chloride	2 gtt.	3 gtt.	4 gtt.	5 gtt.	6 gtt.	7gtt.	8gtt.			
1		Not done						11 min.		Not done.
2		Not done						7 min.	5 min.	Not done.
3		Not done						6 min.	4 min.	Not done.
4	0	26 min.	25 min.	26 min.	27 min.			8 min.	14 min.	Not done.
5	0	19 min.	15 min.	15 min.	16 min.			12 min.	8 min.	Not done.
6	8 min.	8 min.	7 min.	7 min.	7 min.			9min.	10 min.	Not done.
7	10 min.	10 min.	10 min.	9 min.	9 min.	9min.	9min.			178,000 per c.m.m.
	With one-half cc. oxalate:									
	9 min.	9 min.	9 min.	9 min.	8 min.	8min.	8min.	4 min.	4 min.	
8		Not done.						15 min.	Not done.	Not done.
9		Not done.						8 min.	Not done.	Not done.
10	6 min.	7 min.	8 min.	8 min.	9 min.	9min	9min	6 "(1clot)	5 min.	215,000 per c.m.m.

MYELOGENOUS LEUKEMIA.

There has been little note taken in this connection of the blood of myelogenous leukemias. In this series of seven cases, it will be noted that they present a tendency to prolonged prothrombin times although the coagulation times are quite short. [6] E. B. Cohen has shown experimentally that a marked leukocytosis very definitely delays coagulation.

It is evident that these cases have the optimum amount of calcium for the addition in vitro of 3 drops of calcium noticeably delays coagulation.

(Table - Myelogenous leukemia)

Drinker and Hurwitz [15] found prothrombin to be slightly diminished in all cases of pernicious anemia. I have found that to be true in the one case examined here. The platelet counts are, however, relatively normal.

The three splenomegaly cases present delayed prothrombin times. Coagulation times are rather long but addition of calcium tends to retard.

Among this miscellaneous group there are several types of conditions. None of them present abnormal pictures, however.

(Table - Miscellaneous)

In doing these prothrombin tests we have noted that reducing the amount of blood used to just half, the results were identical and the test more economical, - the amount of potassium oxalate being reduced proportionately of course. Care must be taken to use the same needle for measuring calcium and serum, for the time varies appreciably if the size of drops is not uniform. I have also done parallel prothrombin tests on several cases, using ½ cc. of potassium oxalate to 8 cc. of blood. In the jaundice cases, great difficulty was experienced in avoiding a clot while centrifugalising the blood. If a clot had formed, the serum it expressed would not clot upon the addition of calcium. The serum of those which did not clot while spinning, however, manifested a shorter prothrombin time when only ½ cc. of oxalate was used. In these cases there was not sufficient oxalate to precipitate all the calcium, and in one case there was so much native calcium that the optimum amount of calcium brought the shortest time of clotting in the first tube following by an excess of calcium in the rest of the tubes and a consequent retarding of the clotting process.

The method employed for platelet enumeration is that described by Wright and Kinnecutt[16]. Blood is mixed with the diluting fluid in the proportion of one to a hundred by means of the ordinary red blood corpuscle pipette and counted in the blood counting chamber with a high dry objective. The diluting fluid consists of two parts of an aqueous solution of brilliant cresyl blue (1 : 300) and three parts of an aqueous solution of potassium cyanid (1 : 1400). These two solutions must be kept separately and mixed and filtered only as used or a precipitate forms and obscures the platelets. In order to get an even distribution of platelets it is well to fill the chamber at once after mixing blood and fluid in pipette.

I find that waiting an appreciable length of time and shaking as for red blood corpuscles and white blood corpuscles is not satisfactory.

Wright[17] demonstrated several years ago that platelets tend to adhere to any foreign body and form clumps. This perhaps explains the reduced counts after shaping the pipette. Shaking also tends to form larger and denser clumps which makes the count very inaccurate. There are three main requisites for reliable platelet counts; namely, the red corpuscles must be laked, the protoplasm of the leucocytes well stained and the platelets evenly distributed.[18]

After the counting chamber has been filled, it may stand for hours before making the count. It must surely stand ten minutes to allow the platelets to thoroughly settle. The cresyl blue solution will keep indefinitely if kept on ice to prevent growth of yeasts. Potassium cyanid should be made up fresh at least every ten days. It must be made of pure potassium cyanide not undergoing degeneration.

Duke, in doing platelet counts, finds them fairly constant in normal individuals but fluctuating to extremes in pathologic conditions. By various experimental devices he showed that the platelet count fluctuated in exact proportion to the degree of toxicity. He found that the injection of diphtheria toxin in small doses raised the count and that the same toxin in lethal or nearly lethal doses decreased the count rapidly. He concludes from his experiments that when increased counts are found associated with pathologic conditions the case is usually mild. In other words, the toxins act as irritants or poisons according to the size of dosage.[19] Duke here cut his teeth in humans; his average counts of patients in febrile condition was 114,000 per c.m.m. - the convalescent counts going as high as 750,000 per c.m.m.

SUMMARY.

Technic of various laboratory methods used are described.

There is a marked calcium deficiency in jaundice cases of several weeks duration. Platelets are present in normal numbers.

Blood of purpuras is deficient in platelets. There is no retraction of the clot. Estimation of platelets is of value in differentiating between purpuras and hemophiliss.

Coagulation time of epileptic blood is within normal limits when controlled by normal individuals.

Prothrombin is slightly diminished in pernicious anemia.

There is a tendency to prolonged prothrombin time in myelogenous leukemia although the coagulation time is short. Normal prothrombin time ranges from six to fourteen minutes.

There is a characteristic delay in coagulation in the blood of hemophiliac cases. There is also a deficiency in prothrombin. Platelets are present in normal numbers and have normal retractile powers. There is apparently no deficiency in calcium.

One case of special note among the hemophilias had an extremely long coagulation time though his prothrombin time was within normal limits. His mother had a normal coagulation time but a markedly delayed prothrombin time.

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