The factors of coagulation in primary pernicious anemia / Cecil K. Drinker, M.D. and Samuel H. Hurwitz, M.D. Boston.

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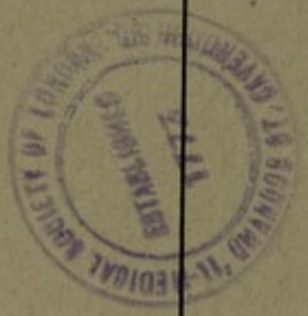

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The Factors of Coagulation in Primary Pernicious Anemia

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THE FACTORS OF COAGULATION IN PRIMARY PERNICIOUS ANEMIA*

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Within the past two years it has become more and more possible to study the factors concerned in blood coagulation. The literature of this period has even given promise of an etiological classification of hemorrhagic disease, but developments have not borne out this promise. If we accept the theory of Howell,[1] there are five factors in coagulation — antithrombin, thromboplastin, calcium salts, prothrombin and fibrinogen — which may show variations in disease. Antithrombin, prothrombin, calcium salts and fibrinogen are present in the circulating blood. The prothrombin, however, is held in combination with antithrombin and thus prevented from activation into thrombin by calcium. Without thrombin there can be no coagulation. The presence of thrombin is secured through the fixation or neutralization of antithrombin by thromboplastin. This last substance, thromboplastin, frees the blood of antithrombin; under these conditions calcium at once forms thrombin from prothrombin; thrombin reacts with fibrinogen and gives fibrin.

If, on the other hand, we accept the theory of Morawitz, with which most other theories can be brought into accord, we have four possible factors to consider. The existence of antithrombin is admitted by this investigator, but it is not regarded as an essential part of the process. According to Morawitz, thrombokinase (Howell's thromboplastin) transforms thrombogen — normally circulating in the blood — to prothrombin; prothrombin later is converted into thrombin by calcium salts. Thrombin reacts with fibrinogen and gives fibrin. It is not possible to differentiate thrombogen and prothrombin so that the latter alone represents this factor in our experiments.

QUANTITATION OF THE COAGULATION FACTORS AND THEIR VARIATIONS IN DISEASE

1. *Antithrombin.*—Howell[2] has given us a rapid method for preparing thrombin. Making use of this thrombin and of a normal salt

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* From the Peter Bent Brigham Hospital, Boston.

1. Howell, W. H.: The Rôle of Antithrombin and Thromboplastin (Thromboplastic Substance) in the Coagulation of the Blood, Am. Jour. Physiol., 1911, xxix, 187.

2. Howell, W. H.: Rapid Method of Preparing Thrombin, Am. Jour Physiol., 1913, xxxii, 264.

solution of dried oxalated plasma, which contains active fibrinogen, he has shown that we may get coagulation in from three to ten minutes. Such a system can be rendered non-coagulable, or coagulation can be greatly delayed by the addition of oxalated plasma which has been heated to 60 C. This prevention of coagulation is ascribed to the antithrombin present normally in the blood, and on this basis one may readily test the antithrombin in different clinical conditions. Our technic for these determinations has been that described by Howell[3] and is illustrated in the protocol which follows. Making use of this method, Howell[3] has shown a diminution of antithrombin in three cases of thrombosis; Whipple[4, 5] an increase in one case of profound septicemia; in a case of typhoid fever with complicating liver disease; in a case of miliary tuberculosis with epistaxis; in a case of generalized thrombosis; in a case of leukemia with purpura; in a case of aplastic anemia with purpura and hemorrhage from the nose and gums. These are diverse conditions, and the method of taking the blood has not been uniform. In many of his determinations Whipple used blood from the heart collected some time after death, and his controls in antithrombin have not been as complete as Howell's present methods seem to us to require. Austin and Pepper[6] found an increase in antithrombin in one case of simple purpura.

2. *Thromboplastin* (*thrombokinase of Morawitz*).—Thromboplastin can be shown to be present in blood in many ways, but for quantitation there is at present no better method than the platelet count. It must be noted, however, that all the formed elements of the blood have been shown to have thromboplastic properties and that the platelets have also been shown to contain prothrombin,[7] so that by this count we do not accomplish our purpose either completely or exactly. The literature on the platelets is large, and it suffices to say that they have been shown to be increased in pneumonia, post-hemorrhagic anemia, and myeloid leukemia; in short, in diseases leading to multiplication of bone-marrow cells. They are decreased in most cases of pernicious anemia, in lymphatic leukemia, in typhoid and many other fevers, and in purpura hemorrhagica, whether primary or secondary. With the

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3. Howell, W. H.: The Condition of the Blood in Hemophilia, Thrombosis and Purpura, The Archives Int. Med., 1914, xiii, 76.

4. Whipple, G. H.: Hemorrhagic Disease — Septicemia, Melena Neonatorum and Hepatic Cirrhosis, The Archives Int. Med., 1912, ix, 365.

5. Whipple, G. H.: Hemorrhagic Disease. Antithrombin and Prothrombin Factors. The Archives Int. Med., 1913, xii, 637.

6. Austin, J. H., and Pepper, O. H. P.: Experimental Observations on the Coagulation of Oxalated Plasma, with a Study of Some Cases of Purpura, The Archives Int. Med., 1913, xi, 305.

7. Morawitz, P.: Beiträge sur Kenntniss der Blutgerinnung, Deutsch. Arch. f. klin. Med., 1904, lxxix, 215; Baynes-Jones, S.: The Presence of Prothrombin and Thromboplastin in the Blood Platelets, Am. Jour. Physiol., 1912, xxx, 74.

exception of one observation by Austin and Pepper[6] we know of no cases of hemophilia in which they have been found deficient. Sahli[8] and Morawitz and Lossen[9] ascribe hemophilia to defective formation of thromboplastic material by injured vessel walls. This opinion is arrived at by a process of exclusion of other factors, but not by direct experiment.

3. *Calcium.*—The third factor in the coagulation system, calcium, has not been studied in our series of cases. Wright[10] has advocated the treatment of hemophilia by administration of calcium, and the weight of his advice has led to the indiscriminate use of calcium salts in bleeding conditions. Nolf[11] has absolutely denied calcium diminution in hemophilia, and it appears probable that this factor may be neglected in hemorrhagic disease.

4. *Prothrombin.*—This cannot be determined with entire certainty. If one takes oxalated plasma and to a series of tubes adds dilute calcium chlorid, coagulation will result and the coagulation time will be shortest in the tube which happens to receive the optimum amount of the salt. Howell[3] has held that this is a quantitative test for prothrombin, and making use of it he has shown a great prolongation of coagulation time (on recalcification) in three cases of hemophilia, and he therefore ascribes the disease to a prothrombin deficiency. We believe the test most useful, but think it should be subjected to certain precautions. Lee and Vincent,[12] using human blood, have shown that the time of coagulation of recalcified oxalated plasma varies directly with the length of time of centrifugalization and they have felt that this is due to removal of formed elements. Perfectly clear plasma, the result of prolonged high-speed centrifugalization, clots in forty-five minutes on recalcification; cloudy plasma poorly centrifugalized in fifteen minutes at most. It seems proved, therefore, that the speed of Howell's prothrombin reaction can be modified by centrifugalization, and it is probable that this is due to alterations in the solid content of the plasma. Since each prothrombin test must be controlled by a similar test on normal plasma it becomes of prime importance that the test and control material be similarly treated.

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8. Sahli, H.: Ueber das Wesen der Hämophilie, Ztschr. f. klin. Med., 1905, lvi, 264.

9. Morawitz, P., and Lossen, J.: Ueber Hämophilie, Deutsch. Arch. f. klin. Med., 1908, xciv, 110.

10. Wright, A. E.: Remarks on Methods of Increasing and Diminishing the Coagulability of the Blood, with Especial Reference to Their Therapeutic Employment, Brit. Med. Jour., 1894, ii, 57.

11. Nolf, P.: Eine Neue Theorie der Blutgerinnung, Ergebn. d. inn. Med. u. Kinderh., 1913, x, 275.

12. Lee, R. I., and Vincent, Beth: The Coagulation of Normal Human Blood. The Archives Int. Med., 1914, xiii, 398.

Without mentioning the use of such precautions, Whipple[4, 5] has reported two cases of melena neonatorum with diminished prothrombin. Addis[13] also believes that a diminution of prothrombin is the cause of hemophilia.

5. *Fibrinogen.*—This remains as the fifth factor in the system. It may be estimated very readily by the heat coagulation method outlined by Whipple and Hurwitz.[14] By a slight modification of this method Whipple[15] has demonstrated an increase in fibrinogen in two cases of lobar pneumonia and in one of acute hemorrhagic colitis, a great decrease in chloroform poisoning, experimental and clinical, a decrease in two cases of cirrhosis of the liver and in five cases of cachexia from varying causes. The same observer reports normal fibrinogen in eclampsia, aplastic anemia and cancer of the liver.

During the past winter we have used the methods outlined above in the following cases:

Purpura	5
Spontaneous thrombosis	1
Cirrhosis of the liver	4
Chronic lymphatic leukemia	1
Secondary anemia and sarcoma	1
Pernicious anemia	7
Total	19

Our results in the non-anemic cases may be summarized as follows:

1. Purpura: Platelet count was reduced in two cases. Other factors were normal.

2. Spontaneous Thrombosis: Platelets were not studied. Other factors were normal.

3. Cirrhosis of the Liver: Platelets were not studied. Fibrinogen was low in one advanced case with bleeding from the gums and purpura. Other factors were normal in the other cases.

4. Chronic Lymphatic Leukemia: Platelets were not studied. Other factors were normal.

We shall report one case of pernicious anemia in full, since it seems to illustrate the bleeding type of this disease, and we shall mention other cases as they control these observations.

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13. Addis, T.: The Pathogenesis of Hereditary Haemophilia, Jour. Path. and Bacteriol., 1911, xv, 427.

14. Whipple, G. H., and Hurwitz, S. H.: Fibrinogen of the Blood as Influenced by the Liver Necrosis of Chloroform Poisoning, Jour. Exper. Med., 1911, xiii, 136.

15. Whipple, G. H. Fibrinogen: 1. An Investigation Concerning its Origin and Destruction in the Body, Am. Jour. Physiol., 1914, xxxiii, 50.

CASE REPORT

History.—P. L. C., aged 26, salesman, unmarried, was admitted June 3, 1914. Complaint, "Washed-out looking — weakness." Family history and habits are entirely negative. There is no history of bleeding in the family.

Previous Medical History.—Measles and diphtheria in childhood. No history of whooping-cough, scarlet fever, typhoid, pneumonia, pleurisy, nor malaria. Cardiorespiratory: no history of dyspnea, nor edema of the feet nor ankles. He has never been subject to colds, tonsillitis, chronic cough nor night sweats. Gastro-intestinal: digestion always has been good. "Can eat anything." He has never had periods of vomiting nor epigastric distress. Genito-urinary: he has had no polyuria, dysuria nor nocturia. Nervous: there is no history of paralysis, injury nor operation; of areas of anesthesia nor paresthesia. No headache nor vertigo were present prior to the present illness. For the past three years he has noticed that the sight of his left eye has been somewhat diminished and indistinct.

Present Illness.—In August, 1913, the patient's friends called his attention to his loss of color. From this time until March, 1914, the patient kept at his work and took iron with fair steadiness, but became constantly paler and more yellow. About May 10 severe occipital and frontal headaches developed. These lasted all day and were accompanied by periods of vertigo, especially noticeable when the patient suddenly sat upright. At the same time there was marked weakness in the muscles, with dyspnea and frequent attacks of sharp cramps in the legs when walking. Three days ago the headaches became less severe, but his appetite disappeared completely. There were no nausea, vomiting, gastric pain, nor discomfort with this. Two weeks ago he noticed dark colored stools on one occasion. There has been no history of large gastric nor intestinal hemorrhage. For several weeks there has been a marked tendency to bleed from the gums. The patient has been compelled to stop brushing his teeth as this starts bleeding which will last several hours.

Of late there has been increased dimness of vision in both eyes. His best weight was 138 pounds one year ago; present weight 124 pounds.

Physical Examination.—The patient subjectively is entirely comfortable. Skin is very pale, yellow, moist and smooth.

Eyes: Pupils are equal, round, regular and react promptly to light and distance. There is no nystagmus or strabismus. Eye-grounds: O. D., disc is pale, vessels over it are poorly made out. Entire remaining area of fundus is covered with radiating hemorrhage. O. S. disc is outlined with fair sharpness. Hemorrhagic condition similar to that of O. D. is present.

Ears and Nose: Normal.

Mouth: Mucous membranes are very pale. Teeth are in good condition. At the junction of teeth and gums there are a few small blood clots. Tongue is protruded in mid-line without tremor. Tonsils are not enlarged.

Neck: Normal.

Chest: Lungs are clear, resonant and normal throughout.

Heart: There is no enlargement. There is a soft systolic murmur obscuring the first sound. This is well heard at the apex but is not transmitted to the axilla. At the base a rough, blowing systolic murmur is present, best heard in the third left interspace. Pulmonic second is greater than aortic second.

Pulses: Are regular, rapid, equal, synchronous and collapsing. Rate 128. Marked pistol shot sound is heard in the groin. Blood-pressure: systolic, 145; diastolic, 70.

Abdomen: No masses, tenderness, nor rigidity made out. Slight distention is present.

Liver is not enlarged.

Spleen is not enlarged.

TABLE 1.—Factors of Coagulation and Blood Examinations

Date	Coagulation Time	Prothrombin		Antithrombin		Fibrinogen, Gm.	Platelets	Hemoglobin, Per Cent.	R.B.C.	W. B. C	Polynuclears, Per Cent.	Large Round, Per Cent.	Lymphocytes, Per Cent.	Eosinophils, Per Cent.	Nucleated cells Per Cent.
		P. L. C.	Control	P. L. C.	Control										
June 4.....	.....	.....	.....	.....	.....	.....	2,800	29	752,000	3,200	54	4	41	1	0
June 5.....	27 min.	2-19 min. 3-25 min. 4-25 min. 5-72 min.	11 min. 10 min. 10 min. 12 min.	4-7 hrs. 5-34 min. 6-18 min.	7 hrs. 37 min. 27 min.	0.4204									
June 11.....	21 min.	2-19 min. 3-17 min. 4-18 min.	6 min. 6 min. 4 min.	4-12 hrs. 5-26 min. 6-18 min.	12 hrs. 12 hrs. 26 min.	0.375	40,000	24	512,000	3,600	60	15	25	0	2
Before transfusion															
After transfusion	.....	5-18 min.	7 min.	.....	.....	.....	.....	39	1,360,000	6,800					
June 12.....	25 min.	2-9 min. 3-8½ min 4-9½ min. 5-15 min.	4 min. 3½ min. 3½ min. 4 min	4-0 min. 5-12 hrs. 6-30 min.	0 min. 60 min. 7 min.	0.500	112,000	44	1,100,000	3,200	66	2	32	0	1
June 16.....	.....	.....	.....	.....	.....	.....	3,200	34	920,000	2,800	48	16	36	0	1
June 17*.....	45 min.	2-33 min. 3-24 min. 4-29 min. 5-33 min.	† 8 min. 6½ min. 6½ min.	4-28 min. 5-17 min. 6-17 min.	28 min. 16 min. 16 min.	0.453	.....	..	1,040,000	2,600					
Before transfusion															
June 18.....	.....	.....	.....	.....	.....	.....	.....	46	2,100,000	3,300					
June 20.....	.....	2-21 min. 3-18 min. 4-18 min.	22 min. 16 min. 20 min. 22 min.	4-7 hrs. 5-21 min. 6-10 min.	7 hrs. 10 min. 5 min.	0.400									

June 24.....	.....	.....	.....	.....	.....	.....	21,000	43	2,020,000	.....	38	21	38	3	0
June 25..... Transfusion June 24	.....	.....	.....	.....	.....	.....	.....	58	2,840,000	2,600	56	10	33	1	0
June 30.....	.....	.....	.....	.....	.....	.....	6,600	43	1,040,000	2,600	51	13	35	1	0
July 1..... Transfusion June 30	.....	.....	.....	.....	.....	.....	12,000	49	2,000,000	2,200	56	14	30	0	2
July 7..... Before transfusion	22 min.	2-19 min. 3-42 min. 4-27½ min. 5-42 min.	15 min. 14 min. 10½ min. 17 min.	4-20 min. 5-6 min. 6-6 min.	17 min. 17 min. 5 min.	0.420	25,000	36	1,140,000	2,900	44	14	40	2	0
After transfusion	.....	.....	.....	.....	.....	.....	23,000	45	1,710,000	2,800	40	22	36	2	0
July 14.....	18 min.	2-45 min. 3-16 min. 4-16 min. 5-90 min.	9 min. 8 min. 8 min. 7 min.	4-20 min. 5-45 min. 6-45 min.	45 min. 11 min. 11 min.	0.350	.....	46	1,940,000	3,000	58	10	30	2	0
July 20.....	.....	.....	.....	.....	.....	.....	48,000	38	1,400,000	3,400	62	8	27	3	0
July 21..... After transfusion	.....	.....	.....	.....	.....	.....	62,000	60	2,060,000	3,000	65	5	26	4	0
July 27.....	.....	.....	.....	.....	.....	.....	.....	50	2,000,000	5,000	49	3	37	1	1
July 29..... After transfusion	.....	.....	.....	.....	.....	.....	.....	57	2,600,000	2,400	74	7	18	1	0
August 11....	18 min.	2-18½ min. 3-22½ min. 4-22½ min. 5-29 min.	4½ min. 4 min. 4 min. 3½ min.	4-1½ hrs. 5-1½ hrs. 6-10 hrs.	1½ hrs. 1½ hrs. 1½ hrs.	0.300	40,000	32	1,050,000	4,500					

* On and after this date antithrombin plasma diluted 1:1 with 0.9 per cent. NaCl.
† Lost.

Extremities: There are no edema, scars, cyanosis, or sclerosis of peripheral vessels. Color of the skin everywhere is very light yellow.

Reflexes: Knee, ankle, biceps, triceps, supinator, and pronator reflexes are easily obtained and very active. There is a marked patellar clonus. No ankle clonus, Gordon sign, Oppenheim sign, nor Babinski sign made out.

On admission the temperature was 99.2 F. Pulse, 128. Respiratory rate, 21.

BLOOD EXAMINATIONS AND CLINICAL NOTES

June 4. Blood:

Hemoglobin	29 per cent.
R. B. C.	752,000
W. B. C.	3,200
Platelets (23)	2,800

Differential Count: Polymorphonuclear neutrophils, 54 per cent; large mononuclear cells, 4 per cent.; lymphocytes, 41 per cent.; eosinophils, 1 per cent. Red cells show very slight anisocytosis and poikilocytosis, no polychromatophilia, stippling, or basophilia. No myelocytes, normoblasts, or megaloblasts are seen.

The puncture wound from which blood was taken for counting bled for forty-five minutes and was finally checked with nitrate of silver. This prolonged bleeding time was constant and necessitated subsequently the use of a very fine needle. Warned by this experience, the venous punctures recorded later were made with a fine needle and no trouble occurred.

Urine: Negative.

Wassermann reaction blood serum, negative.

The patient was at once placed on ascending doses of Fowler's solution, dilute hydrochloric acid with meals, and forced house diet. He was kept at rest in bed out of doors all of the time.

June 5, blood obtained by venous puncture.

Coagulation time, twenty-seven minutes. (Howell's method.)

TABLE 2.—Case P. L. C. Determination of Antithrombin

Thrombin, Drops	Heated Plasma, Drops	Fibrinogen, Drops	Result
4	1	10	Clot in 7 hours.
5	1	10	Clot in 34 minutes.
6	1	10	Clot in 18 minutes.
	CONTROL C. K. D.		
4	1	10	Faint clot in 27 minutes; firm clot in 7 hours.
5	1	10	Clot in 37 minutes.
6	1	10	Clot in 18 minutes.

PROTOCOLS

The following protocols illustrate the methods used for determining antithrombin and prothrombin. For further studies of these factors and for their correlation with the changing blood picture, reference must be made to Table 1.

Antithrombin was determined by Howell's method. The test plasma is heated slowly to 60 C. and then centrifugalized to throw down the fibrinogen which has been precipitated. If a drop of the supernatant fluid is added to a known thrombin solution it can be shown to delay the action of this thrombin on fibrinogen most markedly. In every test the supposedly abnormal plasma

must be compared with plasma from a normal individual, the two being treated in the same way, their comparison indicating the abnormality, if it exists.

The patient's antithrombin was entirely comparable to that of the control and in this factor no abnormality existed. For tests made on June 17 and following dates heated plasmas were diluted 1:1 with 0.9 per cent. NaCl in order to shorten the time necessary for the experiment.

Prothrombin was determined by recalcifying oxalated plasma. Ability to invert a 10 mm. tube without dislodging the clot has been taken as the end-point throughout our entire series of observations on prothrombin. In these tests, as with antithrombin, comparison with normal plasma is necessary. Prior to July 7 the test bloods and the controls were centrifugalized simultaneously to obtain the plasma, but the duration of centrifugalization varied on different occasions. On and after this date the same speed and same time were used.

TABLE 3.—Case P. L. C. Determination of Prothrombin

Oxalated Plasma, Drops	0.5 Per Cent. $CaCl_2$, Drops	Result
5	2	Invertible in 19 minutes.
5	3	Invertible in 25 minutes.
5	4	Invertible in 25 minutes.
5	5	Invertible in 72 minutes.
	CONTROL C. K. D.	
5	2	Invertible in 11 minutes.
5	3	Invertible in 10 minutes.
5	4	Invertible in 10 minutes.
5	5	Invertible in 12 minutes.

The patient's plasma coagulated more slowly than the control, indicating a prothrombin deficiency.

Fibrinogen was determined by the heat coagulation method: 10 c.c. of oxalated plasma are heated to 60 C. and kept at this temperature for twenty minutes. The resultant coagulum is filtered off, washed and weighed. This process is adequate for showing gross alterations in fibrinogen but very inaccurate for small variations.

Fibrinogen.—0.4204 gm. in 100 c.c. oxalated plasma.

June 10: For the past two days the patient has been spitting blood constantly and this evening vomited 500 c.c. of dark bloody material. He refuses nourishment and appears to be failing fast.

June 11: Condition is unimproved. Transfusion was decided on and 750 c.c. of whole blood were introduced by the indirect method from the patient's father. During exposure of the patient's veins there was a large amount of troublesome oozing. This occurred in subsequent transfusions, but always decreased as the new blood was given. About one-half hour after transfusion a few purpuric spots appeared on the patient's forearms. Bleeding from the gums stopped promptly and there was no subsequent hemoglobinuria nor elevation in temperature.

June 12: Transfusion has resulted in an increased platelet count and increased prothrombin. Fibrinogen has risen slightly but not enough to be significant.

June 14: Bleeding from the gums has recommenced.

June 16: Oozing from gums continues. Pulse rate has risen. The rapidly falling red count is an indication for a second transfusion.

TABLE 4.—Anemic Cases with Slightly Decreased Prothrombin

Case	Prothrombin		Hemoglobin, Per Cent.	R. B. C.	W. B. C.	Polynuclears, Per Cent.	Large Round, Per Cent.	Lymphocytes, Per Cent.	Eosinophils, Per Cent.	Nucleated Cells
	Case, Min.	Control Min.								
VI	2- 9	9	67	2,400,000	5,400	54	5	38	3	0
	3- 9¼	6								
	4-10	8								
	5-13	8½								
III	2-11½	9	43	1,080,000	4,600	70.5	5	23	1	0
	3-12	9								
	4-12	9								
	5- 9½	9								
IV	2- 9	6	60	1,724,000	6,400	83	3	10	4	6
	3- 9	5								
	4- 9	5								
	5-12	5								
V	2- 0	6	21	620,000	3,000	68	3	29	0	0
	3- 9½	5								
	4- 9½	5								
	5-11½	5								

June 17: 750 c.c. of blood were given. There was immediate cessation of bleeding and immediate improvement.

June 20: Gums are not bleeding and the patient is in fine spirits, with excellent appetite. Prothrombin observed on this day parallels the control.

June 24: Gums bled severely all last night and are bleeding this morning. Pulse is weak. 750 c.c. of blood by indirect transfusion from father caused immediate cessation of bleeding and general improvement.

June 30: A great deal of bleeding from the gums recurred yesterday and last evening. During the night 50 c.c. of defibrinated human blood were injected intramuscularly. To-day the bleeding is not so rapid nor profuse and clots tend to form on the bleeding surfaces. Transfusion was again done, 650 c.c. being given. Hemorrhage stopped at once and a comfortable night's sleep ensued.

July 4: Patient has developed a sore throat with peritonsillar swelling on the right side. Gums bled constantly all afternoon and he vomited his supper with a quantity of swallowed blood.

White blood cells, 2,400. No increase of leukocytes was noted with this infection, which however, was severe enough to send the temperature to 102 F.

July 5: Gums are bleeding more severely; 11 c.c. human blood serum were given intramuscularly.

July 6: Fowler's solution was omitted; 10 c.c. human blood serum were given intramuscularly. This injection was followed by slight abatement of

bleeding during seven or eight hours, but then it started again and became very severe; 0.2 gm. salvarsan was given intramuscularly.

July 7: Excessive bleeding from the gums was present this morning and after a very restless night. Defibrinated human blood, 44 c.c., were given in the morning but the bleeding was not affected in the least; 750 c.c. of blood were given by transfusion during the afternoon and bleeding ceased immediately.

July 14: Slight oozing is present this morning between the two upper right pre-molars.

July 16: Salvarsan, 0.2 gm., was given intravenously.

After this date the patient's course continued much the same. On July 21 he received 750 c.c. of blood and on July 29, 900 c.c. and 0.2 gm. of salvarsan intravenously. These transfusions like the others were necessitated by a rapidly falling blood count due to bleeding from the gums and to failure of regeneration. Thorough removal of tartar collections from the teeth remedied somewhat the bleeding tendency but did not prove of permanent value. August 10 splenectomy was proposed and refused. Following refusal of operation the patient left the hospital for his home. He was seen one week later and was evidently failing fast. In ten more days he died and no autopsy could be obtained.

DISCUSSION OF CASE AND CONCLUSIONS

If we consider the entire course of this anemia it seems to have been distinguished chiefly by failure to regenerate blood-cells and by a tendency to bleed. In a recent analysis of aplastic pernicious anemia, Musser[16] emphasizes certain essential characteristics of this disease. These are:

1. Young males are most frequently affected.

2. Remissions do not occur.

3. Subcutaneous hemorrhages and hemorrhage from mucous membranes are extremely frequent. In four of the fifty-nine reported cases sudden hemorrhage was the first manifestation of the disorder.

4. Fever is a constant symptom and often reaches a high point in the disease. In our case fever was constant, but 102 F. was the highest point reached.

5. A low color index is the rule. This was not observed by us, the color index being constantly above 1.

6. Leukopenia is constantly present and is caused by absence of granular forms. Leukocyte counts rarely exceed 2,000 and polymorphonuclear forms constitute from 8 to 20 per cent., instead of the usual 70 per cent. There is relative lymphocytic increase.

We noted constant decrease of polymorphonuclear cells with increased lymphocytes, but our percentages have never been so marked as those mentioned by Musser.

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16. Musser, J. H.: Study of a Case of Aplastic Anemia, The Archives Int. Med., 1914, xiv, 275.

7. Nucleated red forms, polychromatophilia, stippling and poikilocytosis are absent. Anisocytosis is found occasionally, with a tendency to macrocytosis. In twenty-five differential counts we found nucleated red cells ten times, three being the highest number seen. Other characteristics of the red cells corresponded very well with the ruling observations in these anemias.

It seems safe to regard the case as one of fairly complete aplasia. We have not found any extensive studies of the factors of coagulation in bleeding anemias. Musser records a prolonged coagulation and bleeding time in his case, and also notes the fact that 20 c.c. of horse serum with 1 gm. doses of calcium lactate four times a day did not check the tendency. Whipple[5] reports a case of undoubted aplastic anemia in which there was epistaxis and constant uncontrollable oozing from the gums. This patient was given 500 c.c. of defibrinated blood by indirect transfusion, with no effect on the hemorrhagic process. Bleeding time was prolonged, but coagulation time appeared normal. Blood was taken from the heart one hour and twenty-five minutes after death and an increase in antithrombin found. Prothrombin was normal and fibrinogen undetermined. The prothrombin and antithrombin studies used in this case were not subjected to the controls which Howell's later paper emphasized as necessary.

In our case we have noted the following facts:

1. Coagulation time was distinctly prolonged once only (July 17); bleeding time was always long.

2. Platelets were always far below normal and were not consistently increased by transfusion.

3. Antithrombin was consistently normal and was not altered by transfusion.

4. Fibrinogen was normal throughout and was unaffected by transfusion.

5. Prothrombin was constantly decreased, but was subject to transient slight increase by transfusion.

We have felt that throughout the entire clinical course of this patient the prothrombin reaction has given us an excellent indication of the effective clotting power of the plasma. The end-point used in the test expresses complete solid coagulation. Clotting may begin in normal time, but the process, instead of requiring a few minutes as in ordinary plasmas, takes many minutes. We have been interested to note that the plasma from other cases of pernicious anemia, essentially formative in character, shows the same tendency, but to a very slight degree. In none of these, however, has there been a history of hemorrhage and all have been regenerative and have passed into periods

of remission. Table 4 presents four such cases. Unfortunately, these observations are not accompanied by platelet counts, the importance of this factor being unappreciated when they were made. Fibrinogen and antithrombin were normal and the blood picture indicates the severity of the anemia.

Our studies seem to emphasize the following points:

1. Prothrombin is diminished slightly in all cases of pernicious anemia.

2. This diminution is not great and is unimportant if active regeneration is in progress.

3. Antithrombin and fibrinogen are normal even in the presence of very low cell counts.

4. In one case in which there has been pronounced diminution in prothrombin, platelet counts have been strikingly low, and the picture throughout has been that of fairly complete aplasia.

We wish to express our thanks to Dr. K. R. Drinker for many fibrinogen determinations throughout this work.