mine a regional symptom of a septicemia or abscess of the gravest character. The micro-organisms, if they act on the spot, first seek the alveolus (alveolodental periostitis) then the mandible (osteoperiostitis, osteomyelitis of the jaws), or conjointly bone and mucous lining. If they follow the contiguous tissues of the mouth, we get stenoparotiditis; if they penetrate through the alveolus of an upper tooth (first or second molar), maxillary sinusitis. If they pass on to the air-passages, bronchopneumonia follows. If they enter into the digestive apparatus they produce or help to produce in people subject to chronic abscessed teeth, anemia or so-called "dental cachexia" of Lejars,[9] or the acid putrid intoxication of Richet.[10] Everyone who has followed the clinical evolution of the lymphophlegmonous septicemia of the neck knows that it may be either simple septicemia or septic pyemia. If an incision is made in the phlegmonous parts, it is with great trouble that one will find in the deep parts a minute suppurating point containing only a dram or so of a secretion which may not be pus in character; or nothing at all may be found. Here is a clear proof that we must distrust surgical infections which do not suppurate. Suppuration may be a means of defense for the organism. In many of these severe cases death comes on very rapidly, the nerve centers being profoundly affected and not giving the brain time to react under the cellular intoxication, while the patient has a slight delirium, but depression irregularity and weakness of the pulse, respiratory insufficiency, dyspnea, toxins thrown off by sweats, diarrhea and albuminuria.

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ABSTRACT OF DISCUSSION

DR. M. H. FLETCHER, Cincinnati: The thing that presents itself most forcibly to me is the lack of knowledge in parents of the laws of physiology. That is, the lack of proper knowledge of the conditions under which to bring up children, and from our view-point the mouth is very important. I have read in various works that the saliva of animals is strongly alkaline, but to go to the abattoir, apply a bit of litmus paper to the saliva of animals and find it change as quickly from acid to alkaline as it would be in a solution of bicarbonate of soda, and find this in absolutely every case, is something that should be considered by us. I take it that civilized environment has changed the physiology of man to almost the opposite condition. For it is a rare thing to find human saliva more than barely alkaline. Now, with the strong alkaline condition found in the mouths of animals, no acid decay could exist. Again, the eating of the rough food by these animals constantly rubbing against their gums, keeps the tissues healthy and strong. This feature is of great importance for there is a development of large rolls of connective tissue or callus at the necks of the teeth of these animals, especially just inside of the lower front teeth, where the food comes in contact with the mucous membrane. This is true in carnivora, where the teeth are conical, but not to the degree found in the herbivora; the biting with conical teeth also cleans them to the gums. When animals are kept from their normal diet and fed on civilized food, there is a marked delicacy or softening of the gums in consequence. I do not believe these points have been brought before our present generation strongly enough to impress them properly, and, since our teeth are not cleansed by our food, and our mouths do not have this protective alkaline saliva, by all means let us use the superior intelligence Providence has given us and give our gums this hard rubbing that they need, and the mouth and tongue the proper cleansing and the result will be to the development of healthy, strong gums and good teeth. Our intelligence should lead us to know where to begin and how to correct these defects; then we will know how to teach our children about them.

9. Lejars, Felix: Leçons de Chirurgie, Masson, Paris, 1895, p. 330.

10. Richet: De l'intoxication putride qui accompagne certaines fractures dites simples du maxillaire inférieur, Bull. Soc. de Chir., 1865, Series 2, iii, 410-431.

THE RELATION OF BLOOD PLATELETS TO HEMORRHAGIC DISEASE

DESCRIPTION OF A METHOD FOR DETERMINING THE BLEEDING TIME AND COAGULATION TIME AND REPORT OF THREE CASES OF HEMORRHAGIC DISEASE RELIEVED BY TRANSFUSION *

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It is my purpose in this paper to report three cases and experiments which furnish additional evidence to show that the blood platelets play a part in stopping hemorrhage, and that one type of hemorrhagic disease may be attributed to an extreme reduction in the number of platelets. The cases possibly explain the relief which sometimes follows transfusion in hemorrhagic disease. It is my purpose also to describe a method for studying hemorrhage called the bleeding time, and to describe briefly a simple method for determining the coagulation time.

In the cases there was marked hemorrhagic diathesis, a normal coagulation time, and almost an absence of platelets. Transfusion was performed in each case. After transfusion there was a marked increase in the number of platelets and remarkable relief of hemorrhage. When the platelet counts returned to their previous low level, hemorrhages returned. Later in the course of the disease in two of the cases, the platelet count rose spontaneously and this rise also was followed by relief of hemorrhage. The cases are reported to show the marked dependence of pathologic hemorrhage in this type of disease on the reduced numbers of platelets. The experiments are reported briefly to show that platelet counts reduced experimentally by benzol are not associated with changes in the coagulability of the blood which account for the hemorrhages of the condition and suggest that this type of hemorrhagic diathesis is due directly to the lack of platelets.

A METHOD FOR DETERMINING THE BLEEDING TIME

A small cut is made in the lobe of the ear. At half-minute intervals the blood is blotted up on absorbent paper. This gives a series of blots of gradually decreasing size. Each blot represents one-half minute's outflow of blood. The rate of decrease in the size of the blots shows the rate of decrease of the hemorrhage. The cut should be made of such a size that the first half minute's outflow of blood makes a blot 1 or 2 cm. in diameter. The total duration of such a hemorrhage is called the bleeding time.

Figure 1 (A, B, C) was made from cuts of different size. These sets of blots show that within certain limits the duration of a hemorrhage does not depend on the size of the cut. If these figures represent capillary hem-

* Read in the Section on Practice of Medicine of the American Medical Association, at the Sixty-first Annual Session, held at St. Louis, June, 1910.

orrhages it is evident that a large number of capillaries will stop bleeding as rapidly as a small number.

The normal bleeding time varies from one to three minutes.

The bleeding time is slightly delayed (five to ten minutes) in severe anemia (Fig. 2).

Great delays in the bleeding time were found in, (1) cases in which the platelet count was excessively reduced (ten to ninety minutes—Fig. 3), (2) cases in which the fibrinogen content of the blood was excessively reduced (ten minutes to twelve hours), and (3) experimental animals in which both platelets and fibrinogen were reduced.

It is remarkable that the bleeding time is independent of the coagulation time. The bleeding time was normal in several cases of jaundice in which the coagulation time was very much delayed. Two of these patients died of pathologic hemorrhage.

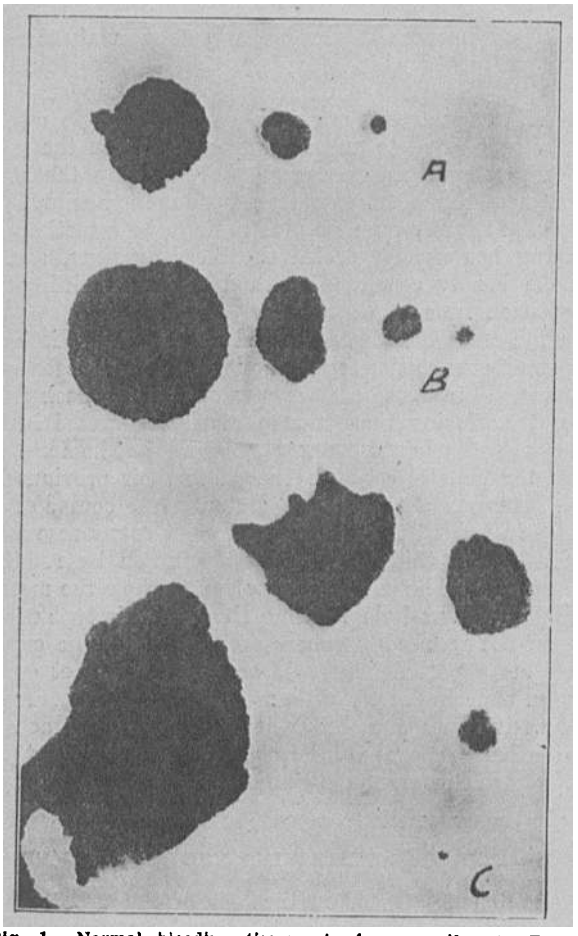

Fig. 1.—Normal bleeding times; A, from small cut; B, from larger cut; C, from very large cut.

It was also normal in a patient with hemophilia, who had a slight delay in the coagulation time and pathologic hemorrhage. The bleeding time was found to be normal in several types of purpura hemorrhagica in which the platelet counts were normal. It is difficult to explain why these patients had hemorrhage into the tissues, from mucous membranes, and from operation wounds, and at the same time had normal bleeding from ear-pricks.

The bleeding time, then, in types of disease associated with low platelet counts, or with a reduced quantity of fibrinogen shows a tendency to prolonged hemorrhage. In these types of disease, a delayed bleeding time is a more reliable indication of hemorrhagic diathesis than hemorrhagic symptoms, for such symptoms usually depend on general and local causes. The latter are, of course, not constant. In the cases reported in this paper the bleeding time was invariably delayed when pathologic hemorrhage was evident, and was often considerably delayed before hemorrhage began.

The method is apparently of no value in determining the tendency to bleed in jaundice and hemophilia, and in the types of purpura hemorrhagica which have normal platelet counts.

A SIMPLE METHOD FOR DETERMINING THE COAGULATION TIME [1]

The apparatus consists of a slide on which are mounted two 5 mm. disks. One disk is covered with the blood to be tested. The other is covered with normal blood. The two drops of blood should be of about the same depth. The slide is then inverted over a glass nearly full of water kept at 40 C. and is covered with a warm, damp cloth. The coagulation time is determined by holding the slide in a vertical position for a moment. When the end point is reached the drop does not hang, as in Figure 4 *a*, but retains the contour of a perfect sphere

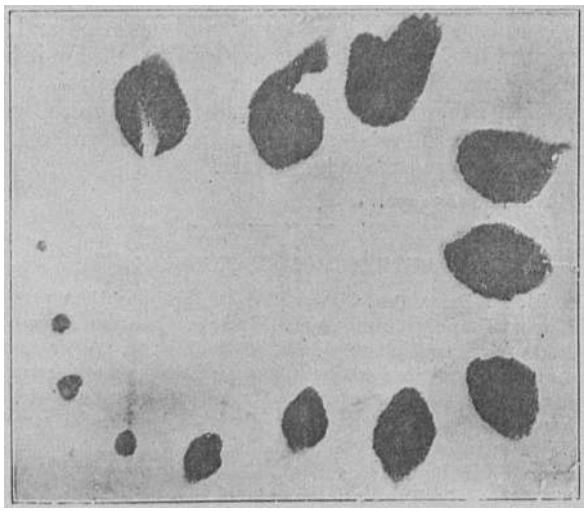

Fig. 2.—Slightly delayed bleeding time. From a case of secondary anemia.

(Fig. 4 *b*). The end point appears sharply and is easily determined.

The normal coagulation time by this method varies from five to seven minutes. A very shallow drop clots one to two minutes sooner than a very deep one. The normal blood can be used for a control, or can be used for obtaining a comparative time.

If simply the comparative time is desired, the temperature of the water may be allowed to vary between 35 and 40 C., and the glass may be covered with the hand instead of a damp cloth. A delay of two minutes can be easily determined by this method.

PLATELET COUNTS

Wright's method[2] was used in making the platelet counts. According to this method the blood is drawn up in a 1-100 pipette, mixed with a solution of cresyl blue and potassium cyanid and counted by the red cell

1. This method is a modification of Hinman and Sladen's slide method (Johns Hopkins Hosp. Bull., 1907, xviii, 207). The principle was first used by Millian.
2. Wright and Kinnicut: Tr. Assn. Am. Phys., May, 1910.

technic. The red cells are laked by this solution and the leukocytes and platelets are stained. This is a great advantage, for the platelets can be easily recognized and can be counted with a high dry lens. The counts made by this method are uniformly lower than those made by Pratt's method.[3] This method, however, gives constant results if care is used in the technic. The normal count, according to Wright and Kinnicut, varies from 250,000 to 400,000.

TABLE 1.—CASES OF HEMORRHAGIC DISEASE IN WHICH THE PLATELET COUNT, COAGULATION TIME AND BLEEDING TIME WERE DETERMINED

Disease.	No. of Cases.	Symptoms.	Plate Count.	Coag. Time.	Fibrinogen Content of Blood.	Bleeding Time.	Other Diseases which may Give Similar Blood and Similar Symptoms.
Idiopathic purpura hemorrhagica.	3	Purpura, spontaneous hemorrhages.	Below 20,000...	Normal...	.....	60 min.+	Penicious anemia, lymphocytic leukemia, nephritis, typhoid fever.
Aplastic anemia.....	2	Ecchymoses, epistaxis....	Low.	Normal...	Nor. in experimental aplastic anemia.	Delayed.	
Chronic Ulcerative colitis.	1	Melena.....	20,000 to 30.000	Normal...	.....	10-20 min.	
Chloroform poisoning.....	Dogs. 3	Bleeding from gums and operation wounds.	Normal or slightly reduced.	Normal...	Excessively reduced.	Hours....	Phosphorus poisoning, hemorrhagic smallpox.
Jaundice..	2	Hemorrhage after operation.	Adundant in smears.	30 min.. .. 40 min....	.....	1-2 min....	
	1	Purpura hemorrhagica....	850, 00.	8 min.	Probably normal in jaundice.	3 min.....	
	8	No symptoms.....	Abundant in smears.	Nor. or delayed.	.....	1-3 min...	
Hemophilia.....	1	Bleeding from wound; hematoma in knee.	350,000.....	9 min.	Normal in hemophilia.	2 min.....	
Purpura simplex.....	2.	Purpura.....	Abundant in smears.	Normal...	.....	Normal...	
Henoch's purpura.....	1	Purpura, intestinal crisis, melena.	275,000.....	Normal...	.....	Normal...	
	1	Purpura, urticaria, angioneurotic edema.	300,000.....	Normal...	.....	Normal...	
Nephritis.	4	Epistaxis.....	Abundant in smears.	Normal...	.....	Normal...	
	1	Ecchymoses					

TABLE 2.—DETAILED FINDINGS IN CASE 1

Date.	Platelet Counts.	Plates in Stained Blood Smears.	Bleeding Time. (Minutes.)	Coagulation Time.	Urine.	Stools.	Epistaxis.
May 8.....	6,000.	1-2 per smear.....	47	5 minutes.....	Smoky.....	Tarry.....	Moderate.
May 9.....	None seen.....	None seen.....	90	5 minutes.....	Smoky.....	Tarry.....	Moderate.
May 10.....	3,000.	.....	.....	5 minutes.....	Smoky.....	Tarry.....	Moderate.
May 11.....	.....	2 per smear	50 +	4½-5 minutes	Smoky.....	Tarry.....	Extreme.
(Transfusions).							
May 12.....	.....	.....	.....	.....	.....	.....	.....
May 13.....	123,000.	1-3 in each field.	8	4½ minutes.....	Clear.....	Tarry.....	None.
May 14.....	.....	1 in 3-4 fields.....	3	.....	.....	Yellow.	None.
May 15.....	.....	.....	30	.....	Clear.....	.....	None.
May 16.....	.....	3 per smear.....	40	.....	Clear.....	Occult blood.	Slight.
May 17.....	.....	1 per smear	50	5 minutes.....	.....	.....	Moderate.
	1,500.....	3 per smear.....	50	.....	Clear.....	Fresh blood.	Moderate.
(Spontaneous increase in the number of platelets).							
May 18.....	.....	.....	.....	.....	.....	.....	.....
May 19.....	.....	.....	.....	.....	.....	Occult blood.	None.
May 23.....	.....	1-6 per field	2	.....	.....	.....	None.
May 24.....	.....	.....	2	5 minutes.....	Clear.....	No blood.....	None.
	84,000.....	3-8 per field.....	4	.....	.....	.....	None.

BLOOD EXAMINATION

May 8, R. C., 3,264,000; Hbg., 50%; W. C., 5,000
May 10, R. C., 3,260,000; Hbg., 50%.
May 11, R. C., 2,700,000; Hbg., 40%; W. C., 7,000
May 12, R. C., 3,600,000; Hbg., 46%
May 14, R. C., 3,500,000; Hbg.
May 16, R. C., 3,444,000; Hbg., 55%; W. C., 6,000
May 24, R. C., 5,000,000; Hbg., 70%; W. C., 2,400

REPORTS OF CASES*

CASE 1. — *Summary.* — Acute purpura hemorrhagica. Purpura; spontaneous hemorrhages; practical absence of platelets; delayed bleeding time; normal coagulation time. This case is of interest in showing relief of hemorrhage, both after the rise in the platelet count following transfusion, and after a spontaneous rise in the count which occurred later in the disease.

History.—S. M., a man aged 20, Armenian, tailor, was admitted to Massachusetts General Hospital May 8, 1909, complaining of epistaxis. The family history is negative for hemorrhagic disease. The patient has always been strong and well, and has had no serious illnesses. He has never had prolonged epistaxis, spontaneous ecchymoses, joint trouble, urticaria, nor abdominal crises. His digestion has always been good. For three weeks before admission to the hospital he had been feeling run down, and had had slight sore throat. For five days he had been troubled with persistent epistaxis. He noticed that his urine was high-colored, his stools black, and that he was covered with purpuric rash. There was nothing further of importance in the history.

Examination.—The patient was a well-developed and well-nourished young man, pale and weakened by loss of blood. A small amount of blood was then oozing from the border of his gums, and nasal mucous membranes. Scattered over his entire body, including the soles of his feet, mucous membranes, tongue, and scleræ, were fine muscular purpuric blotches, 1 to 5 mm. in diameter. In places, especially on the lower extremities, they were confluent, and covered areas 2 to 3 cm. in diameter. Retinæ were free from hemorrhage. There were a

3. Pratt, J. H.: A Critical Study of the Various Methods Employed for Enumerating Blood Platelets, THE JOURNAL A. M. A., Dec. 30, 1905, p. 1999.

4. I wish to express my thanks to Dr. F. T. Murphy, Dr. Hugh Cabot, Dr. L. A. Conner and Dr. R. D. McClure for permission to report these cases, and to Dr. J. H. Wright for his kind assistance in making the platelet counts.

few mucous râles at the lung apices, and a soft systolic blow at the base of the heart. The spleen edge was palpable just below the costal margin. There were no telangiectases on his skin or mucous membranes. Blood-smears showed almost a total absence of blood-plates, 6,000 by count. On the following day the counts were even lower. The bleeding time was forty minutes. The coagulation time was normal.

The course of disease can be followed by the chart (Fig. 5). During the first four days in the hospital there was an almost constant oozing of blood from the nose, which could be controlled for only short periods of time by packing. The stools and urine each day contained considerable blood.

Transfusion.—On May 11, the patient lost over a pint of blood from the nose, and his condition became so critical that he was transfused at 2 a. m. by Dr. F. T. Murphy. An Armenian friend of about the same age was donor. That a

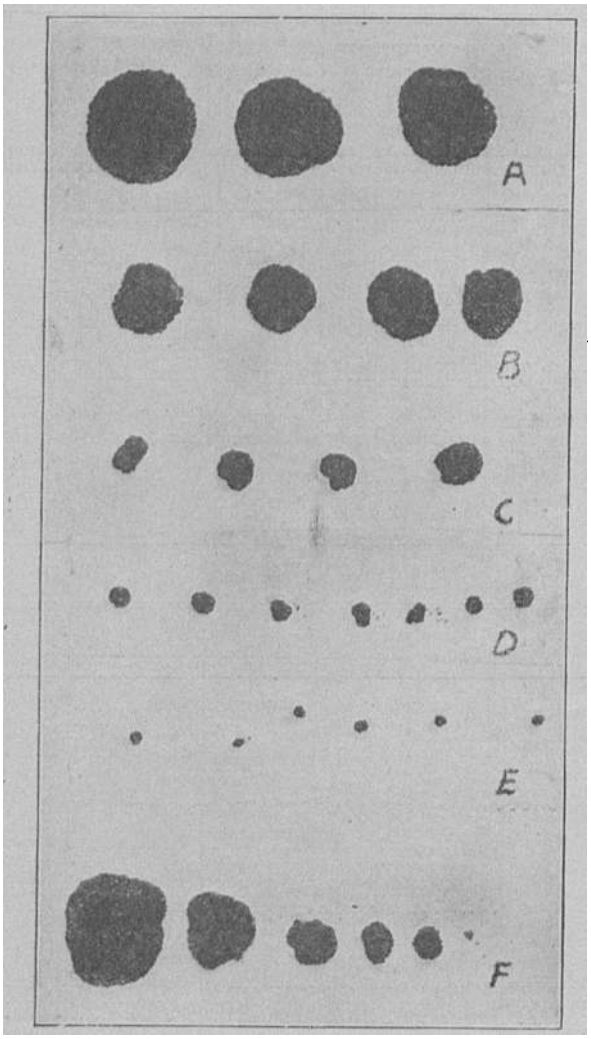

Fig. 3.—Great delay in bleeding time. From Case 1. Platelet count 3,000, coagulation time normal. The blots in Series A were taken immediately after the ear was pricked; Series B, 20 minutes; C, 40 minutes; D, 60 minutes, and E, 80 minutes later. The bleeding time at this time was 90 minutes. Series F, showing a normal bleeding time, was taken after the transfusion. Platelet count was then 110,000.

large amount of blood was given by transfusion was evident from the improvement in the patient's general condition, color, and pulse, and from the rise in the pulse-rate of the donor.

Course of Disease.—The platelet count, taken six hours after transfusion, was 123,000. The bleeding time had dropped to three minutes. The coagulation time was practically unchanged. Epistaxis had stopped before this time, and the packing had been removed from the nose. The urine was then free from blood. The stools on the following morning were light yellow, but contained a small amount of occult blood. No fresh purpuric spots appeared and the ones present began to fade, disappearing completely in five days. Thirty-six hours after transfusion it could be seen from stained smears that the platelets were decreasing rapidly in number, and on the third day one could be found only after prolonged search. At this time the bleeding time was again delayed. The day following this the patient's nose began to bleed and fresh blood appeared in the stools. Since the onset of the disease the patient had had an irregular temperature, varying from 99 to 103 F. This came to normal, except for slight remissions, on May 20. Apparently the disease had run its course, for at this time plates reappeared in the blood (80,000), and hemorrhage from ear-pricks would last for only three minutes. There was no further epistaxis or melena. Convalescence was uneventful, and since then the patient has continued his vocation without symptoms.

Differential Counts.—Made on May 8, 9, 12, 15, 23. Polymorphonuclear neutrophils made up from 80 to 86 per cent. of the cells. The remainder were lymphocytes with an occasional mast-cell and eosinophil. Only one blast was seen.

Red Cells.—Moderate variation in size. Shape normal. Moderate amount of achroma and polychromatophilia. An occasional stippled cell.

Coagulation Time.—The comparative method was used. The temperature was kept constant at 40 C. My blood, which had a coagulation time of five to six minutes, was used as a control. Usually several determinations were made and the average taken.

Platelet Counts.—Pratt's method was used in making the platelet counts on May 8, 9 and 10. The other determinations were made by Wright's method. The variations in the platelet count were so marked that estimations from stained cover-glass preparations of the blood proved satisfactory. Smears were looked over carefully with oil immersion lens on the days mentioned, and the number seen per smear or field averaged.

Retraction of Clot.—The clot was non-retractile after standing forty-eight hours on May 11 and 16. It retracted normally on May 12 and May 23.

Bleeding Time.—Determined by the method described. As a rule several determinations were made and the times averaged.

Urine.—Normal except that it contained a sediment of red cells and a slight trace of albumin on May 8 to 11. It contained no sugar, bile, peptone, albuminose, or nucleoproteid.

Stools.—May 8 to 12, rather copious, soft and black; from May 13 to 16, soft and light yellow (milk diet). Guaiac test was faintly positive on May 13 and 14; strong on May 15. On May 17, the stools were brown and soft and mixed with about 50 c.c. of fresh blood and a little mucus. On May 18, the stools gave the guaiac test. May 19 to 23, the guaiac test was negative. No parasites or ova were found.

The patient was seen eleven months after his illness and was then apparently strong and healthy. White count 4,700. Polymorphonuclears, 66 per cent.; lymphocytes, 34 per cent.; hemoglobin, 85 per cent. Plates 240,000. Bleeding time one minute.

CASE 2.—*Summary.*—Chronic ulcerative colitis; melena; reduced platelet count; delayed bleeding time; normal coagulation time. The bleeding time was normal after the rise in the platelet count following transfusion. The melena was slightly increased by transfusion. The case is of interest in showing a difference between the curative influence of transfusion in normal and in pathologic hemorrhage. Although the general tendency to hemorrhage (shown by the shortened bleeding time) was markedly diminished by transfusion, hemorrhage from the intestinal ulcers was increased. The case shows the difficulty of judging the tendency to abnormal hemorrhage by hemorrhagic symptoms alone.

History.—A. C., American, a boy aged 8, was admitted to Massachusetts General Hospital Nov. 15, 1909, complaining of weakness and diarrhea. The family history is negative for hemorrhagic disease. The patient's early life was normal. He had had no serious acute illnesses. After the age of 2 he suffered almost continually from diarrhea. He developed slowly, was always thin, and never strong enough to go to school. After the age of 4, there were four periods of a month or less in which the stools contained considerable blood, and the patient became pale and weak. He bled excessively from a trivial cut once. He never had ecchymosis on slight injury, joint disturbance, nor other evidence of hemorrhagic disease. For a month before admission to the hospital, the diarrhea was more severe, the stools contained blood, and the boy was becoming pale and weak.

Examination.—The patient was poorly developed, thin and pale, skin clear. Except for evidence of anemia, there was nothing of interest on physical examination. There were no telangiectases on the skin or mucous membranes, and no jaundice. Blood-smears showed a scarcity of the plates. Counts varied from 20,000 to 30,000. The bleeding time was twenty minutes. The coagulation time was normal.

During the first two and one-half weeks in the hospital a prominent symptom was diarrhea. The patient had from eight to thirty stools a day, which consisted mostly of thin pus, and often contained a small amount of blood and mucus. The patient's temperature varied from 98 to 103 F.

Transfusion.—On November 3 the patient was transfused by Dr. Hugh Cabot, preparatory to cecostomy. The child's father was donor. Following transfusion there was improvement in general condition and color. The temperature came to normal, and the pulse-rate dropped from 150 to 110.

Course of Disease.—The platelet count, taken two hours after transfusion, was 90,000, and the bleeding time was two minutes. The coagulation time was unchanged. The amount of blood in the stools, however, was increased. In interpreting this result it must be borne in mind that the patient had an extensive chronic ulcerative colitis (proved by autopsy), a condition which may cause melena when the blood is normal. The increase following transfusion was thought to be due to overfilling of the blood-vessels. Cecostomy was performed on the following day without excessive hemorrhage. As in the previous case, the platelets introduced by transfusion disappeared rapidly, and in a few days the count reached its former low level. The bleeding time again became delayed. The melena continued. The boy gradually became anemic, febrile, and died about a month later of septicemia.

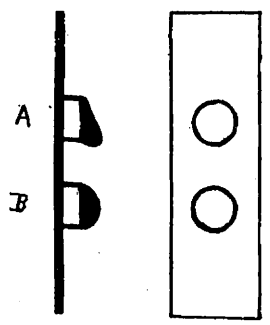

Fig. 4.—Instrument for determining the coagulation time.

Autopsy.—Chronic ulcerative colitis and enteritis. Extensive inflammatory thickening of the intestinal walls. Chronic pleuritis. Hyperplasia of mesenteric lymph-nodes. Streptococcus obtained from heart blood.

DETAILED FINDINGS IN CASE 2

Date.	Platelet count.	Bleeding time (min.).	Coagulation time.
10/26	32,000	20	Normal
10/28	23,000	20	.....
10/30	22,000	20	Normal
11/ 2 ..... (Transfusion).	20,000	20	5 min.
11/ 3	89,000	3	5 min.
11/ 4	72,000	2½	.....
11/ 6	25,000	3	Normal
11/ 8	.....	..	.....
11/ 9	25,000	10	.....
11/13	.....	10	.....

BLOOD EXAMINATION

10/15, R. C.....3,600,000	Hbg., 42%	White Counts, 3,700
10/19, R. C.....1,600,000	Hbg., 20%	White Counts, 3,100
10/31, R. C.....1,224,000	Hbg., 15%	White Counts, 4,700
11/ 2, R. C.....1,200,000	Hbg., ...	White Counts, ...
11/ 3, morning.....3,280,000	Hbg., 70%	White Counts, 3,800
11/ 3, afternoon ...3,416,000	Hbg., ...	White Counts, 2,200
11/ 4, ...	Hbg., 85%	
11/ 9, ...	Hbg., 90%	
11/13, ...3,600,000	Hbg., 70%	

Differential Counts.—Polymorphonuclear neutrophils varied from 40 per cent. to 60 per cent. The remainder were lymphocytes with an occasional mast-cell and eosinophil. No blasts seen.

Red Cells.—Moderate variation in size. Shape normal. Moderate amount of achroma and polychromatophilia. No stippling.

Coagulation and Bleeding Time.—Determined as in Case 1. The platelets were counted by Wright's method.

Retraction of Clot.—On October 26 there was a very slight retraction of the clot after twenty-four hours; on November 3 and 4 a moderate amount of retraction; on November 9 no retraction.

Urine.—Normal.

Stools.—Eight to thirty a day, throughout the patient's illness. Small in amount and of pea-soup consistency. Stools contained considerable pus, a small amount of food residue and mucus. During the first few days, after admission, they contained considerable fresh blood. For ten days before transfusion they contained very little blood. After transfusion the stools were port-wine in color and contained considerable blood. Melena continued until death. Stools contained no parasites or ova. Cultures taken frequently showed only the colon bacillus.

CASE 3.—*Summary.*—Chronic purpura hemorrhagica[5]: Ecchymoses; purpura; hemorrhages from mucous membranes; low platelet count; delayed bleeding time; relief of hemorrhage for three days followed transfusion; relief of hemorrhage after a spontaneous rise in the platelet count.

History.—Georgiana ——, American, a girl aged 3, was admitted to New York Hospital Oct. 3, 1909, complaining of epistaxis. The patient's parents, and three brothers and sisters are living and well. There is no history of hemophilia in the family. The patient has had no acute illnesses. She has had prolapse of the rectum several times. Since the age of 19 months, she has been subject to nose bleed, and ecchymosis following slight injury. Four months before admission to the hospital, symptoms were more severe, and at one time she became pale and weak from epistaxis and bleeding from

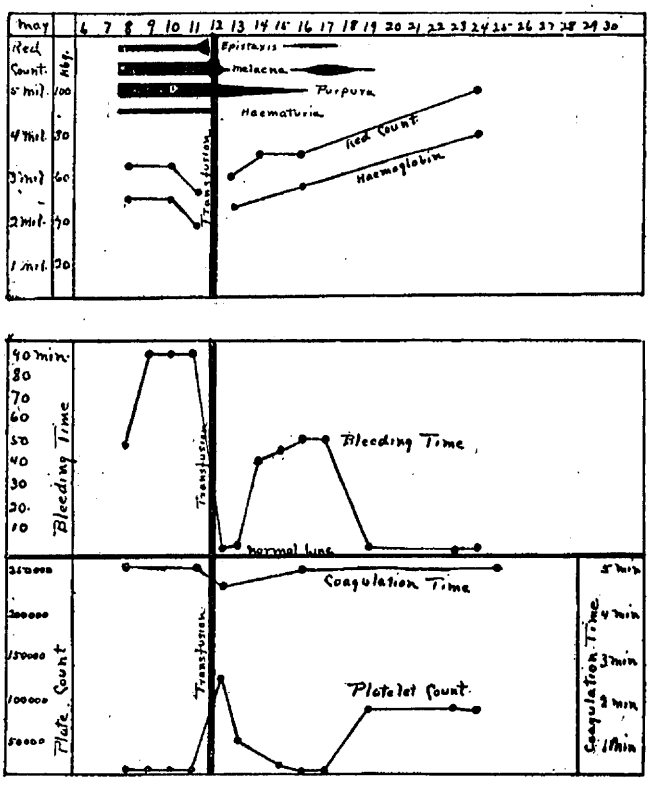

Fig. 5.—Chart of Case 1.

a small cut on the head. She improved somewhat after this, and for the following two months there was little bleeding. Two days before she came to the hospital, epistaxis began again and continued until admission to the hospital.

Examination.—The patient was a moderately developed and nourished little girl. She was pale and rather weak from loss of blood. On the right shoulder, cheek, and lower extremities were several small ecchymoses. There were no telangiectases. The physical examination was otherwise unimportant. Epistaxis continued almost without ceasing for five days, and the child became almost pulseless.

Transfusion.—She was transfused on October 7 by Dr. R. D. McClure. The patient's father was donor.

Course of Disease.—Transfusion improved the patient's pulse—volume and color, but owing to bronchopneumonia, which developed at about the same time, her condition remained serious for a few days. The temperature, which had ranged from 98 to 102 F., began to decrease and reached

5. This case has been reported in another connection by Pool and McClure, Annals of Surgery, September, 1910.

normal about a week later. The pulse-rate immediately dropped from 160 to 120 and a few days later to 90, where it remained. There was no bleeding for three days after transfusion. On the fourth day there was slight epistaxis, and hemorrhage from the vagina and transfusion wounds. Later, she had slight epistaxis and melena, as marked on the chart, and a fine petechial rash which followed straining at stool.

Blood Examinations.—August 8—red cells 2,300,000, hemoglobin 34 per cent. Other estimations showed about the same ratio between the red count and hemoglobin. The white count varied from 16,000 to 21,000. Blood smears on some occasions showed an excess of lymphocytes (71 per cent.), but usually polymorphs predominated. The red cells showed polychromatophilia and moderate variation in size. There were no blasts. The coagulation time was about normal (Boggs' instrument). The urine was not remarkable.

For five weeks after leaving the hospital the patient had no further bleeding. During the sixth week, however, she had prolapse of the rectum with bloody stools. One week later, she noticed that ecchymoses followed slight injuries. When seen at this time, (Nov 24, 1909), her color and general health were fairly good. On her head, elbow and legs, were

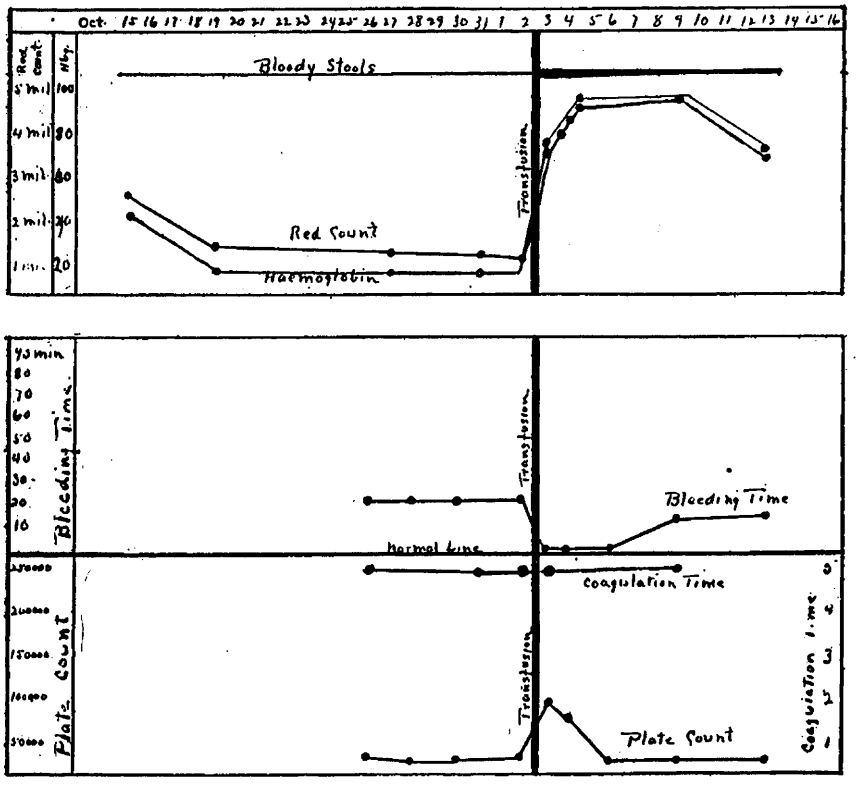

Fig. 6.—Chart of Case 2.

several small ecchymoses. Blood plates, as determined from stained smears and counting chamber, were extremely scarce. The bleeding time was about sixty minutes. The coagulation time was normal. The clot was firm and non-retractile. The white count was 7,000; polynuclears, 45 per cent.; lymphocytes, 55 per cent.; hemoglobin, 90 per cent. The patient was seen again four months later (April 7, 1910). She had been free from hemorrhagic symptoms for some time. Plates were then abundant in stained smears, and hemorrhage from ear pricks would last for from five to ten minutes. The hemoglobin was 85 per cent.

Platelet counts were not made in this case at the time of transfusion. It seems probable, however, that, as in the previous cases, the relief of hemorrhage, after transfusion, was associated with an increase in the platelet count.

COMMENT

A review of the cases shows a striking dependence of hemorrhagic diathesis on the reduced number of platelets. In Cases 1 and 2 the platelet counts before transfusion were 3,000 and 20,000; the bleeding times were, respectively, ninety and twenty minutes. After transfusion the counts were 110,000 and 89,000, and the bleeding time in each case was three minutes. After the disappearance of these platelets, apparently introduced into the patients' circulation by transfusion, the bleeding times were again delayed (forty minutes and twenty minutes). In Cases 1 and 3 the bleeding times (forty minutes and one hour) came to normal after spontaneous rises in the platelet counts.

As to spontaneous hemorrhages, there was complete relief in Cases 1 and 3 for three days after transfusion and after spontaneous rises in the platelet counts. In Case 2 intestinal hemorrhage was slightly increased by transfusion, in spite of the fact that the general tendency to bleed (shown by the shortening of the bleeding time) was less marked. This apparently contradictory result may be accounted for by the fact that intestinal hemorrhage in this case was not entirely pathologic hemorrhage, but was due largely to bleeding from intestinal ulcers. The increase after transfusion may have followed the more complete filling of the blood-vessels.

In each of the cases the coagulation time of the blood bore no relation either to the platelet count or to hemorrhagic symptoms. The coagulation time was practically the same before and after transfusion, and before and after the spontaneous rises in the platelet count.

Other cases of hemorrhagic disease with a reduced number of platelets (twenty) have been reported by Denys, Hayem, Ehrlich, Helber, Bensaude and Rivet, Coe, Pratt and Selling. In one case reported by Bensaude and Rivet[6] there was a low count (6,000) during a hemorrhage crisis. During a remission in the disease the count was 161,000. Coe[7] has attached more importance to the relationship between the reduced number of platelets and hemorrhage than other observers. In one of his cases, the most severe epistaxis occurred when the platelets, estimated from stained smears, were almost absent. Previously they had been present, but in diminished number. In another case of purpura hemorrhagica, platelets, frequently estimated from smears, were almost absent during two hemorrhagic periods, and were present during remissions.

The reported cases differ in etiology. Many belong to the group known as idiopathic purpura hemorrhagica. Some of the cases were evidently symptomatic. One of Pratt's cases[8] accompanied nephritis. The platelet count was 9,000. Benzol poisoning was the etiologic agent in Selling's cases. The clinical condition was aplastic anemia. In one of his cases the platelet count was 2,500. In Case 2 reported in this paper, the hemorrhagic diathesis may have been secondary to ulcerative colitis. Plate-

6. Arch. gén de méd., 1905, I, 193.
7. Coe, J. W.: The Treatment of Purpuric Conditions and Hemophilia, THE JOURNAL A. M. A., Oct. 6, 1906, p. 1090.
8. Osler's Modern Medicine, 1908, iv.

let counts may also be low in lymphocytic leukemia, pernicious anemia, and early typhoid fever, and in each disease purpura hemorrhagica is a recognized complication.

The data leads one to believe that a reduced number of platelets is not simply a phenomenon accompanying some types of hemorrhagic disease, but rather that it may be the direct cause of hemorrhagic diathesis in several diseases.

EXPERIMENTAL WORK

Experimental work seemed desirable to determine whether the hemorrhagic diathesis was due directly to the lack of platelets, or whether it was due to an abnormal coagulability of the blood which might accompany a reduced number of platelets. It seemed desirable also to know to what extent the platelet count must be reduced to cause hemorrhage.

In benzol poisoning we have a condition simulating idiopathic purpura hemorrhagica. Santessin[9] has reported cases and experiments in which hemorrhages were produced by benzol. Selling's cases[10] of a similar nature clinically, had very low platelet counts. He has found[11] that subcutaneous injections of benzol in animals reduces the platelet count. This reduction is thought to be due largely to the aplastic condition of the bone-marrow caused by the poison.

My experiments were performed mainly on dogs, and, according to a method suggested by Dr. Selling. Benzol was given daily for six to twelve days. The platelet count would usually rise at first, but later would fall and continue low for a number of days after the injections of benzol had been stopped. In several instances the count was reduced to 30,000. The white count was usually high even in the late stages of the poisoning.

The results[12] support a conclusion which might be drawn from this series of cases, namely, that when other conditions are normal, moderately low platelet counts are not associated with hemorrhagic diathesis. The platelet counts, after transfusion, in Cases 1 and 2 were only one-third of the normal, and yet there was no evidence of pathologic hemorrhage. The bleeding time was only moderately delayed (ten to twenty minutes) in Case 2, when the platelet counts varied from 20,000 to 30,000. The tendency to bleed in Cases 1 and 3 was extreme only during the practical absence of platelets. In the experimental work the platelet counts in dogs and rabbits were reduced from the normal (200,000 to 600,000) to from 50,000 to 75,000 without the appearance of hemorrhagic diathesis. Only a more extreme reduction (to 30,000) caused a delay in the bleeding time, and hemorrhages into the organs. There is an analogy between this observation and the observations of Whipple and Hurwitz on chloroform poisoning.[13] They found that, when other conditions are normal, a moderate reduction in the quantity of fibrinogen does not cause hemorrhagic diathesis. In their experiments hemorrhage was prolonged only when the reduction was extreme. It seems likely, then, that both platelets and fibrinogen play a striking rôle in the control of hemorrhage. Either one may be moderately reduced without symptoms, but after an extreme reduction there is a tendency to bleed.

The experiments failed to show abnormalities in the coagulability of the blood accompanying low platelet counts, which account for prolonged hemorrhage. The coagulation time was normal, or slightly shortened when the platelet count was as low as 30,000. The quantity of fibrinogen was normal or slightly increased (0.55 per cent. to 0.65 per cent.); furthermore, the fibrinogen present was all convertible into fibrin, and the fibrin examined in a number of ways had a normal microscopic appearance.

The serum in one instance was examined by Professor Howell, and found to contain thrombin. The only abnormality in the clot noted was diminished retractibility, a peculiarity shown by Hayem and others to be associated with and probably due directly to a lack of platelets. Normal plasma deprived of platelets in various experimental ways clots quickly, but does not retract from the sides of the vessel containing it, and extrude serum.

The hemorrhagic diathesis is explained, possibly, through investigations on experimental thrombi. In a bleeding vessel, there are conditions suitable for the formation of a thrombus, that is, injured intima and a flowing stream of blood. Platelets, although they have little, if any, influence on the clotting of still blood, play a striking rôle in the formation of thrombi. The investigations of Hayem, Eberth and Schimmelbusch, Welch, Pratt, and others, have shown that after trauma to a blood-vessel platelets are the first element to adhere to the injured intima, and that within a few minutes they are massed in great numbers at the injured point. Later, leukocytes, fibrin, and red cells are included in the process, and a plug is formed consisting of masses of each of these elements. The investigations of J. H. Wright[14] show more clearly the rôle which the thrombus plays in stopping hemorrhage. His experiments were made by puncturing vessels with a needle. The resulting thrombi were likewise made up largely of platelets, and were evidently a factor in plugging the opening. An absence of platelets would lead to abnormality in the formation of thrombi, and might be a cause of prolonged hemorrhage. Pratt has laid more emphasis than other observers on the rôle which red cells play in thrombus formation. The failure of erythrocytes in carrying out this function explains, possibly, the delayed bleeding time noted in severe anemia.

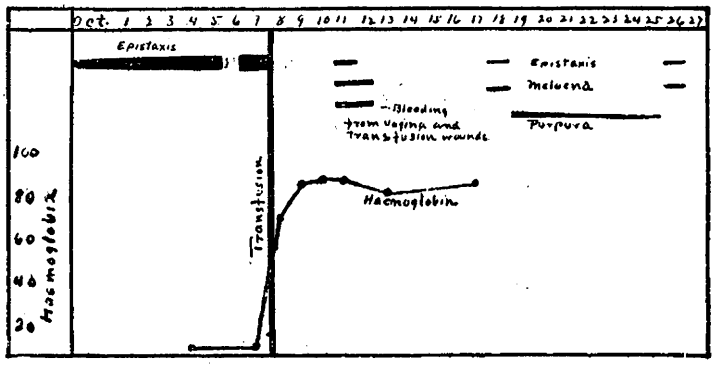

Fig. 7.—Chart of Case 3.

9. Santessin: Arch. f. Hyg., 1897, xxi, 336; Skand. Arch. f. Physiol., 1900, x, 1.
10. Selling: Bull. Johns Hopkins Hosp., 1910, xxi, 32.
11. Unpublished experiments which will appear in the Journal of Experimental Medicine.
12. A complete report of results will be made later.
13. Unpublished experiments which will appear in the Journal of Experimental Medicine.
14. Personal communication.

CONCLUSIONS

The question now arises whether the facts admit the conclusion that an extreme reduction in the number of platelets is a cause of hemorrhagic diathesis, or whether the low platelet count must be considered a phenomenon which is sometimes found in hemorrhagic disease. The facts are as follows:

1. In the cases of hemorrhagic disease summarized, evidently differing in nature and etiology (acute and chronic idiopathic purpura hemorrhagica, chronic ulcerative colitis, aplastic anemia, nephritis), the constant features associated with the tendency to bleed were the reduced number of platelets, and the modification of the clot probably dependent on it, namely, diminished retractility.

2. In the cases reported in this paper, relief of the tendency to bleed followed not only the rises in the platelet count occurring at a remission in the disease, but followed also the rise brought about by transfusion. In the latter case, the tendency to bleed returned when the platelets disappeared.

3. Experiments in which the platelet count was reduced by benzol failed to show an abnormality in the coagulability of the blood, which accounts for the hemorrhages of benzol poisoning.

4. The structure and the mode of formation of experimental thrombi suggests, from an anatomic standpoint, that platelets play a rôle in stopping hemorrhage.

It may be permissible to mention two more points of interest suggested by the cases.

None of the patients showed so marked a tendency to bleed after transfusion as before, even after the platelet counts had dropped to their previous low level. In Cases 1 and 2, the bleeding times were ninety minutes and twenty minutes before transfusion. On the fifth day after transfusion, when the count was again low, the bleeding times were only half as long, fifty minutes and ten minutes. The spontaneous hemorrhages in Cases 1 and 3 were never so severe after as before transfusion. Since anemia is associated with a delayed bleeding time, this relief might be accounted for by the rise in the red count. In interpreting the beneficial results following transfusion, this point should always be considered.

In each of the cases, the platelets introduced by transfusion disappeared rapidly. It is granted that these platelets may have been destroyed prematurely by the disease from which the patient suffered, or by processes analogous to hemolysis, etc. The uniform rapidity in the rate of disappearance, however, suggests that platelets are short-lived bodies. This interpretation is supported by the results obtained from the study of transfusion in benzol poisoning. In this case also, platelets introduced by transfusion disappear rapidly. It is also supported by results, to be reported later, which show that the normal rate of formation of platelets is probably extremely rapid, and may amount to as much as one-fourth of the entire number in the body per day. The evidence suggests strongly that platelets disintegrate or are utilized by the body in enormous numbers, and that the count is kept constant under a given set of conditions by a correspondingly rapid rate of formation.

The type of hemorrhagic disease described in this paper can be sharply differentiated from other types of disease, such as hemophilia, melena neonatorum, purpura simplex, Henoch's purpura, etc., which are due to other abnormalities. To this type of disease belong the so-called idiopathic purpura hemorrhagicas, and some cases of symptomatic purpura. The latter will probably be found most frequently in aplastic anemia, pernicious anemia, lymphocytic leukemia, typhoid fever and intestinal diseases. The symptoms may be mild, or may be so severe and acute that the patient bleeds to death in a few days. In mild cases, purpura may not appear. The only demonstration of the disease may be (as in Case 2) excessive hemorrhage from a local lesion.

The diagnosis is easy. If the platelet count is reduced to a sufficient degree to cause hemorrhage, the fact may be determined by examining carefully made cover-glass preparations. The absence of retractility of the clot is considered by Hayem and his pupils characteristic of the condition, and is of diagnostic import. A point which I have found of value in following the cases and also in the diagnosis is the marked delay in the bleeding time.

Transfusion gives good results in the treatment of the disease. In addition to replacing blood, it stops hemorrhage for a few days, and may tide the patient over a serious crisis. The treatment is probably applicable to the symptomatic as well as to the idiopathic types of disease, and may be useful in the treatment of some cases of typhoid hemorrhage.

In concluding, I wish to acknowledge my indebtedness to Dr. E. H. Whipple, of the department of pathology, to Professor W. H. Howell of the department of physiology, and to Dr. L. Selling for their kind assistance in the experimental work.

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ABSTRACT OF DISCUSSION

DR. J. H. PRATT, Boston: There seems to be some relation between the blood platelets in the blood and purpura hemorrhagica. Normally, the number of blood platelets is about 450,000 to the cubic millimeter. In simple purpura I found the platelet count was greatly reduced; in one fatal case it fell as low as 7,000. This patient had continuous hemorrhages from the lips and mouth. The platelet count was made 3 times on different days, and the largest number of platelets found was 16,000. In a case of mild purpura hemorrhagica there were 105,000 platelets per cm. The only other condition in which I have found very low platelet counts is lymphatic leukemia. The relation between purpura and the coagulation time is less clear. Wright asserted that purpura was due to delay in the coagulation time and that the treatment of the disease consisted in reducing the coagulation time to the normal by the administration of calcium chlorid or calcium lactate. I found the records of the Johns Hopkins Hospital and the Massachusetts General Hospital those of 34 cases of purpura in which the coagulation time of the blood had been determined. The average coagulation time of the blood in this series of cases was 5½ minutes, which is within the normal limits. In only a few cases did I find a delay in the coagulation. I have seen a patient with purpura bleeding to death from the mucous membrane when the coagulation time was normal. Over the lobe of the ear at the site of the puncture a thick, moist clot formed, but blood continued to ooze from the wound for a long time. I believe that Dr. Duke's method of determining the "bleeding time" will be found to have great clinical value. In the case I have just cited in which the coagulation time was normal the bleeding time was doubtless greatly increased.

DR. W. W. DUKE, Kansas City, Mo.: Transfusion must be done by the direct method. Defibrinated blood is free from platelets and therefore in itself would not increase the count. There is a special indication for transfusion preparatory to operation in this condition. In addition to the usual results which follow transfusion, the tendency to bleed is diminished.