PRIMARY THROMBOCYTOPENIC PURPURA AND ACQUIRED HEMOLYTIC ANEMIA

Evidence for a Common Etiology

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MANY EXPLANATIONS have been advanced for the low thrombocyte (platelet) count in primary or idiopathic thrombocytopenic purpura, but so far all theories lack substantial proof. The disease is somewhat commoner in females and occurs more frequently in the first half of life, although it has been seen in persons of all age groups. A familial history of easy bruising and prolonged bleeding is frequently mentioned in case histories, but few hematological data are offered to support the supposition that thrombocytopenia has occurred in other members of the family. Reports of transitory thrombocytopenia in infants of women with thrombocytopenic purpura are of particular interest, since these cases suggest that an agent producing the thrombocytopenia is transmissible through the placenta.[1] Both increased destruction and decreased formation of thrombocytes have been advanced as causes of primary thrombocytopenia. Since there is no technic comparable to the reticulocyte count for estimating the rate of formation of thrombocytes or to the determination of the pyrrhole pigment excretion for measuring the rate of their destruction, it has not been possible to measure the rate of thrombocyte destruction or formation.

It is now generally accepted that thrombocytes are formed from the cytoplasm of megakaryocytes, as first demonstrated by Wright.[2] The absence of thrombocytes around the megakaryocytes and the paucity of granules in the megakaryocyte cytoplasm in primary thrombocytopenic purpura have been interpreted by some to be evidence of diminished formation of thrombocytes in this disease.[3] The pro-

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2. Wright, J. H.: The Histogenesis of the Blood Platelets, J. Morphol. **21**:263, 1910.

3. Dameshek, W., and Miller, E. B.: The Megakaryocytes in Idiopathic Thrombocytopenic Purpura, Blood **1**:27, 1946.

duction of a hormone-like agent by the spleen which inhibits the formation of thrombocytes and leukocytes has been postulated, and it is claimed that by this mechanism splenic hyperfunction (hypersplenism) is responsible for primary thrombocytopenic purpura. This view is partly based on the observation that thrombocytosis may follow the removal of normal and pathological spleens. However, this does not necessarily imply that the spleen normally exerts an inhibitory influence on the megakaryocytes. The thrombocytosis may simply be due to the removal of a normal site of thrombocyte destruction. In addition, the morphological changes in the megakaryocytes observed in primary thrombocytopenic purpura could be due to accelerated utilization of the cytoplasmic granules and rapid removal of thrombocytes from the site of their formation. Another objection to the theory that primary thrombocytopenia is due to diminished formation of thrombocytes arises from the observation of patients in whom thrombocytopenia, and sometimes leukopenia, occurs in association with acquired hemolytic anemia.[4] In such instances it would be necessary to postulate that two diametrically opposite mechanisms are in operation, one involving the excessive destruction of red cells and the other an inhibition of thrombocyte and leukocyte production. It is reasonable to explain the reduction of all three elements on the basis of the one demonstrable mechanism, excessive destruction.

The observation of abnormal phagocytosis of thrombocytes [5] by the macrophages of the spleen in supravital preparations is not a quantitative measure of thrombocyte destruction, and histological studies of fixed preparations of spleens from patients with primary thrombocytopenic purpura indicate that excessive phagocytosis does not take place in vivo.[6] Even if excessive destruction of thrombocytes by phagocytosis plays a definite role in primary thrombocytopenia, the stimulus for such aberrant activity of the macrophages is not explained.

Troland and Lee [7] and subsequent workers have reported the production of thrombocytopenia in animals by the injection of splenic extracts. However, others have failed to show that extracts of the spleen are more active than extracts of other organs in producing thrombocytopenia.[8] In addition, extracts of spleens from patients with primary thrombocytopenic purpura have not been consistently more active than extracts of normal organs. While these experiments represent well considered attempts to elucidate the problem, the variables attending the injection of crude extracts of human organs into animals and the measurement of the effect on so labile a tissue as circulating thrombocytes make the application of these observations to human disease difficult.

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4. Evans, R. S., and Duane, R. T.: Acquired Hemolytic Anemia: I. The Relation of Erythrocyte Antibody Production to Activity of the Disease: II. The Significance of Thrombocytopenia and Leukopenia, Blood **4**:1196, 1949.

5. Doan, C. A., and Wright, C. S.: Primary Congenital and Secondary Acquired Splenic Panhematopenia, Blood **1**:10, 1946.

6. Von Haam, E., and Awny, A. J.: The Pathology of Hypersplenism, Am. J. Clin. Path. **18**:313, 1948.

7. Troland, C. E., and Lee, F. C.: Thrombocytopen: A Substance in the Extract from the Spleen of Patients with Idiopathic Thrombocytopenic Purpura That Reduces the Number of Blood Platelets, J. A. M. A. **111**:221 (July 16) 1938.

8. Singer, K., and Rotter, R.: Studies on Thrombocytopen: I. A Reliable Test for This Principle in Organ Homogenates and in Urine, J. Lab. & Clin. Med. **34**:1336, 1949.

Excessive utilization of thrombocytes, rather than abnormal destruction, appears to be the cause of the low thrombocyte count in thrombotic thrombocytopenia, in which numerous thrombocytic thrombi are found throughout the body. This syndrome, described by Singer,[9] must represent only a small proportion of thrombocytopenias, since in most instances of the primary disease there is no clinical or histological evidence of multiple small thromboses. Moreover, recent histological studies of the skin of patients with primary thrombocytopenic purpura have shown that thrombocytic thrombi do not form in injured arterioles and capillaries.[10] Regardless of whether decreased formation, increased destruction or accelerated utilization of thrombocytes best explains the thrombocytopenia, it is obvious that the spleen alone is not the cause of the low thrombocyte count, since the condition of a fair proportion of patients is not improved by splenectomy [11] and many others whose purpura disappears continue to show some degree of thrombocytopenia.

The frequent association of thrombocytopenia and thrombocytopenic purpura with acquired hemolytic anemia [4] in which an autoantibody for red cells is con-

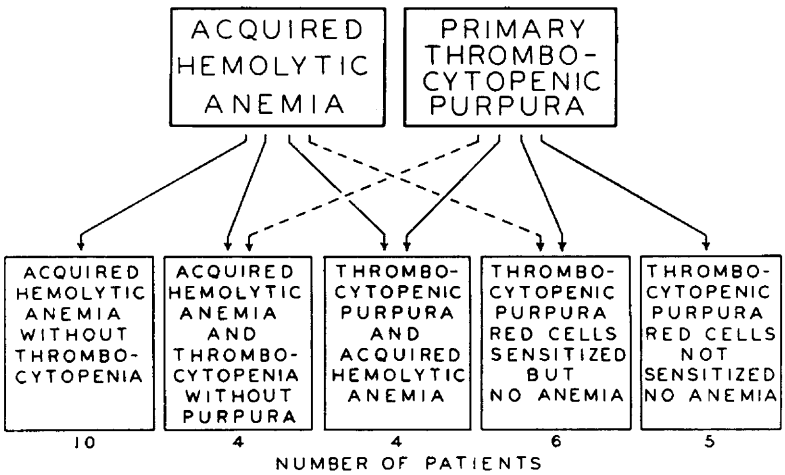

Chart demonstrating the spectrum-like relationship between acquired hemolytic anemia and primary thrombocytopenic purpura.

sistently demonstrable suggests that a similar mechanism is responsible for the reduction in circulating thrombocytes and that a similar autoantibody for thrombocytes may be responsible for the low thrombocyte count in primary thrombocytopenic purpura. To test this hypothesis, we have studied patients with primary thrombocytopenic purpura for evidence of a thrombocyte-agglutinating factor in the serum and for the stigmas of acquired hemolytic anemia. To date, in more than half the patients for whom the original diagnosis was primary thrombocytopenic purpura there has been consistent evidence of sensitization of the red cells and, in some cases, active hemolytic anemia. As a result of these observations, we

9. Singer, K.; Bornstein, F. P., and Wile, S. A.: Thrombotic Thrombocytopenic Purpura: Hemorrhagic Diathesis with Generalized Platelet Thromboses, Blood **2**:542, 1947.

10. Zucker, H. D.: Platelet Thrombosis in Human Hemostasis: A Histological Study of Skin Wounds in Normal and Purpuric Individuals, Blood **4**:631, 1949.

11. Bogardus, G.; Allen, J. G.; Jacobson, L. O., and Spurr, C. L.: Role of Splenectomy in Thrombocytopenic Purpura, Arch. Surg. **58**:16 (Jan.) 1949.

have been able to divide our patients with acquired hemolytic anemia and primary thrombocytopenic purpura into five distinct groups, as shown in the chart, which illustrates the close relationship of the two disorders. In addition to the evidence of a spectrum-like association of the two diseases, we are presenting evidence that there is a thrombocyte-agglutinating factor in the serum of patients with primary thrombocytopenic purpura.

TABLE 1.—*Basic Hematological Data*

	Patient	Sex	Age	Hemoglobin, Gm. per 100 Cc.	Reticulocytes, %	Thrombocytes, per Cu. Mm.	Purpura	Icterus Index or Fecal Urobilinogen, Mg. per Day	Highest Dilution of Antiglobulin Serum Showing Agglutination
I.	Acquired Hemolytic Anemia Without Thrombocytopenia								
	J. Z.	F	57	5.0	28	220,000	—	622	1:320
	A. D.	M	50	10.2	13	450,000	—	1,800	1:80
	J. D.	M	47	7.6	40	272,000	—	1,650	1:160
	J. L.	M	48	6.8	41	250,000	—	...	1:640
	E. S.	M	78	7.8	20	120,000	..	(I. I. 30)	1:640
	C. A.	F	24	6.0	9	160,000	—	(I. I. 50)	1:640
	S. G.	M	..	11.4	11	Normal	—	...	1:640
	B. T.	F	64	9.2	9	Normal	—	1,500	.....
	W. G.	M	31	9.5	18	Normal	—	450+	1:320
	H. S.	F	37	9.8	13	Normal	—	950	1:320
II.	Acquired Hemolytic Anemia with Thrombocytopenia But No Purpura								
	O. W.	F	47	7.5	12	12,000	—	1,360	1:320
	D. B.	F	55	5.3	9	35,000	—	425+	.....
	C. S.	F	22	7.7	8	70,000	—	2,080	1:320
	J. F.	M	34	4.6	72	60,000	—	(I. I. 40)	1:160
III.	Acquired Hemolytic Anemia with Thrombocytopenic Purpura								
	F. R.	F	42	9.5	22	10,000	+	530	.....
	Y. W. L.	F	38	9.0	9	50,000	+	...	.....
	O. P.	M	39	11.5	13	10,000	+	1,100	1:160
	E. R.	M	49	7.0	5.4	21,000	+	(I. I. 16)	1:10
IV.	Thrombocytopenic Purpura with Positive Reaction to Antiglobulin Serum Test								
	deG.	M	7	14.4	0.5	10,000	+	...	1:20
	F. F.	M	49	15.0	..	10,000	+	...	1:5
	E. T.†	F	26	9.0	4.2	52,000	+	(I. I. 5)	1:40
	J. P.	F	61	14.0	2.3	26,000	+	...	1:20
	LaT.	F	3	14.7	..	12,000	+	...	1:10
	S. A.	M	51	15.3	..	83,000	+	...	1:20
V.	Thrombocytopenic Purpura with Negative Reaction to Antiglobulin Serum Test								
	A. F.	F	4	13.4	..	26,000	+	...	.....
	M. N.	M	3	12.4	..	110,000	+	...	No
	D. S.	F	31	14.0	1.2	45,000	+	...	agglutination
	D. N.	F	24	12.8	1.7	15,000	+	...	
	N. W.	F	45	15.0	..	38,000	+	...	.....

† Patient E. T. had had severe menorrhagia for three months and was bleeding profusely on admission. The anemia in this patient was due to hemorrhage.

CRITERIA FOR DIAGNOSIS OF ACQUIRED HEMOLYTIC ANEMIA AND PRIMARY THROMBOCYTOPENIC PURPURA

The criteria for the diagnosis of acquired hemolytic anemia were as follows: (1) the presence of anemia with reticulocytosis, increased blood bilirubin and increased fecal urobilinogen; (2) absence of family history of hemolytic disease; (3) immunologic evidence of sensitization of the red cells by an antibody active at 37 C.; (4) rapid destruction of transfused cells when measured. The criteria

for the diagnosis of primary thrombocytopenic purpura were (1) the presence of purpura, prolonged bleeding time and diminished clot retraction in patients with low thrombocyte counts; (2) the observation of normal or increased numbers of megakaryocytes in the bone marrow aspiration smears; (3) the lack of evidence that the thrombocytopenia was due to exogenous toxic agents or was secondary to a disease known to be associated with thrombocytopenia. Table 1 summarizes the basic hematological data in the series of patients studied.

ACQUIRED HEMOLYTIC ANEMIA WITH NORMAL THROMBOCYTE COUNTS

Only 10 of 18 patients with acquired hemolytic anemia exhibited normal thrombocyte counts. In no instance was a serious leukopenia noted in this group. An example of uncomplicated acquired hemolytic anemia is presented.

A 57 year old white woman (J. Z.) was admitted to the Oakland Veterans Hospital Nov. 14, 1949, because of weakness and dizziness for eight months. Four months before entry pallor was noted, and the hemoglobin concentration was found to be 6.3 Gm. per 100 cc. and the red blood cell count 1,700,000 per cubic millimeter. Her disorder failed to respond to treatment with vitamin B_{12} and iron preparations, and she continued to spend most of the time in bed. Her past and family history was not contributory. She was well developed and somewhat obese, with slight icterus of the scleras and pallor of mucous membranes and nail beds. There were no petechiae or hemorrhages. The spleen was palpable 4 cm. below the costal margin. The packed cell volume was 15 per cent and the hemoglobin content 5.0 Gm.; red cells numbered 1,500,000, with 28 per cent reticulocytes. The leukocyte count was 4,650, with a normal distribution, and the thrombocyte count 220,000 per cubic millimeter. The serum bilirubin was 3 mg. per 100 cc. and the fecal urobilinogen 622 mg. per day. Sternal marrow aspiration showed erythrocytic hyperplasia.

The patient's washed red cells were consistently agglutinated by two antihuman globulin serums to a high dilution (1:320). Normal red cells (0.1 cc.) incubated in 5 cc. of the patient's plasma for two hours at 37 C. showed evidence of minimal sensitization by agglutinating in the antiglobulin serum in a 1:5 dilution.

During the next three weeks the above observations were made repeatedly with little variation. One transfusion was without benefit. Splenectomy was performed December 7 without incident. One transfusion of 500 cc. of whole blood and 250 cc. of pooled plasma were given during the procedure. The spleen weighed 1,800 Gm. Fresh supravital preparations of the spleen failed to show evidence of excessive phagocytosis of erythrocytes. There was a low grade fever during the first few weeks of her postoperative course. Three days after splenectomy, the hemoglobin concentration was 10 Gm. and the red cells numbered 3,400,000, with 10 per cent reticulocytes. The counts remained unchanged for two weeks; from then on there was a gradual rise to a normal level, along with a fall in the reticulocyte count to normal. The excretion of fecal urobilinogen was 310 mg. per day one week after splenectomy. During the period of recovery there was evidence of less antibody absorbed on the surface of the red cell. This patient died of acute hepatitis three months after splenectomy without recurrence of her hemolytic anemia.

It is worthy of note that the above patient with active acquired hemolytic anemia and splenomegaly showed no evidence of thrombocytopenia during her long course. This indicates that thrombocytopenia, when it does occur in association with acquired hemolytic anemia, is not due to a nonspecific side effect of the abnormal destruction and rapid formation of red cells or to the mechanical effect of a large spleen.

ACQUIRED HEMOLYTIC ANEMIA WITH THROMBOCYTOPENIA WITHOUT PURPURA

Four patients comprise this group. The following case is an example in which leukopenia was also a prominent feature.

O. W., a 47 year old woman, complained of headaches and weakness for four weeks. Pallor and jaundice had not been noted. For a week prior to entry she had been febrile. Her past and family history was not contributory.

She was a thin, nervous woman without jaundice. There was a systolic murmur. The spleen was palpable 3 cm. and the liver 9 cm. below the costal margin. The hemoglobin concentration was 4.2 Gm. and the red blood cell count 1,200,000. The leukocytes numbered 1,700, with 70 per cent neutrophils, 1 per cent eosinophils, 20 per cent lymphocytes and 9 per cent monocytes. There were nucleated red cells in the peripheral blood, and reticulocytes were 12 per cent. Thrombocytes were diminished in the smear, and three counts on separate days varied from 4,000 to 15,000 per cubic millimeter. Marrow biopsy showed hyperplasia of all elements of the marrow. Megakaryocytes of all stages of maturity were numerous. The red cells showed evidence of maximum sensitization with red cell antibody. The icterus index was 15, and fecal urobilinogen was 1,360 mg. per day.

The spleen weighed 930 Gm. and, other than hemosiderosis, showed no abnormality on histological examination. Her condition improved rapidly following operation. The number of circulating thrombocytes and leukocytes became normal within three days, and she was discharged from the hospital seven days later with a hemoglobin content of 12.3 Gm. and 1.5 per cent reticulocytes. Three months later the hemoglobin value was 11.1 Gm., with 1.6 per cent reticulocytes, and the fecal urobilinogen was 220 mg. per day. The amount of antibody absorbed on the red cells was distinctly reduced during the recovery period.

Six months later severe anemia again developed, with signs of rapid blood regeneration and a leukocyte count of 3,500, with 45 per cent neutrophils. Thrombocyte counts were not done. She died of severe anemia two months later in a distant part of the state, and autopsy was not performed.

This patient's condition is an example of severe thrombocytopenia associated with acquired hemolytic anemia. An obvious bleeding tendency, petechiae or easy bruising was never present. The absence of bleeding tendency in severe thrombocytopenia of primary or secondary origin is not uncommon. It is also worthy of note that she did not appear jaundiced, even when the production of bilirubin was many times normal. The absence of jaundice in patients with active hemolytic anemia of all types has been a common observation in our experience and has been responsible for delay in diagnosis of the true nature of the disorder.

The three other patients with acquired hemolytic anemia and a comparable degree of thrombocytopenia without purpura underwent splenectomy. In two there was a sustained remission, and the thrombocyte count returned to normal. The fourth patient continued to show constant hemolytic anemia and low thrombocyte counts until the time of his death from a ruptured appendix about 18 months after splenectomy. The persistent hemolytic process was accompanied with the presence of high antibody concentration on the surface of the red cell.

PRIMARY THROMBOCYTOPENIC PURPURA AND ACQUIRED HEMOLYTIC ANEMIA

This group, which forms the center span between the two diseases, includes four patients, two women and two men. The women were pregnant at the time of onset of the disorder and successfully underwent splenectomy during the sixth month of gestation. One of the men was recovering from an injury to the back when the purpura began, while the other was found to have tuberculosis of the spleen and represents an example of "secondary hypersplenism."

Mrs. F. R., a 41 year old white woman, had been well until the third month of her third pregnancy, when she displayed Vincent's angina, for which she received four injections of oxophenarsine hydrochloride (mapharsen®). Two months later, a hemorrhagic lesion developed

in the left conjunctiva and she was found to be anemic, with a thrombocyte count of 20,000 to 37,000. She received seven transfusions without notable improvement.

She was pale, and there were numerous purpuric spots in the skin. No adenopathy was present; the liver and spleen were not palpable, and the uterus was consistent with a six months pregnancy.

The packed cell volume was 28 per cent, the hemoglobin concentration 9.5 Gm. and the red blood cell count 2,500,000, with 22 per cent reticulocytes. The leukocytes numbered 8,600, with a normal distribution. The bleeding time was 30 minutes, and clot retraction was absent. Thrombocyte counts varied from 0 to 10,000. Sternal marrow smears showed marked erythroid hyperplasia, and megakaryocytes were numerous. The icterus index was 10, and the fecal urobilinogen was over 540 mg. per day.

Because of increasing anemia and persistent purpura, splenectomy was performed. Several hours after operation, the patient vomited 30 cc. of blood; otherwise her course was uneventful. The spleen weighed 250 Gm. and was unusual in that the sinusoids contained many immature and adult megakaryocytes.

During the weeks following operation, the bleeding tendency improved and the purpura disappeared, although the thrombocyte count remained below 10,000. The hemolytic anemia persisted; at the time of delivery the hemoglobin content was 9.3 Gm., and she still exhibited severe thrombocytopenia. One transfusion was administered during delivery, which was carried out without excessive bleeding. The baby was a normal boy weighing 6 pounds 7 ounces (2,920 Gm.).

During the immediate postpartum period there was no change in her blood picture, but during the subsequent months she gained strength, and 10 months after delivery was found to have a hemoglobin concentration of 13 Gm. per 100 cc. and 50,000 thrombocytes per cubic millimeter. The red cells showed a positive reaction to the agglutination test with antiglobulin serum to a dilution of 1:40.

The failure of both the hemolytic anemia and thrombocytopenia to respond immediately to splenectomy and the sluggish response following delivery indicate that neither removal of the spleen nor delivery of the fetus was of crucial importance in the subsequent improvement. Splenectomy changed dramatically the bleeding tendency, since capillary fragility became normal and the bleeding time fell promptly from approximately 25 minutes to five and six minutes within 24 hours.

Mrs. Y. W. L. was a 38 year old Chinese woman whose symptoms of purpura and anemia appeared in the fifth month of her third pregnancy. She was pale, and the skin was covered with petechiae and ecchymoses. The spleen was palpable, but the liver was not enlarged.

The hematocrit was 24 per cent, the hemoglobin content 9.0 Gm. and the red blood cell count 2,570,000, with 9 per cent reticulocytes. Nucleated red cells were present in the peripheral blood. Leukocytes were 3,100 with 86 per cent neutrophils. Thrombocytes numbered 50,000 per cubic millimeter or less; the bleeding time was 17 minutes, and capillary fragility was greatly increased. Sternal marrow smears showed hyperplasia of all elements.

The patient's blood type was O-Rh+. Attempts to cross match her blood with the cells of four group O donors were unsuccessful because of intense agglutination at 37 C. Her own washed cells were agglutinated when centrifuged in her own serum or in 30 per cent beef albumin at 37 C. This agglutinability was not present when sodium chloride solution was used as a diluent. A commercial antiglobulin serum of low potency available at the time gave a negative reaction with her cells.

She underwent splenectomy without transfusion on July 2, 1949. The spleen weighed 550 Gm. The only abnormalities noted were hemosiderosis and hyperplasia of the reticulo-endothelial cells.

She made a rapid recovery following splenectomy, with a return of the thrombocyte and leukocyte counts to normal in 24 hours. The thrombocyte count fell back to 100,000 to 150,000 per cubic millimeter in several weeks, where it has remained since. The hemolytic process subsided more gradually, and the mild anemia and reticulocytosis persisted for several months. She was delivered October 15 of a normal male baby. Since then she has shown no evidence of a hemolytic process but has continued to have a subnormal thrombocyte count of

100,000 to 150,000. From time to time, her red cells have given a positive reaction to the test with antiglobulin serum and her serum has exhibited hemolytic activity for her cells and normal cells.

McElin, Mussey and Watkins [12] have recently summarized the literature on splenectomy during pregnancy and added five cases. Splenectomy had been performed on patients with primary thrombocytopenic purpura, congenital hemolytic jaundice and Banti's syndrome. Our cases are apparently the first recognized examples of splenectomy during pregnancy in patients with both acquired hemolytic anemia and primary thrombocytopenic purpura. Our experience with these patients leads us to concur with the opinion of Barnes and Doan [13] that the indications for splenectomy during pregnancy are the same as those governing splenectomy in general.

The following is an example of both primary thrombocytopenic purpura and acquired hemolytic anemia in a man.

O. P., a 39 year old white painter, entered the hospital because of bloody urine for one week. Four months before he had fallen 8 feet (2.4 meters), sustaining a compression fracture of the third lumbar vertebra, for which he remained in a body cast three months. During the first few days after his injury he had vomited dark material several times and was told that there was blood in his stools. Later, he noted persistent bleeding of gums and petechiae on his legs.

The past history was normal except for frequent nosebleeds for a brief period three years before. Other than morphine and aluminum hydroxide (amphojel®), he had received no medicaments in the recent past.

He was well developed and pale but not icteric. The skin of both legs and feet was covered with petechiae and bruises. There were hemorrhages under the nails, and the gums were oozing in several places. A few 1 cm. lymph nodes were palpated in the left axilla. The spleen and liver were not palpable, and the results of the remainder of the physical examination were not remarkable.

The hematocrit was 31 per cent, the hemoglobin level 11.5 Gm. and the red blood cell count 3,450,000, with 13 per cent reticulocytes. The leukocytes were 12,400, with a normal differential count. The osmotic fragility of the red cells was normal. Tests with antiglobulin serum showed agglutination of the patient's cells to high dilution (1:160), although the cells failed to agglutinate when centrifuged in 30 per cent beef albumin. The patient's serum sensitized normal cells when 0.1 cc. of cells was incubated in 4 cc. of serum. The total serum bilirubin was 1.25 mg. per 100 cc., and the daily fecal urobilinogen was 1,100 mg.

Thrombocyte counts were approximately 10,000 per cubic millimeter on several daily determinations. Bleeding time was 32 minutes, and clot retraction was absent. Sternal marrow smears showed a relative increase in megakaryocytes. The blood Wassermann reaction was 1+ positive and the Hinton reaction negative. Urinalysis showed a persistent macroscopic hematuria during the eight days of hospitalization prior to splenectomy.

The spleen, which was removed without incident, weighed 400 Gm. No accessory spleens could be located. The sections of spleen showed a proliferation of reticuloendothelial cells and an increase in eosinophils.

The day following splenectomy the bleeding time and capillary fragility were normal, and the thrombocyte count had increased to 70,000. Five days later thrombocytes were 370,000, and the hematocrit was 36 per cent with 3.7 per cent reticulocytes. The cells showed less agglutinability in antiglobulin serum, indicating a distinct reduction in the amount of adsorbed antibody. The fecal urobilinogen was 364 mg. per day. The urine became free of red cells.

12. McElin, T. W.; Mussey, R. D., and Watkins, C. H.: Splenectomy During Pregnancy, with a Report of 5 Cases and Review of the Literature, Am. J. Obst. & Gynec. **59**:1036, 1950.

13. Barnes, A. C., and Doan, C. A.: Splenectomy in Pregnancy: Its Hematological Indications and Obstetrical Management, Am. J. Obst. & Gynec. **55**:864, 1948.

The postoperative course was complicated by low grade fever, rales and, later, fluid at the base of the left lung. This was followed by an increase in amount of adsorbed antibody on the red cells and a drop in thrombocyte count to 52,000. This trend continued, and reticulocytes rose to 9 per cent 13 days postoperatively. The downward trend was then reversed, and six weeks after splenectomy the thrombocyte count was 89,000 and the hemoglobin concentration 15 Gm. The red cells continued to show agglutination in antiglobulin serum to a dilution of 1:80.

The above patient showed a good initial response to splenectomy, with evidence of decreased hemolysis and higher thrombocyte count during the first 10 days, followed by a flare-up with return of anemia, reticulocytosis and thrombocytopenia, but without purpura. However, on a return visit to the hospital his condition had improved, although it still was not normal. Further follow-up studies have not been possible.

The fourth patient in this group presented a much more complicated situation in that the anemia, leukopenia and thrombocytopenic purpura were observed in connection with tuberculosis of the spleen.[14] He exhibited an anemia with reticulocytosis (5 to 16 per cent) and an elevated icterus index. Thrombocyte counts varied from 20,000 to 60,000, and leukocytes were as low as 1,600. Bone marrow smears showed a panhyperplasia, with numerous megakaryocytes. His red cells were agglutinated in the antiglobulin serum only in a 1:10 dilution. Although the immunologic abnormality of acquired hemolytic anemia was present, the amount of adsorbed antibody was, according to the method of measurement, less than we have usually found associated with active disease.[4] However, the presence of the immunologic abnormality in this patient suggests that this mechanism may be responsible for "secondary hypersplenism."

PRIMARY THROMBOCYTOPENIC PURPURA WITH EVIDENCE OF RED CELL SENSITIZATION

Five patients were included in this group because of persistent evidence of sensitization of their red cells. In contrast to the previous group none of these patients showed evidence of accelerated hemolysis, although one of them (F. F.) had mild hemolytic anemia following splenectomy. As will be noted in table 1, the red cells of the patients in this group, in contrast to most of the patients with active hemolysis, were agglutinated only by higher concentrations of the antiglobulin serums, indicating less adsorbed antibody on the cell surface. The absence of hemolytic activity is probably related to the relatively weak sensitization of the cells. In this respect the patients of this group resemble patients with acquired hemolytic anemia in remission.

A 7 year old boy (S. deG.) was admitted to the hospital because of frequent epistaxis and easy bruising during the 10 days before entry. A transient rash was noted at the onset of these symptoms.

He was a well developed child who did not appear ill. There were scattered pinpoint petechiae over the entire body, more numerous about the ankles, and ecchymoses over the coccyx and lower extremities. Several petechiae were on the buccal mucosa and palate. No lymphadenopathy was present. The liver and spleen were palpable under the costal margins.

The hemoglobin concentration was 14.4 Gm. and the red blood cell count 4,500,000. Leukocytes numbered 8,000, with 24 per cent neutrophils, 70 per cent lymphocytes, 3 per cent monocytes and 3 per cent eosinophils. Thrombocytes numbered 10,000 and reticulocytes 0.5 per

14. This patient was studied at the Fort Miley Veterans Hospital, San Francisco.

cent. The bleeding time was 10 minutes, and capillary fragility was increased. Bone marrow examination showed an increase in megakaryocytes without surrounding thrombocytes. The patient's red cells persistently showed agglutination in a 1:20 dilution of the antiglobulin serum.

Because of the persistent thrombocytopenia the spleen was removed 12 days after his admission. The spleen weighed 70 Gm. and showed hyperplasia of the lymph follicles and a moderate number of eosinophilic leukocytes. There was a steady rise in thrombocyte count to 900,000 per cubic millimeter during the six days after splenectomy. The evidence of sensitization of the red cells disappeared five days after splenectomy. During the 12 months since splenectomy he has remained well.

The next case is an example of a more chronic course of primary thrombocytopenic purpura in an older person.

F. F., a 49 year old man, entered the hospital because of easy bruising, intermittent purpura and bleeding of his gums for 10 years. His main complaint, however, was a sense of weakness and chronic fatigue for many years. Six months prior to entry one of his three daughters was found to have thrombocytopenic purpura (see history of A. F. below) and had undergone splenectomy with a complete remission. At that time the father was noted to have 10,000 thrombocytes per cubic millimeter, a prolonged bleeding time, increased capillary fragility and a hemoglobin concentration of 15.7 Gm.

He was a heavy-set man. There were small petechiae on the soft palate. No adenopathy was present. The liver and spleen were not palpable. The hemoglobin concentration was 15 Gm., the red blood cell count 5,500,000 and the hematocrit 43 per cent. The leukocytes were 13,600, with a normal differential count. The thrombocytes were 10,000 to 27,000; the bleeding time was 25 minutes, and there was minimal clot retraction at 72 hours. Capillary fragility was abnormal. Prior to splenectomy the patient's red cells showed agglutination in the antiglobulin serum only in a 1:5 dilution.

The spleen was removed without difficulty and weighed only 210 Gm. He received one transfusion of 500 cc. of whole blood during the operation. The postoperative course was uneventful. The thrombocyte count did not rise rapidly and was still 24,000 on the third postoperative day. The bleeding time and capillary fragility were normal the day following operation. Thrombocyte counts varied from 117,000 to 191,000 during the second and third postoperative weeks.

During the first week after splenectomy the red cells became agglutinable in high dilutions (1:320) of antiglobulin serum, indicating a high degree of sensitization. During this time anemia developed, with 10 Gm. of hemoglobin, hematocrit 29 per cent and 7.3 per cent reticulocytes. There was 1.5 mg. serum bilirubin per 100 cc. The evidence of mild hemolytic activity was present 16 days after splenectomy at the time he left for his home in a distant part of the state, where follow-up studies have indicated a subsidence of the hemolytic process and no recurrence of thrombocytopenic purpura. Since splenectomy he has noted a sustained sense of well-being.

This patient presented an unusual course in that the degree of sensitization of the red cells increased rather than decreased following splenectomy. It was only after splenectomy that the reaction to the antiglobulin test became strongly positive, and with that he showed for the first time signs of hemolytic anemia, with hyperbilirubinemia and reticulocytosis. There was no blood loss or explanation for the anemia other than abnormal hemolysis.

The third patient in this group, a 26 year old woman, is worthy of special note in that the purpura and abnormal bleeding did not subside following splenectomy but persisted along with the chronic thrombocytopenia for several months. It finally became necessary to perform hysterectomy to control the vaginal bleeding. Following this operation, there was slow but sustained improvement over the course of weeks.

PRIMARY THROMBOCYTOPENIC PURPURA WITHOUT EVIDENCE OF SENSITIZATION OF RED CELLS

Six patients were in this group. In age and sex distribution there was no significant difference from the group described above in whom the disease was accompanied with definite evidence of sensitization of the red cells. The following case is presented because of the unusual familial incidence of the disease.

A. F., the 4 year old daughter of F. F., described above, was hospitalized for consideration of splenectomy for severe thrombocytopenic purpura of three years' duration. Her birth and infancy had been normal, but from the age of 1 year her mother noted that she bruised easily. Chronic fatigue and irritability became noticeable about six months before entry; her physician noted large purpuric areas, and the thrombocyte count was reported to be 65,000 per cubic millimeter.

She was a well developed child. There were numerous 1 cm. ecchymoses on the elbows and legs; a few small petechiae scattered over the arms, legs and trunk, and there was blood in the left nostril. No lymphadenopathy was present, and the spleen was not palpable.

The hemoglobin concentration was 14.6 Gm. and the red blood cell count 5,000,000; leukocytes numbered 13,000, with a normal distribution. The thrombocyte counts varied from 26,000 to 34,000. The bleeding time was 15 minutes; there was no clot retraction at 24 hours, and capillary fragility was increased. Bone marrow examination revealed an increase in megakaryocytes, and 9 per cent of the nucleated marrow cells were eosinophils. The red cells gave persistently negative reactions with all dilutions of the antiglobulin serum.

The spleen weighed 70 Gm. Supravital preparations of splenic pulp cells showed some increase in eosinophils, but no phagocytosis of thrombocytes was observed.

The thrombocyte count began to rise following splenectomy, and the next day it was 190,000 per cubic millimeter. Subsequent thrombocyte counts varied from 258,000 to 422,000 per cubic millimeter. There has been a complete disappearance of purpura, and the symptoms of chronic fatigue have completely disappeared for the 16 months since splenectomy.

Of the other patients in this group, a boy, aged 5 years, showed spontaneous clearing after several weeks of purpura. The others whose spleens were not removed have remained in a chronic state of mild purpura for periods of observation ranging from five to nine months.

The patients with primary thrombocytopenic purpura without evidence of red cell sensitization are notable, since they indicate that sensitization of the red cells when it does occur in primary thrombocytopenic purpura is not a constant corollary of the disease.

ATTEMPTS TO DEMONSTRATE A THROMBOCYTE-AGGLUTINATING FACTOR IN SERUM OF PATIENTS WITH THROMBOCYTOPENIC PURPURA

While the results of observations designed to demonstrate an antithrombocyte antibody in the serum of patients with thrombocytopenia have not been conclusive, our experience is sufficiently encouraging to report. Preliminary studies of thrombocyte agglutination were made with anti-guinea pig–thrombocyte serum and anti-human-thrombocyte serum produced in rabbits. We confirmed the observations of Bedson[15] that the red cell agglutinins could be adsorbed, leaving the thrombocyte agglutinins intact. After observations of agglutination of guinea pig thrombocytes by anti-guinea pig–thrombocyte serum, similar studies were conducted with human thrombocytes and rabbit antiserum. Tests were then set up to study the effect of human serums on suspensions of human thrombocytes. Briefly, suspensions of

15. Bedson, S. P.: Blood-Platelet Anti-Serum: Its Specificity and Role in the Experimental Production of Purpura, J. Path. & Bact. **25**:94, 1922.

human thrombocytes, free of other cellular elements, were prepared by differential centrifugation of whole blood diluted 30 to 50 per cent with 10 per cent citrate solution or by similar treatment of the buffy layers from 1 day old blood.[16]

A 5 per cent thrombocyte suspension was made in human serum which had been heated at 56 C. for one-half hour. Three drops of the above suspension were added to 0.5 cc. of inactivated serum to be tested in a 12 by 75 mm. tube and incubated for one hour at 37 C., followed by storage for 12 to 24 hours at 0 C. Two drops of the suspension were examined for agglutination microscopically, and an equal portion was centrifuged at 1,000 revolutions per minute for two minutes and studied for agglutination. Approximately 50 per cent of the early observations were inconclusive because of agglutination in control serums, as well as in serums

TABLE 2.—*Results of Observation Designed to Demonstrate a Thrombocyte-Agglutinating Factor in Serum from Patients with Primary Thrombocytopenic Purpura*

Source of Serum	Agglutination Magnification, 10 ×	Suspension Centrifuged at 1,000 R. P. M. 2 Min.; Magnification, 950 ×
Primary thrombocytopenic purpura		
O. P.	+	++
J. P.	±	+
F. F.	+++	+++
D. S.	++	++
A. M.	±	++
N. W.	±	+
S. A.	±	+
Other diseases		
C. S.	−	−
E. N.	−	−
W. F.	−	−
L. J.	−	−
M. M.	−	−
B. B.	−	−
Normal serums		
G. M.	−	−
M. L.	−	−
R. D.	−	−
C. L.	−	−
R. N.	−	−

from patients with thrombocytopenic purpura. However, when the original thrombocyte suspension was smooth and stable, there was an absence of agglutination of thrombocytes in control serums and an active agglutination of thrombocytes in the serum from patients with primary thrombocytopenic purpura. The results of a typical observation are shown in table 2. While all the variables which determine the outcome of the observations are not understood, the following conditions appear to be important in demonstrating an agglutinating factor in serums from patients with primary thrombocytopenic purpura:

1. The serums used may be fresh or frozen but should be inactivated to reduce nonspecific agglutination.

2. Passage through a Seitz filter should be carried out to free the serum of particulate matter, since the latter tends to promote aggregation of the thrombocytes.

16. Most of the material used was obtained from the Plasma Division of the Cutter Laboratories, Berkeley 1, Calif.

3. The thrombocyte suspension should not be more than four days old and should be examined for agglutination before adding to the test serums.

4. We have avoided the use of sodium chloride solution because of the probability that a univalent antibody might be present which would require a colloidal medium for demonstration.

5. It has been our experience that repeated saline washing of thrombocytes produces an irreversible agglutination which may account for some or all of the inconclusive results in our early observations. It has been shown that use of saline solution contributes to the clumping of thrombocytes by affecting their cataphoretic velocity.[17]

POSITIVE REACTIONS TO ANTIGLOBULIN SERUM TESTS IN DISEASES OTHER THAN ACQUIRED HEMOLYTIC ANEMIA AND PRIMARY THROMBOCYTOPENIC PURPURA

The observation that primary thrombocytopenic purpura is often accompanied with a positive reaction to the antiglobulin serum test without evidence of abnormal

TABLE 3.—*Results of Antiglobulin Serum Test in Conditions Other Than Acquired Hemolytic Anemia and Primary Thrombocytopenia*

	Number of Persons Tested	Antiglobulin Reaction	
		Positive	Negative
Normal	75	0	75
Miscellaneous patients	468	2	466
Lupus erythematosus disseminata	4	4	0
Periarteritis nodosa	7	4	3
Nephrosis	11	5	6
Rheumatic fever	3	1	2

hemolysis prompted us to determine whether this phenomenon may occur in other conditions. A survey was made of normal persons and patients with medical and surgical conditions. The results are summarized in table 3.

Two positive antiglobulin reactions were observed among 468 miscellaneous patients. One of these was in a young man recovering from infectious mononucleosis. His red cells agglutinated in a 1 : 40 dilution of the antiglobulin serum when he was clinically well, and the hemoglobin content was 12.6 Gm., with a reticulocyte count of 2.5 per cent. Three other patients with infectious mononucleosis failed to give positive reactions. The other patient was an elderly woman who had an old fibrocalcific pulmonary tuberculosis and an adenomatous polyp of the sigmoid colon. She had a normocytic, normochromic anemia, with 9.7 Gm. of hemoglobin and a reticulocyte count of 0.4 per cent. The blood urea, serum bilirubin and fecal urobilinogen were within the normal range; there was no evidence of gastrointestinal bleeding. During four weeks of observation her red cells consistently agglutinated in antiglobulin serum dilutions of 1 : 80 to 1 : 1,280. The sensitizing agent, unlike that found on the red cells in acquired hemolytic anemia, could not be transferred to normal cells in eluate from stroma preparations. It is possible that her anemia is the only manifestation of one of the diseases listed in table 3 in which a positive antiglobulin reaction is frequent.

17. Starling, W., and Sametnik, S.: Über die Entstehungsbedingungen der spontanen Venenthrombose, Klin. Wchnschr. **6**:1269, 1927.

Four patients with disseminated lupus erythematosus showed agglutination of their red cells in 1:40 to 1:320 dilutions of the antiglobulin serum. Although these patients had mild anemia, none had evidence of excessive hemolysis. Red cells of four of the seven patients with periarteritis nodosa consistently gave positive reactions in 1:10 to 1:320 dilutions of antiglobulin serum but did not exhibit evidence of hemolytic anemia. One of three patients with active rheumatic fever showed a positive antiglobulin reaction. Among the 468 miscellaneous patients showing negative antiglobulin reactions were two with erythema nodosum, two with scleroderma, one with dermatomyositis, one with Henoch-Schönlein purpura, 24 with rheumatoid arthritis, 14 with various common allergies of the respiratory tract and several with secondary thrombocytopenia.

Among patients with nephrosis, the red cells of five gave positive reactions when tested with the antiglobulin serum. In four of these agglutination of the red cells occurred in 1:20 or 1:80 dilutions of the antiglobulin serum. In none was there evidence of abnormal hemolysis. The fifth patient showed red cell agglutination in 1:80 to 1:320 dilutions of the antiglobulin serum over a period of several weeks. When 0.05 cc. of normal cells was exposed to 4 cc. of the patient's serum, they were subsequently agglutinated by a 1:80 dilution of the antiglobulin serum. Evidence for excessive hemolysis in this patient was questionable, since neither hyperbilirubinemia nor increased fecal pigment excretion was present, although there was a mild anemia associated with reticulocyte counts of 10 to 12 per cent during the administration of cortisone.

None of the 16 patients with positive antiglobulin reactions had thrombocytopenia, except one with disseminated lupus erythematosus whose thrombocyte count was 84,000 per cubic millimeter. In no case were their red cells agglutinated when centrifuged in 30 per cent beef albumin. In eight of the patients attempts were made to sensitize 0.05 cc. of normal cells in 4.0 cc. of the patient's serum. Results were positive in three. Preliminary studies suggest that there may be qualitative differences between the "sensitizing agent" found in these patients and in patients with acquired hemolytic anemia. We have been able to elute the autoantibody from red cell stroma prepared from patients with acquired hemolytic anemia and to demonstrate the transfer of the antibody to normal cells. On the other hand, we have not been able to demonstrate a similar phenomenon in five of the six cases described above in which elution and transfer were attempted.

COMMENT

The explanation of the pathogenesis of primary thrombocytopenic purpura proposed here is well supported by the animal experiments reported by Bedson and Johnson [18] which showed clearly that injection of an antithrombocyte serum into animals produced thrombocytopenia, purpura and a proliferation of megakaryocytes in the bone marrow. While Bedson was struck by the close resemblance of the disease produced in animals to primary thrombocytopenic purpura, he did not suggest that the human disease is due to a thrombocyte autoantibody. These studies nevertheless provide excellent experimental background for the belief that the disease is due to an immune mechanism similar to that of acquired hemolytic anemia.

18. Bedson, S. P., and Johnson, M. E.: Further Observations on Platelet Genesis, J. Path. & Bact. **28**:101, 1925.

In addition to the frequent occurrence of the two diseases in the same person, there are other features common to both which suggest a close relationship. Both disorders are characterized by great variability of onset, course and duration. Spontaneous remission or exacerbation may occur at any time. We observed spontaneous remission in three of the patients in this series with primary thrombocytopenic purpura and in four with acquired hemolytic anemia.

The similarity in response of primary thrombocytopenic purpura and acquired hemolytic anemia to splenectomy is also striking. Welch and Dameshek [19] have reported that remission followed splenectomy in 50 per cent of 34 patients with primary acquired hemolytic anemia and in 61 per cent of 92 patients with primary thrombocytopenic purpura. The criteria for judging complete remission are not given, but these figures are in substantial agreement with previously published studies. Bogardus and co-workers [11] have reviewed the literature concerning splenectomy in primary thrombocytopenic purpura, and it is apparent that the results are characterized by uncertainty, as is the case with acquired hemolytic anemia.[4] In fact, the course of both diseases following splenectomy is subject to the same variations as are seen prior to operation, although removal of the spleen has an over-all beneficial effect in both conditions. We consider the similarity of the behavior of the two diseases following splenectomy as further evidence of the identity of the causative mechanism.

In our opinion the principal role of the spleen in acquired hemolytic anemia lies in its function as antibody-producing tissue rather than a "slaughterhouse" of red cells. Activity of the disease is, in general, more closely related to the concentration of antibody on the cell than to the presence or absence of the spleen.[4] When splenectomy is successful, it appears that the amount of antibody production has been reduced below a critical level. Relapse may occur if other tissues increase the production of immune agent above such a level. That other tissues are always involved in the production of red cell antibody is indicated by the observation that all cases of acquired hemolytic anemia studied so far have shown persistent sensitization of red cells after splenectomy. It is probable that the same variables of antibody production attend the removal of the spleen in primary thrombocytopenic purpura and account for the uncertainty of the final result.

Our studies demonstrating a thrombocyte-agglutinating factor in the serum of patients with primary thrombocytopenic purpura support the theory that the disease is produced by a thrombocyte autoantibody. However, the in vitro agglutination of thrombocytes which we have observed could be due to substances other than thrombocyte antibodies. For instance, Quick [20] has shown that the serum of patients with thrombocytopenia contains more prothrombin than does normal serum. It is conceivable that other substances which may be capable of agglutinating thrombocytes are increased in primary thrombocytopenic purpura. Obviously, further studies with improved technic are necessary to show conclusively the presence of a thrombocyte autoantibody in the serums of patients with the disease. It is likely that the serum concentration of such an agent may be low as it is in acquired hemolytic anemia, evidently owing to the large amount of antigen

19. Welch, C. S., and Dameshek, W.: Splenectomy in Blood Dyscrasias, New England J. Med. **242**:601, 1950.

20. Quick, A. J.; Shanberge, J. N., and Stefanini, M.: The Role of Platelets in the Coagulation of the Blood, Am. J. M. Sc. **217**:198, 1949.

present. The observation of transient thrombocytopenia in newborn infants from mothers with primary thrombocytopenic purpura is consistent with the passive transfer of an antithrombocyte antibody from the mother's serum but does not eliminate the possibility that other substances are involved.

Since there is good evidence that tissues other than the spleen are always involved in the causation of acquired hemolytic anemia and probably of primary thrombocytopenic purpura, some term other than splenic panhematopenia or hypersplenism would more adequately describe the underlying nature of these disorders. We suggest the terms immunohemolytic anemia and immunopancytopenia for those disorders in which abnormal immune mechanisms can be shown to be operative. The present evidence indicates that immunothrombocytopenic purpura is preferable to the terms primary or idiopathic.

The status of the neutropenia which responds to splenectomy is less well defined. Study of published cases indicates that it is usually associated with hemolytic disease and thrombocytopenia. The neutropenia observed in four of our cases of immunocytopenia has been part of a leukopenia and not a selective reduction in neutrophils. As yet, we have no direct evidence that the leukopenia was due to an abnormal immune mechanism. It is obvious that all patients with unexplained neutropenia or leukopenia should be studied for evidence of red cell sensitization, accelerated hemolysis and thrombocytopenia.

The terms symptomatic hemolytic anemia, secondary hypersplenism and secondary panhematopenia may also prove inadequate. In our experience most patients with hemolytic anemia associated with other disease states, including acute and chronic lymphatic leukemias, tuberculosis of the spleen and viral pneumonia, have shown red cell sensitization indistinguishable from that found in uncomplicated acquired hemolytic anemia. The patient with viral pneumonia had a high titer of cold agglutinins, but we obtained evidence to show that the cold agglutinin was a separate immune body from that adsorbed on the patient's cells at 37 C.

Ellis and co-workers [21] have demonstrated a hemolysin in the serum of a patient with infectious mononucleosis and hemolytic anemia. Recently, Sawitsky and his associates [22] have reported a positive reaction to antiglobulin test serum in a similar instance of hemolytic anemia accompanying infectious mononucleosis. We have also observed red cell sensitization with the same disease.

While there is evidence that abnormal immune activity was present in the patients we have described here, it would be misleading to suggest that immune mechanisms are always responsible for hematological disorders which may respond to splenectomy. For instance, congenital hemolytic anemia responds consistently to splenectomy, yet the fundamental defect appears to be a structural abnormality of the red cell, and the spleen acts as an organ of stasis. In addition, we have recently studied one patient with hemolytic disease which was not due to a known cell defect or to a demonstrable immune agent and who nevertheless responded to splenectomy. It seems likely that similar unknown mechanisms may operate in at least a minority of patients with thrombocytopenia or leukopenia. On the other

21. Ellis, L. B.; Wollenman, O. J., and Stetson, R. P.: Autohemagglutinins and Hemolysins with Hemoglobinuria and Acute Hemolytic Anemia, in an Illness Resembling Infectious Mononucleosis, Blood **3**:419, 1948.

22. Sawitsky, A.; Papps, J. P., and Wiener, L. M.: The Demonstration of Antibody in Acute Hemolytic Anemia Complicating Infectious Mononucleosis, Am. J. Med. **8**:260, 1950.

hand, patients with hemolytic anemias due to congenital cell defect may display coincidentally the aberrant immune activity seen in acquired hemolytic anemia.

As stated elsewhere, we do not believe that there is sufficient evidence to decide whether the thrombocytopenia is due to decreased production or to increased destruction of thrombocytes. It is possible that both factors play a role and that the activity of an immune body brings about increased destruction of thrombocytes by agglutination and phagocytosis and might also decrease thrombocyte production by affecting the megakaryocytes. We are inclined to think that decreased production of thrombocytes does not occur in this manner, since suppression of erythropoiesis is not seen in acquired hemolytic anemia. In this disease erythropoiesis is not suppressed by the presence of a red cell antibody in the serum. It may be, however, that the mass of circulating red cells adsorbs or neutralizes the antibody so that the erythropoietic tissue is protected, whereas in thrombocytopenia the megakaryocytes may not be similarly protected.

One of the features of primary thrombocytopenic purpura which has attracted much attention is the apparent lack of direct relationship between the presence of purpura and the number of circulating thrombocytes. It should be noted that this lack of correlation between capillary and thrombocytic factors is not confined to primary thrombocytopenic purpura but is also observed in various types of secondary thrombocytopenia [23] in which an immune mechanism does not appear to play a role. It appears to us, therefore, that the discrepancy may be due to variables of capillary and thrombocytic function in general and does not need to be explained by the mechanism peculiar to primary thrombocytopenic purpura. Robson [24] has shown that bleeding time and capillary fragility diminish prior to the rise of the thrombocyte count following splenectomy and presents some evidence to indicate that these changes are seen following all operative procedures. However, the possibility that there is damage to the capillaries by an antibody has been suggested by the work of Clark and Jacobs.[25] They have recently reported preliminary observations on the production of nonthrombocytopenic purpura in animals by use of an antiendothelial serum and have reviewed the Japanese literature on the subject.

The one instance of familial occurrence of primary thrombocytopenic purpura in our series (F. F. and his daughter A. F.) is of interest. At first, it was thought that a familial disease comparable to congenital hemolytic anemia existed, which in this instance was manifested by an inherent defect in the thrombocytes. However, the demonstration of sensitization of the red cells in the father and the in vitro agglutination of thrombocytes by his serum showed clearly that immunologic abnormalities were present in his case. Sensitization of the red cells was not demonstrable in the daughter, and her presplenectomy serum was not studied for thrombocyte agglutination. Although this familial occurrence of the same disease may have been a coincidence, it may be that the tendency to produce an antithrombocyte antibody was inherited, since other disorders thought to have an immunologic

23. Aggeler, P. M.; Howard, J., and Lucia, S. P.: Platelet Counts and Platelet Function, Blood **1**:472, 1946.

24. Robson, H. N.: Idiopathic Thrombocytopenic Purpura, Quart. J. Med. **18**:279, 1949.

25. Clark, W. G., and Jacobs, E.: Experimental Nonthrombocytopenic Vascular Purpura: A Review of the Japanese Literature with a Preliminary Confirmatory Report, Blood **5**:320, 1950.

basis, such as rheumatic fever [27] and nephritis, have been shown to have a definite familial incidence.[28]

The high incidence of red cell sensitization in periarteritis nodosa, disseminated lupus erythematosus and nephrosis is of great interest, since these disorders have all been thought to be due to aberrant immune processes. Creger and associates [29] have recently demonstrated that these same diseases are found in persons who show an unusually active response to antigenic stimuli. The relation of these diseases to acquired hemolytic anemia is not clear, nor can we account for the absence of evidence of hemolysis in those patients whose red cells seemed to be heavily sensitized. As we have indicated above, there may be qualitative differences in the sensitizing agents in the two varieties of disorders. The relation of the red cell–sensitizing agent to the leukocyte factor in serum in acute disseminated lupus erythematosus described by Hargraves [30] is under investigation.

SUMMARY AND CONCLUSIONS

Evidence is presented for the existence of a spectrum-like relationship between acquired hemolytic anemia and primary thrombocytopenic purpura. On the one hand, acquired hemolytic anemia with sensitization of the red cells is often accompanied with thrombocytopenia, while, on the other, primary thrombocytopenic purpura is frequently accompanied with red cell sensitization with or without hemolytic anemia.

Since acquired hemolytic anemia has been shown to be due to an autoantibody, its close association with primary thrombocytopenic purpura suggests that the latter disease is due to a thrombocyte autoantibody.

The similarity of the behavior of the two diseases with or without splenectomy is considered further evidence of the identical nature of the causative mechanism.

The demonstration by previous workers that injection of an antithrombocyte serum into an animal produces a picture which closely simulates primary thrombocytopenic purpura in human beings provides the experimental background for the above hypothesis. The demonstration of a thrombocyte-agglutinating factor in the serum of patients with primary thrombocytopenic purpura supports the same hypothesis.

The terms hypersplenism and splenic panhematopenia should be supplanted, since it is evident that the spleen alone is not at fault in these diseases. The terms immunohemolytic anemia, immunothrombocytopenia and immunopancytopenia are suggested for the various disorders shown to have an immunologic basis.

The demonstration of a positive reaction to the antiglobulin serum test in various types of disorders of unknown etiology but thought to be on a hypersensitivity basis is of interest for future investigation.

26. Footnote deleted.

27. Wilson, M. G.: Heredity and Rheumatic Disease, Am. J. Med. **2**:190, 1947.

28. Addis, T.: Glomerular Nephritis: Diagnosis and Treament, New York, The Macmillan Company, 1948.

29. Creger, W. P.; Choy, S. H., and Rantz, L. A.: Experimental Determination on the Hypersensitive Diathesis in Man, to be published.

30. Hargraves, M. M.: Production in Vitro of the L. E. Cell Phenomenon: Use of Normal Bone Marrow Elements and Blood Plasma from Patients with Acute Disseminated Lupus Erythematosus, Proc. Staff Meet., Mayo Clin. **24**:234, 1949.