PRIMARY CONGENITAL AND SECONDARY ACQUIRED SPLENIC PANHEMATOPENIA

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In the consideration of human health and disease, the spleen has now become of much greater interest pathologically than physiologically. This is a distinct reversal of the situation even of a few years ago. That the spleen is nonessential at any age to the maintenance of life and health is amply attested by experimental extirpation of that organ in many animal species, and by the accumulated experience of emergency splenectomy for traumatic rupture of the normal human spleen. Most of the recent progress, therefore, in our understanding of this enigmatic organ has been made through an increasingly critical study of human disease syndromes. The inferences suggested by the available histologic and physiologic data have become magnified, thereby, into an increased awareness of the importance of splenic pathology. Furthermore, if and when such pathology remains unrecognized in the human patient, chronic invalidism or acute, fatal hemoclastic crises may result.

In the interest of simplification and clarity, a correlation of the currently accepted knowledge relating to the spleen may be attempted diagrammatically (fig. 1). There are three rather obvious structural subdivisions in the spleen which serve as the natural basis for functional and pathologic considerations: (1) the vascular system; (2) the lymphoid system; and (3) the reticulo-endothelial system. Without attempting here to enter into a discussion of the controversial and conflicting evidence relative to the anatomical details of the sinusoidal circulation, it is quite evident that the smooth muscle in capsule and trabeculae, together with the vascular system of the splenic parenchyma, serves admirably as the structural basis for the reservoir function for blood cells and plasma, so well established by the classical experiments of Barcroft and others. Pathologically, there may be parenchymal congestion with splenic enlargement and excessive sequestration of plasma and cellular elements secondary to myocardial incompetence, bacterial toxemia, or hepatic cirrhosis with portal hypertension. The spleen is a lymphatic organ with typical lymph sinuses and follicles, the germinal centers of Fleming reflecting normal lymphopoiesis. The physiologic function or functions of the lymphocytes continue under investigation and discussion. It has become more obvious with each succeeding study that they are not simply precursors of other blood cell types, as originally hypothesized. Probably they have to do with endogenous protein metabolism, more specifically with globulin antibody elaboration in association with the reticulo-endothelial phagocytes. The characteristic, nonspecific, postinfective peripheral lymphocytoses, and the infiltrative phenomena in localized tubercle formation and chronic abscesses are the obvious pathologic evidence of the more subtle role played by these elements in the body's cellular and humoral
The lymphopoietic foci in the splenic parenchyma reflect and parallel the general lymphocytic responses in the body, participating in the hyperplastic reactions in chronic lymphatic leukemia, infectious mononucleosis, serum sickness, and other types and varieties of protein sensitizations and intoxications. It is, however, within the reticulo-endothelial system of phagocytic cells that the principle mysteries of the pathologic role of the spleen in human disease probably reside. The R-E system of cells is made up of "specific endothelia" and reticulum cells endowed with special phagocytic capacities. The reticulum cells of the adult diffuse connective tissues behave as do primitive mesenchymal elements with embryonic potentialities. They give rise to other reticulum cells and to the primitive free cells from which monocytes differentiate and mature. The fixed endothelial cells, lining the vascular and lymphatic sinusoids, have a marked phagocytic capacity both in situ and as free, desquamated clasmocytes. Under appropriate circumstances, this focus of potentially developmental and embryonic-like mesen-
chymal tissue in the spleen may revert to a compensatory type of ectopic blood cell formation in the adult (myeloid metaplasia).

The normal spleen, thus, is an organ in which blood cell formation, blood cell sequestration, and blood cell destruction are balanced physiologic functions. If this be true, at any time a pathologic dysfunction in any one of these categories may develop with the appearance of a variety of clinical syndromes. It may also be conceded that a congenital accentuation or diminution in these physiologic functions might be expected occasionally, and that under certain circumstances, as the spleen becomes involved secondarily in a general constitutional disease process, a delicately balanced splenic equilibrium may be upset.

During the past fifteen years in our Hematologic Spleen Clinic we have observed a large variety of disturbances in the circulating blood cell equilibria, due to splenic dysfunction. This does not mean, of course, that the bone marrow and other organs may not also modify and contribute to the hematologic and clinical picture in a given syndrome. The definitive proof of the primacy of the splenic influence in any given instance is the favorable result of total extirpation of all splenic tissue, medical management having proved completely ineffective. When this test of surgery has been applied in acquired secondary, as well as in apparent primary splenic disease syndromes, the completeness and permanency of the resulting cellular and clinical re-equilibration furnish the ultimate criteria of the physician's diagnostic acumen.

The acute or chronic selective sequestration and destruction of red blood cells (congenital or acquired hemolytic icterus), platelets (thrombocytopenic purpura hemorrhagica), and granulocytes (primary splenic neutropenia), respectively, associated with a hyperplasia of highly phagocytic R-E cells, with or without demonstrable splenic enlargement, have been treated successfully by splenectomy. Definite, though secondary and usually asymptomatic, decreases in one or more of the circulating cell types not primarily involved have been noted in the previous communications dealing with each of the above as a separate clinical entity. Under such circumstances, it has been possible usually to observe a modified degree of abnormal clasmatic orotic phagocytosis of the affected elements in supravital studies of the cellular detail of the freshly removed spleen. In one of our patients with acute splenic neutropenia, for example (case 412), there was an accompanying profound thrombocytopenia with clinical manifestations of purpura, without any appreciable hemolytic anemia, which emergency splenectomy completely and permanently corrected. In another chronic neutropenic syndrome in a 65 year old woman (case 312), followed for more than a year before surgery, there developed under observation, secondary thrombocytopenic and anemic cellular and clinical manifestations, entirely absent when the patient was first seen with a selective neutropenia only. Our patients with active congenital hemolytic icterus (see fig. 10) more frequently than not have shown an associated moderate leukopenia and

* These observations are at variance with our own, which indicate an unusual inhibitory effect of an overactive spleen upon the bone marrow, rather than a wholly due to unusual sequestration and phagocytosis within the spleen. Whatever the interpretation, however, the two points of view coincide as to the reality of the pathologic syndromes cited and the effects of splenectomy.—Editor.
thrombocytopenia, which were immediately relieved following successful splenectomy. The normoblastic marrow hyperplasia may have played a myelophthisic role in some of these patients, but a careful study of the fresh splenic parenchyma by the supravital staining technic provided direct evidence of increased granulocyte and thrombocyte inclusions along with the red cells in the numerous R-E phagocytes.*

The recognition of this erratic pathologic physiology of the spleen in these well known and clinically established primary entities led quite logically to a closer scrutiny of the patients referred to us with the peripheral blood picture and clinical symptoms and diagnosis of hypoplastic or aplastic anemia. Likewise, in certain general constitutional disease states involving the spleen more extensively than other organs, we have begun to note in recent years an instability in the functional balance of the spleen, which in extreme instances has resulted in an absolute lack of any discrimination between senile and mature circulating elements, with excessive phagocytosis of all essential cells passing through this organ. Certain selected cases will illustrate the extremes in this series of splenic phenomena.

CONGENITAL SPLENIC PANHEMATOPEANIA

Case i. Betty Jane, aged 14 years when first seen in this clinic, was born in Texas, Dec. 9, 1928, full term, weight 9 pounds, the first child of physically normal parents. During the first six months of extrauterine life she was breast fed, gained weight normally, and the mother noted no unusual symptoms. Toward the end of this period, however, the infant became irritable and began to refuse her feedings; her sleep became broken; she ceased to gain, and a marked pallor without jaundice was noted. Unexplained convulsive seizures, as many as six a day, developed with intermittent cyanosis, and transitory loss of consciousness. At this time, a pediatrician in San Antonio was consulted and a diagnosis of nutritional deficiency anemia was made. However, following four months on an optimum dietary regimen plus iron, the weakness was more marked and the "pallor had become extreme." A second pediatrician was consulted in Austin, from whom we have the first definite blood findings, dated April 30, 1931: total WBC, 4,100; RBC, 1,110,000; hemoglobin, 4.5 Gm.; differential white cell count, PMN 29 per cent; PME, 1 per cent; lymphocytes, 65 per cent; monocytes, 1 per cent. There were marked poikilocytosis, anisocytosis, and polychromatophilia of the red cells. A third pediatrician "made many tests over a period of two years, trying out various treatments without any results." Blood transfusions were discussed but never employed. An x-ray examination of the chest showed a markedly dilated heart. Betty Jane was presented before the Southern Medical Association in 1937 as a diagnostic enigma and therapeutic problem. A hypoplastic anemia was assumed, though duration and other features were atypical. At 4 years of age she had measles; at 4½, pertussis; at 6, mumps; and at 9, chicken pox. There were occasional episodes of unexplained fever. She had a known allergic sensitization to wheat, with resulting nasal congestion. There had been distinct fluctuations in her state of well-being, varying with the degree and intensity of the anemic pallor. The menses had not yet started. She had had almost continuous difficulty with skin disorders, lesions of the toes and fingers, particularly, persisting for months despite the constant care of a dermatolo-

* See footnote, page 12.
gist. Her appetite remained extremely poor, insomnia persisted, with bed wetting regularly, and emotional instability resulted in frequent crying spells. Despite these handicaps, she indulged in limited swimming, skating, and dancing, though developing dyspnea quickly and requiring frequent long periods of rest. She led her classes in school through the years, though climbing school stairs had been physically exhausting.

Betty Jane was referred to our clinic October 13, 1943. There was marked pallor of skin and mucous membranes; the conjunctivae and nail beds were white. Temperature, 99; pulse, 105, regular; respirations, 25 per minute at rest; blood pressure systolic, 110, diastolic, 80 mm. hg. There was no general lymphadenopathy; thyroid gland, normal. The head, hair distribution, eyes, ears, nose, mouth, tongue, teeth, and throat were all normal. Secondary female sex characteristics were well developed and compatible with age. The lungs were clear to physical examination and fluoroscopy. The heart contour was slightly enlarged, the point of maximum intensity being in the fourth interspace in the left anterior axillary line, with a hemic apical systolic murmur, no diastolic murmurs. The spleen was palpable, not tender, 2 cm. below the left costal margin, descending on deep inspiration. The liver was not enlarged to physical examination, and there were no intra-abdominal masses. Genitalia normal, virginal, female, with beginning pubic hair development. The extremities were negative, no edema, no petechiae or ecchymoses. The neurologic examination was physiologic throughout.

The hematologic data (see fig. 2) on admission were as follows: WBC, 1,600; RBC, 1,030,000; hemoglobin, 3.5 Gm.; reticulocytes, 5 per cent; platelets, 228,000 (normal 750,000); hematocrit, 10; MCV, 97 c. mm.; MCH, 35 gg; MCHC, 35 per cent; corrected erythrocyte sedimentation index, 0.2 mm. per min. (normal); erythrocyte fragility range, .412 - .341 per cent NaCl (normal); icterus index, 7; van den Bergh reaction, physiologic; supravital differential count of the white cells, polymorphonuclears, 36 per cent, eosinophiles, 18 per cent, lymphocytes, normal, small, 38 per cent, monocytes 8 per cent. Sternal marrow aspiration: supravital stains of grossly hyperplastic fresh tissue, revealed; myeloid: erythroid ratio of 4:1; neutrophilic myelocytes 'C' 67 per cent, eosinophilic myelocytes 'C' 20 per cent, lymphocytes 5 per cent, clasmatoctyes 2 per cent, megakaryocytes 3 per cent. Erythroid series: normoblasts 30 per cent, late erythroblasts 20 per cent, early erythroblasts 22 per cent, megaloblasts 28 per cent; no foreign or atypical cell types seen. Other laboratory tests: basal metabolic rate plus 15 per cent; fasting blood glucose 95 mgm. per cent; blood urea nitrogen 11 mgm. per cent; phenolsulphonphthalein excretion 85 per cent in two hours; urinalysis, chemical and microscopic, within normal limits; prothrombin, initial concentration 54 per cent, subsequently 95 to 102 per cent. Serology: Wassermann and Kahn tests negative. Electrocardiogram showed sinus tachycardia only without evidence of axis deviation or ventricular preponderance. X-ray of chest and skeleton revealed no significant pathology.

The results of the adrenalin test are indicated on the chart (fig. 2). At the height of the splenic contraction the total white cell count was found to have risen from the base line of 1,450 to 10,250; the red blood cells from 1,300,000 to 1,700,000 per
cu. mm., the hemoglobin from 5.3 to 6.5 Gm., the platelets from 313,000 to 911,000 per cu. mm. The above laboratory data, when interpreted with the background of history and physical findings, served to incriminate the spleen as the major factor in the current syndrome, while minimizing the possible role played by other essential organs.

Splenectomy was, thereupon, advised and accepted, and on October 21, 1943, a 475 Gm. spleen was successfully removed by Dr. Verne Dodd. There was no evidence of perisplenitis, and there were no adhesions. The liver was entirely normal in appearance, with thin, sharp margins, no scarring, and no evidence of portal hypertension. Adrenalin was injected directly into the splenic artery prior to pedicle ligation, with prompt visible contraction of this organ. Preoperatively the total white cell count was 2,100, polymorphonuclear leukocytes 798; immediately postoperatively 17,000, PMN 7,140; at 4:30 p.m. 23,000; RBC from 1,000,000 to 2,010,000 to 2,180,000; thrombocytes from 292,900 to 1,157,000 to 1,521,000; hemoglobin from 4.3 Gm. to 6.3 to 7.8 Gm. Studies of the fresh splenic tissue in supravitally stained preparations showed normal lymph follicles, with increased granulocytes, mature red cells and thrombocytes, within scattered highly phagocytic clasmatocytes. There was diffuse endothelial hyperplasia of the splenic sinuses and considerable intra- and extracellular pigment and debris. There were 3 to 5 eosinophils in each oil immersion field. No increase in fibrous tissue was apparent; no hemopoiesis.

The convalescence was uneventful, and the patient was discharged to her home on the eighteenth postoperative day with 9,000 leukocytes, of which 3,780 were normal mature neutrophilic granulocytes, 3,330,000 red cells, with 9.7 Gm. hemoglobin and 8.2 per cent reticulocytes. The clinical appearance and actions of this patient changed as dramatically as the laboratory data indicate.

On December 5, 1943, Betty Jane's mother reported: "I am happy to say she is looking and feeling better every day. Naturally, even her disposition seems changed. She literally skips, dances, and sings most of the time. I do have a new child, now."

Again on October 6, 1944, approximately one year following splenectomy: "Betty Jane is certainly greatly improved over a year ago. She has grown about 3½ inches and gained 21 pounds. She looks fine and seems to feel fine. For the first time in her life she is trying a regular course in physical education in school. She has absolutely no trouble with menstruation (first menstrual flow Jan. 30, 1944). Everything pertaining to it seems very normal. You might also be interested to know that for months now she has had no skin disorders. I am very happy over her condition."

On May 22, 1945: "I do know that Betty Jane is a different child since she had her operation. She feels much better and is full of fun and life. Her coloring seems to improve all the time and now she is acquiring a fine sun tan. Her height is now 5' 3½" and her weight 126 pounds. We are very happy over her condition."

At the present writing, two years postoperatively, there has been no further evidence of waning bone marrow efficiency. While the red cells have remained stabilized between three and four million for the most part and the hemoglobin between 9 and 11 Gm., the white cells and thrombocytes have persisted at high normal levels.

From the evidence, we have concluded that this individual has probably always experienced excessive splenic sequestration of normal circulating blood elements,
and that, beginning a few weeks after birth, objective signs of the resulting cellular
deficit appeared and, with minor fluctuations, persisted to the point of semi-invailism until this organ was removed fourteen years later. An almost complete cellular
and physical re-equilibration followed immediately and has been maintained for at
least two years, with a very favorable future prognosis.

ACUTE SPLENIC PANHEMATOPENIA

In addition to the chronic relapsing syndrome just described, splenic panhemato-
penia may occur as a relatively acute fulminant medical crisis.

Case 2. Mrs. D. K., aged 24 years, was admitted as a medical emergency to the
Hematologic Service, University Hospital, 6 p.m., August 14, 1944, with a history
of vague symptoms of generalized malaise and fatigability for six months, subacute
manifestations for four weeks, climaxing in an acute fulminant crisis of seventy-two
hours' duration. Increasingly profound prostration with tachycardia, palpitation,
dyspnea, precordial pain, marked pallor with mild fluctuating jaundice, during the
preceding ten days, and nausea and vomiting for seventy-two hours were the
presenting complaints. The past personal and family histories were entirely nega-
tive for any significant illnesses. The patient had been married only six months with
no interruption of or irregularity in the menses. Except for clinical icterus plus
extreme pallor, with evidence of recent weight loss and moderate tissue dehydra-
tion, the only other significant positive physical finding was a large mass in the
upper left quadrant, which moved on respiration and had a readily palpable splenic
notch. Temp. 101°, pulse 120, respirations 25, blood pressure 110/40. The referring
physician had reported the following laboratory data obtained at 9 a.m. the day of
admission: WBC, 3,750; PMN, 68 per cent; lymphocytes, 32 per cent; RBC, 1,450,-
000; hemoglobin, 4.6 Gm. Our own initial studies at 6 p.m. the same day were as
follows: WBC, 1,100; PMN, 59; myelocytes "C" 210; total RBC, 820,000; hemo-
globin, 2.8 Gm.; reticulocytes, 69 per cent; platelets 16,000 (normal 750,000); M.C.V., 90 cu. microns; M.C.H., 30.77; M.C.H.C., 33 per cent; sedimentation
index, 0.2 mm., minute; erythrocyte fragility range, .471 — .341 (normal .412 —
.300); serology, negative. Sternal marrow aspiration revealed a grossly hyperplastic
tissue with microscopic panhyperplasia of all normal marrow elements with nero-
blasts predominating. Myeloid: erythroid ratio, 1:4. Supravital differential: meta-
myelocytes neutrophilic 6.0 per cent, myelocytes "C" 78 per cent, myelocytes "B"
0.5 per cent, myelocytes "A" 0.5 per cent, myeloblasts 0.5 per cent, PMB 1 per cent,
PME 6 per cent, lymphocytes 0.5 per cent, phagocytic clasmocytes 5 per cent,
megakaryocytes 2 per cent; normoblasts 86.2 per cent, late erythroblasts 7.6 per
cent, early erythroblasts 3.6 per cent, megaloblasts 2.6 per cent; there were many
mitotic nuclear figures, particularly in the red cell series.

Emergency splenectomy was successfully accomplished by Dr. George Curtis five
hours after admission, while intravenous glucose-saline was being administered.
The release of cells was dramatic (fig. 3), the immediate pre- and postoperative
hematologic data, uninfluenced by blood transfusion, being as follows: WBC, 2,100
to 4,900; RBC, 1,010,000 to 1,990,000; hemoglobin, 2.8 Gm. to 5.6 Gm.; platelets,
16,000 to 114,000. The spleen weighed 1,400 Gm. and measured 25 x 15 x 5 cm.
Supravital studies of the fresh splenic pulp showed increased numbers of highly phagocytic clasmatocytes, 5 to 6 per oil immersion field, extracellular hemosiderin, with both normoblasts and myelocytes "C" in moderate numbers. A liver biopsy and mesenteric lymph node were secured for histologic study, and both were entirely normal in cellular and connective tissue structure.

There were no complications, and the hematologic and clinical improvements paralleled each other so that by the twelfth postoperative day the patient was discharged by automobile to her home in another city; WBC, 7,050; RBC, 3,030,000; PMN, 68 per cent; PME, 4 per cent; lymphocytes, 20 per cent; monocytes, 7 per cent; reticulocytes, 3.8 per cent; hemoglobin, 9.3 Gm.; hematocrit, 29 per cent; platelets, 2,637,000.

While our preoperative historical inquiry failed to reveal any evidence of a familial basis for this acute crisis, it became possible during the convalescence of this patient to question and examine the immediate blood relatives. The high reticulocyte level, the increased erythrocyte fragility, the clinical jaundice, the size and gross appearance of the spleen, and the "acute hemoclastic crisis," even in the absence of a generalized and uniform microcytosis, were all classical and typical of similar episodes, which we have seen and described in congenital hemolytic icterus. The father, one brother, and two sisters had essentially normal hemograms.

Fig. 3. Summary of five cases of primary splenic panhematopenia which have been followed for a year or more, illustrating the recovery and sustained elevation of all of the depressed circulating blood elements following splenectomy.
The mother, however, had a definite microcytic anemia of 3,250,000 red cells, 10.5 Gm. of hemoglobin, 7,200 leukocytes with 52 per cent neutrophils, 10 per cent eosinophils, 2 per cent basophils, 33 per cent lymphocytes, 3 per cent monocytes, and an increased erythrocyte fragility range of .450 to .366. Thus, it would seem that the evidence for a maternal, familial inheritance of splenic instability is present here, and that in this patient not only was a hemolytic process precipitated spontaneously, but also a concomitant profound neutropenia and thrombocytopenia, all three of which were promptly and dramatically corrected by surgical removal of the spleen.

Figure 3 summarizes the hematologic data in five patients, four females and one male, ranging in age from 6 to 67 years, in whom removal of the spleen was followed by a prompt and sustained "hemolytopoietic" re-equilibration. The bone marrow in every instance showed marked generalized compensatory cellular hyperplasia of all normal cell strains, without invasive foreign cell or toxic manifestations.

SPLENIC PANHEMATOPENIA, SECONDARY TO GAUCHER'S DISEASE

The spleen is secondarily involved in a great many general, constitutional, pathologic states, and we have observed for some time the tendency under such circumstances for the R-E system of cells to exercise their physiologic functions erratically and to an exaggerated degree. In one patient, Mrs. C. P., for example, with proven Hodgkin's syndrome, in whom the spleen was primarily and predominantly involved, both an anemia and neutropenia, requiring weekly whole blood transfusions, were relieved only following splenectomy, and a clinical remission of two years ensued. In another recent patient, Mr. F. J., with known Hodgkin's disease, a thrombocytopenic purpura, refractory to all medical measures, developed, and splenectomy was elected as a last resort and was followed by a return of the platelets and the disappearance of all purpuric manifestations. Another patient, Mr. J. B. G., with characteristic thrombocytopenic purpura hemorrhagica, with an entirely typical megakaryocytic hyperplasia in the bone marrow, and with the spleen not palpable, received an immediate and complete clinical and hematologic remission following excision of the spleen, which when removed, however, was grossly enlarged and showed pathognomonic Hodgkin's lesions microscopically. While without the usual signs and symptoms, and unsuspected preoperatively, the subsequent course of events fully confirmed the histopathologic diagnosis from the spleen.

The most classical, clinical example in our experience, of the indiscriminate sequestration of all circulating cellular elements by a spleen, enlarged and engorged secondary to a generalized constitutional disease, is that of the following young woman with Gaucher's disease.

Case 3. E. S., a 20 year old, white, single female was admitted to the Hematologic Service, University Hospital, April 15, 1945, with the chief complaint of a large abdominal tumor.* She had first noted some discomfort in the left upper quadrant...
two years previously. Enlargement of the abdomen had been gradual and painless but steady. She had bruised easily from early childhood, resulting in a gradually increasing mottled pigmentation of both lower extremities. There were increasingly frequent episodes of epistaxis. Her menstrual periods had become established on a thirty days’ cycle at age 13, with marked menorrhagia regularly lasting seven days or longer. Slowly increasing pallor, associated with the development of exertional dyspnea and an accentuation of all hemorrhagic phenomena, finally led her to seek medical advice from the family physician.

It became evident upon questioning that her reluctance to seek medical attention derived from knowledge of a similar abdominal enlargement in a younger sister some years earlier, requiring surgical management, which this patient feared. The patient was one of three children, two girls and one boy, of maternal Swedish and paternal German-Swiss parentage. In 1933, the sister, who is two years younger, was taken to Dr. Barnwell at the age of 6 years for a large intra-abdominal tumor, which had been noted since infancy by the parents, and was associated with episodes of vomiting and epistaxis. Examination at that time revealed an enormous spleen filling almost the entire abdomen, with a moderate enlargement of the liver. The superficial veins of abdomen and chest were dilated and prominent. Serial laboratory studies during an eight day period of observation revealed a progressive leukopenia, 3,600 to 1,300 white cells with a normal differential; a falling red cell count, 4,200,000 with 13.9 Gm. hemoglobin to 3,140,000, hemoglobin 10.5 Gm., and 74,000 platelets. The bleeding time was 9 min., the coagulation time 3½ min. Banti’s disease was the tentative diagnosis, and splenectomy was advised. A spleen ‘‘10 or 12 times normal size’’ was successfully removed. Convalescence was uneventful, and on discharge three weeks postoperative the white cells were 11,000 with a normal differential, the red cells 4,300,000, hemoglobin 14.3 Gm., and platelets 320,000. Sections from the spleen were subsequently submitted to a number of pathologists, including Dr. E. L. Saylor, Akron, Dr. P. Morse, Detroit, Dr. H. R. Wahl, Kansas City, and to our group, all of whom concurred in the diagnosis of Gaucher’s disease. Four months following splenectomy, this child was severely burned over the back from hair line to heels, requiring rehospitalization. Recovery was prompt and complete, and the blood reacted normally throughout the recovery period. In the intervening years, growth and development have been entirely normal, and no clinical symptoms or obvious signs of any constitutional disturbance have reappeared. The current hemogram as determined in this laboratory, at the time of the sister’s admission, April 15, 1945, was as follows: WBC, 12,950; RBC, 4,110,000; hemoglobin, 12 Gm.; reticulocytes, 1.4 per cent; platelets, 798,000. Supravital differential: PMN, 32 per cent; PMB, 1 per cent; PME, 6 per cent; lymphocytes, 53 per cent; monocytes, 8 per cent. Skeletal x-rays showed ‘‘thinning of the cortex and expansion of the lower third of the femur and also cortical thinning of the tibiae, significant of Gaucher’s disease.’’ A sternal marrow study revealed a hyperplasia with moderate left shift in both erythroid and myeloid elements, with an increase in very young monocytes and monoblasts. A few scattered Gaucher cells were present.

No other member of this family has shown any evidence of familial disease.
On the basis of his preceding experience, a tentative clinical diagnosis of Gau-
cher's disease was made by Dr. Roy Barnwell, when the second sister consulted
him. His initial laboratory data, April 2, 1945, showed: WBC, 3,100; RBC, 
3,170,000; hemoglobin, 10 Gm.; and again on April 10: WBC, 2,900; RBC, 3,000,000; hgb., 9.2 Gm. On admission to the University Hospital, the physical ex-
amination showed a well developed, well nourished young woman with prominent 
abdomen, in no obvious distress at rest. Temperature, 98.6°; pulse, 82; respirations, 
20; blood pressure systolic, 120, diastolic, 84 mm. Hg. There was moderate pallor of
skin, mucous membranes, and nail beds. Glasses corrected for astigmatism and 
hypermetropia, but there had been recurring conjunctivitis and the sclerae were
injected and reading was uncomfortable. There were minimal medial pinguiculae
bilaterally. On the left lower and upper eyelids were small papillomatous growths.
Fundiscopic examination was negative. There was no generalized lymphade-
nopathy. The lungs were clear to percussion and auscultation, but the heart was
displaced upward and to the left with an elevated left diaphragm. The spleen,
somewhat tender to deep palpation, filled practically the entire abdomen, the right
eye with notch extending 3 cm. to the right of the midline and downward to
within 2 cm. of the symphysis pubis. Enlargement of the liver could not be
detected. Extending from the patella to below the malleoli on both legs was a diffuse
mottled, reddish brown pigmentation, without edema. Neurologic examination
was entirely physiologic.

Admission blood studies showed: only 650 total white cells, 3,130,000 red cells,
8 Gm. of hemoglobin, and 68,860 platelets (fig. 4). The differential white count, as
nearly as it could be determined, gave 46 per cent mature neutrophils, 48 per cent
normal lymphocytes, and 6 per cent monocytes, with normochromic, normocytic
erthrocytes. Bleeding time was 6½ min., coagulation time 6 min. The Rumpel-
Leede test was positive. Corrected erythrocyte sedimentation index was 0.1 mm.
per min. Erythrocyte fragility range was 0.450 to 0.280. Sternal marrow aspiration
yielded a grossly hyperplastic tissue with normoblasts predominating, and the
following supravital differential cell count. Myeloid: erythroid ratio, 1:4.2; neu-
trophilic myelocytes "C", 80 per cent; myelocytes "B", 0.5 per cent; PME, 6.5 per
cent; PMB, 0.5 per cent; Gaucher's cells, 1.0 per cent; megakaryocytes, 3.0 per cent;
phagocytic clasmocytocytes, 8.0 per cent; plasma cells, 0.5 per cent. Erythroid ele-
ments: normoblasts, 96 per cent; erythroblasts, 2.7 per cent; megaloblasts, 1.3 per
cent. Single, scattered, but rare Gaucher's cells served to establish the diagnosis,
though no focal accumulations could be found. There was no significant shift
or diminution in the myeloid elements, though there was a moderate relative in-
crease in eosinophils. There was some focal increase in highly phagocytic clasmato-
cytes, none of which, however, contained abnormal fat vacuolization of Gaucher
fibrils, and there was no increase or qualitative change in the monocytes. Only a
rare plasma cell was observed, with qualitatively normal though slightly dimin-
ished megakaryocytes. Mitoses were rare in all cell strains. Other laboratory find-
ings included normal urinalysis, an NPN of 7 mg. per cent, fasting blood glucose
95 mg. per cent, and negative serology. An adrenalin test gave transitory, signifi-
cant increases in all of the circulating blood elements, as recorded in figure 4,
Spleenic Panhematopenia Secondary to Gaucher's Disease

Splenectomy resulted in complete hematologic and clinical recovery.
coincident with an appreciable shrinking of the spleen. X-ray examination of the long bones showed cortical thinning of the distal ends of both femurs and of the proximal ends of both tibiae suggestive of Gaucher's disease.

No contraindications having been discovered, and the particularly profound leukopenia persisting, splenectomy was urgently advised, and on April 19 a 5,100 Gm. spleen, measuring 41 X 20 X 8.5 cm., was removed by Dr. Verne Dodd without incident or surgical difficulty. The fresh organ was soft, pinkish red in color, and on cut surface many small pinpoint whitish areas were noted. On supravital examination of scrapings of the freshly cut surface, great syncytial-like sheets of large Gaucher cells were seen replacing much of the parenchyma. The cells were non-motile, varied from 50 to 50 micra in diameter, with a single eccentric nucleus, and 1 to 2 nucleoli; occasional cells contained as many as 4 nuclei. The cell membrane was delicate and easily ruptured. The cytoplasm was packed with Gaucher fibrils which were from 8 to 10 micra long, with fusiform tapered ends. They were seen as slightly to markedly curved bodies, grouped and arranged in strata-like formation around the nucleus. No mitochondria were seen. There was very little free cytoplasmic substance, owing to the compactness of the fibrils. The nuclei were 5 to 7 micra in diameter, and the chromatin was "blotchy" as described by Erf, with nucleoli occasionally noted. The nuclear membrane was well defined. None of the "spheroid cytoplasmic granules" described by Erf were noted. Films of the splenic scrapings, made by diluting with human serum and stained with Wright's Giemsa stain, confirmed the delicate character of the easily ruptured cell membrane and the thick blotchiness of the nuclear chromatin. The cytoplasm in these fixed preparations appeared to be composed of fine, light-blue-staining, reticular strands, with none of the fibrillar outlines discernible.

Liver biopsy confirmed the normal gross appearance of this organ, and no lymph nodes could be found in the mesentery for histologic study.

On chemical analysis the spleen was found to contain 10.3 per cent lipids. Further lipid fractionation and biologic studies are being carried out and will be reported later.*

The postoperative course was uneventful, with prompt re-establishment of a normal, peripheral hematologic picture (fig. 4). The patient was discharged on the ninth postoperative day and was seen again one month later. Both clinically and hematologically she has resumed a completely normal re-equilibration, with no complaints and an entirely changed psychology.

A survey of the literature, while recording the more or less striking influence of the splenomegaly on the circulating blood cells in Gaucher's disease, as proved by the hematopoietic re-equilibration which follows splenectomy, has failed to show an instance of so extreme a leukopenia with associated anemia and thrombocytopenia as the one cited here. It is a matter of degree only, however, and the inclusion of this case serves only to illustrate the general thesis relating to splenic dysfunction under pathologic conditions. Jaffé has reviewed in great detail the pathogenesis of Gaucher's disease. The younger the Gaucher cell the less distinct is the fibrillation of the cytoplasm, and it is between these fibrils that the specific storage of kerasin

* We are indebted to Dr. George Schett for these analyses.
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and cerebron, hemoglobin, and hydrophobic lipids, takes place, giving these cells their coarsely vacuolated appearance. It is possible that the great predominance of fibrils and the relative paucity of vacuolization of the Gaucher cells in our two patients reflect a generation of older, more mature cells and may correlate with the striking clinical chronicity and tissue localization of the pathognomonic cellular hyperplasia. The distinctive characteristics of these cells, as we have seen them in the supravital technic, have been adequately discussed and effectively illustrated by Erf.13

Differential diagnosis is at times difficult. Petit and Schleicher16 cite an instance in which sternal marrow aspiration established the diagnosis of Gaucher’s disease in an unexplained “atypical” anemia in a Jewish male 79 years of age, and Reisman and Utz17 emphasize their failure to find Gaucher cells in the marrow of a 10 year old Jewish refugee girl, in whom subsequently splenic puncture was performed with confirmation of the diagnosis.

Wilensky15 has reviewed the indications for splenectomy with particular emphasis upon the otherwise uncontrollable hemorrhagic manifestations. Mandelbaum and Berger19 report the removal of a 6,812 gram spleen for thrombocytopenia and hemolytic anemia, secondary to Gaucher’s disease, with lipid analyses by Sobel and Kaye.29 Dameshek21 reports a case of Gaucher’s disease and marked pancytopenia in which splenectomy was performed because of a well defined hemorrhagic tendency and because the spleen was so large that it interfered with the child’s locomotion. Following splenectomy, there was a dramatic response in all the blood elements, which has been sustained for seven years. Naegeli22 attributed the changes in the circulating blood cell equilibrium to a hyperfunction of the spleen, and not to an infiltration of the hematopoietic organs by the Gaucher cells. Dameshek concurs with these observations.

DISCUSSION

Our studies fully confirm Naegeli’s interpretation of splenic pathologic physiology, but we would not limit it to Gaucher’s disease. The additional advantage of observing and analyzing fresh, surgically removed, splenic tissue in the supravital technic, which identifies both the phagocytic cells and their engulfed content, strongly incriminates the splenic macrophages in all of the co-called hypersplenic syndromes. Platelets, as well as leukocytes and erythrocytes, can be readily recognized when present within the living splenic phagocytes, and the proportion of each, thus discovered sequestered and being destroyed in any spleen, is generally a good reciprocal index of the cellular units probably available in the circulation, when the bone marrow is not depressed. The number of phagocytic cells in an enlarged spleen, weighing 2 to 6 kilograms and frequently showing 10 to 12 macrophages per oil immersion field of the microscope, assumes astronomical figures, and the destructive capacity is correspondingly enormous. The immediacy and magnitude of the increase in circulating elements following splenectomy is a measure of the tremendous bone marrow potential, revealed only by the elimination of an abnormal splenic influence.

The differential diagnoses, which must be considered objectively and judicially
by the clinician in the syndrome we are here discussing, are threefold: (1) a hypoplastic bone marrow, either primary, idiopathic, or secondary to some noxious agent;23 (2) splenic panhematopenia secondary to some constitutional pathologic process which involves the spleen predominantly and disturbs its finely adjusted physiologic functional balance; and (3) primary splenic panhematopenia on a congenital or familial basis. Complete data from the adrenalin test* and careful sternal marrow aspiration analyses should provide the information upon which to base an opinion and advise therapy. Elective splenectomy in the first two mechanisms may, and frequently does, result in a more or less temporary and abortive but definite remission of those signs and symptoms dependent upon the disturbed cellular balance, and it may or may not influence materially the fundamental underlying disease; but in the last named syndrome, where the spleen apparently is primarily at fault, a prompt, complete, and permanent re-equilibration, hematologic and clinical, may be anticipated and predicted with some assurance.

SUMMARY

1. The spleen is an organ of multiple structures and many functions, but in the interests of human health and disease, it is probably far more important pathologically than physiologically.

2. It has been abundantly proved that instability in splenic functional balance toward any one of the essential elements of the blood passing through this organ may be an inherited trait, as in congenital hemolytic icterus. Recognition is now made of a syndrome in which, despite intensive compensatory panmyeloid hyperplasia, indiscriminate elimination of all circulating elements occurs, actually simulating panmyeloid hypoplasia. Splenectomy in such a syndrome is often dramatically curative. "Primary splenic panhematopenia" is suggested as an appropriate descriptive designation.

3. The potentially important role which may be played by the spleen, secondarily involved in a wide variety of syndromes, with the precipitation of varying degrees of peripheral cellular disequilibria, demands careful diagnostic discrimination. A dependable experience in the specific technics by which bone marrow and splenic functions are appraised is essential to sound judgment and clinical acumen.

4. The normal spleen is apparently not essential to life and health at any age and, therefore, may be surgically removed without prejudice to future hemopoietic equilibria and longevity. The pathologic spleen may at times constitute a very real hazard to health and an actual threat to survival; in the more acute syndromes, prompt surgical intervention may be lifesaving.

*Technic of the adrenalin test: During a fifteen to thirty minute base-line period, under basal metabolic conditions, the pulse, blood pressure, and two preliminary complete peripheral blood studies are obtained and the splenic outline is traced. Depending upon the age and vascular integrity of the patient, 0.5 to 1 cc. of 1:1,000 adrenalin chloride is injected subcutaneously. Blood studies are repeated at ten minute intervals until the pulse and blood pressure reach their maximum stimulation, which usually coincides with the greatest contraction of the spleen. The peripheral blood studies are then continued at fifteen minute intervals until the spleen has relaxed and the biphasic depression of the curve has been obtained.
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PRIMARY CONGENITAL AND SECONDARY ACQUIRED SPLENIC PANHEMATOPENIA

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