HEMATOLOGIC EFFECTS OF SPLENECTOMY IN STILL-CHAUFFARD-FELTY SYNDROME

A Report of Two Cases

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THE interrelationships of the blood, the bone marrow and the spleen remain among the major problems in hematology. Anemia, granulocytopenia and thrombocytopenia when present alone or occurring together are often associated with splenomegaly and a hyperplastic bone marrow. This triad, with variations and certain complicating factors, has been known for many years and has been noted in such diverse disorders as chronic tuberculous splenomegaly, hepatic cirrhosis, chronic arthritis, as well as in chronic malaria, leishmaniasis and other conditions with splenomegaly. Banti's syndrome, aplastic anemia, splenic anemia, Still's disease, Still-Chauffard's disease, Felty's syndrome, hypersplenism, hypoleukia splenica, myelosplenic syndrome, chronic agranulocytosis, and primary splenic neutropenia are some of the terms which have been more commonly used in describing these cases in the literature.

Confusion has been perpetuated by the lack of complete knowledge of the physiology and pathology of the spleen and its relationships to the bone marrow. In general, two concepts of the pathogenesis of this pancytopenic syndrome have arisen. Most European clinicians have adhered to the theory that a hormonal relationship exists between the spleen and marrow. According to this concept, a pathologically hypertrophied spleen produces a hormone which suppresses the maturation of blood cells in the marrow and their release to the blood. This hormone is thought to be produced by the reticulo-endothelial cells of the spleen and may act on all the cellular elements in the marrow at one time or be selective for the megakaryocytes, erythroid cells or granulocytes. The *normal* physiological maturation and release of blood cells in the marrow is perhaps controlled by a hormone which is also elaborated in the spleen or reticulo-endothelial system. This theory was apparently first publicized in 1912 by Isaac[1] in his interesting description of a case of splenic anemia and was further developed by Türk,[2] Frank,[3] Lauda,[4] Engelbreth-Holm,[5] Schousboe,[6] and Buchem.[7] Naegeli[8] was one of its champions and used the term "hypersplenism" with great effect in his description of cases in which the syndrome appeared. Dameshek[9, 10, 10a] in this country has also used this term and has come out strongly for the hormonal concept of spleen-bone marrow relationships. Most American hematologists on the other hand have fostered the "phagocytic" hypothesis, in which the anemia, leukopenia and thrombocytopenia are thought to be due to the increased phagocytic activities of an enlarged spleen. The rate of destruction of blood cells is thought to exceed the rate of formation in the marrow, and cytopenia of a pure or combined type occurs.

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Wiseman and Doan[11] submit histopathologic evidence of phagocytosis in the spleen in support of the theory. They evidently accord little value to the concept of hormonal "hypersplenism." Doan and Wright[12] have recently re-emphasized their views in an article on "Splenic Panhematopenia."

The occurrence of "hypersplenism" in association with chronic arthritis has been reported many times. Singer and Levy[13] have carefully reviewed the literature which preceded Felty's report. Splenectomy has been used therapeutically in several cases. Steinberg[14] in his investigation of the literature found that the results following splenectomy were not very satisfactory. Craven's case[14] died 14 months after operation and Hanarahan and Miller's case survived only 18 months.[14] Steinberg's patient became mentally depressed and weak following the splenectomy but was alive at the time he wrote his paper. Loeper, Andre and Patel[15] described a case without leukopenia in which death from bronchopneumonia occurred four weeks after splenectomy. Dameshek's patient[10] had a favorable hematologic response in addition to an increased resistance to infection. Of the two cases herein reported, the first is of particular interest because the patient has survived splenectomy five years and has maintained a greatly improved state of health.

Case No. 1. C. K., a white married female, age 35, was admitted to the Medical Service on Oct. 7, 1940, with a history of arthritis, weakness, anemia and a weight loss of 20 pounds during the preceding three years. She had been well until four years prior to her admission. At that time she noted the rather abrupt onset of pain and stiffness in the joints of her hands and feet. It became necessary for her to discontinue her work as an elevator operator. Flexion deformity of the hands soon followed, and pain and stiffness in the shoulders, vertebral column, elbows and knees appeared during the succeeding months. The past history revealed that two years prior to admission she was observed at another hospital where a diagnosis of aplastic anemia was made. Upper respiratory infections, sinusitis, and stomatitis occurred frequently during these years and she stated that a fever of 100° and 101° was present most of the time. Just prior to her admission she was unable to get out of bed because of weakness and deformity. The past history and family history were irrelevant.

Physical Examination: The patient was a small, thin, pale woman. The weight was 42.5 kilo. (93 lbs.), temperature 101°F., pulse 118 per minute. The joints, including those of the vertebral column, showed limitation of motion most marked in both elbows. Flexion deformities typical of the moderately advanced rheumatoid arthritic type were present in the hands and feet. The ankles were surrounded by soft tissue swelling. She was completely unable to walk. A chronic muco-purulent nasal discharge was present. The mouth was normal except for dental caries and hypertrophic pharyngitis. A loud systolic murmur was present over the entire precordium. The liver edge was palpable, smooth and non-tender, and a large non-tender spleen extended to the iliac crest and the mid-clavicular line. No palpable lymph nodes were evident. The skin was normal. A blood study on the day following admission revealed: R.B.C. 3.75 million, Hb. 9.5 Gm., W.B.C. 850, mature polymorphonuclears 0, band forms 7 per cent, lymphocytes 62 per cent, monocytes 31 per cent, hematocrit 32 per cent, M.C.V. 86 cu. microns, M.C. Hb. 25.3 γγ, M.C. Hb. Conc. 29.7 per cent, platelets 130,000 (normal 250,000 to 450,000), reticulocytes 4.5 per cent, 32 stippled erythrocytes per 100 leukocytes, erythrocyte fragility test (Sanford) normal, bleeding time (Duke) 5½ minutes, coagulation time 9½ minutes, capillary erythro-permiability test (Rumpel-Leede) negative, clot retraction time normal. A smear of marrow aspirated from the sternum on Oct. 9, 1940, showed very extensive hyperplasia of all myeloid cells with crowds of myelocytes and metamyelocytes and increased numbers of promyelocytes and myeloblasts. The erythroid cells were normoblastic and numerous. A gastric analysis showed achlorhydria. The icterus index was 9.6 and the Van den Bergh negative. Roentgenograms of the long bones and vertebral bodies were normal, i.e., there was no evidence of osteoporosis or joint destruction. The urine was negative and pyelography was normal. The electrocardiogram showed no abnormalities. Two blood cultures were negative. On Nov. 4, 1940, a splenic puncture was performed. A smear of the aspirated material revealed many lymphocytes and an apparently

increased number of reticulo-endothelial cells. There was no evidence of phagocytosis in several smears. Only a few granulocytes were seen. The culture was negative.

From Oct. 4, 1940, to Jan. 10, 1941, treatment consisted of blood transfusions, pentnucleotide, yellow bone marrow, ferrous sulfate and liver extract. There was no essential improvement in the patient's condition. The temperature varied between 99° and 103° F. During December 1940, an attack of acute maxillary sinusitis occurred. Splenectomy was finally decided upon and performed on January 10, 1941, without difficulty. The spleen was about the size of a football and weighed 1150 Gm. When the hemostats were removed from the pedicle, blood gushed to a height of about four cm. from the splenic vein and the enlarged organ collapsed to about two thirds of its original size. Epinephrine was not used during the course of the operation. Smears made from the splenic pulp were essentially the same as those made from the aspirated pulp obtained in November. Histologic examination of the spleen revealed a lattice-work type of architecture with widely separated malpighian corpuscles. The capsule and trabeculae were thin.

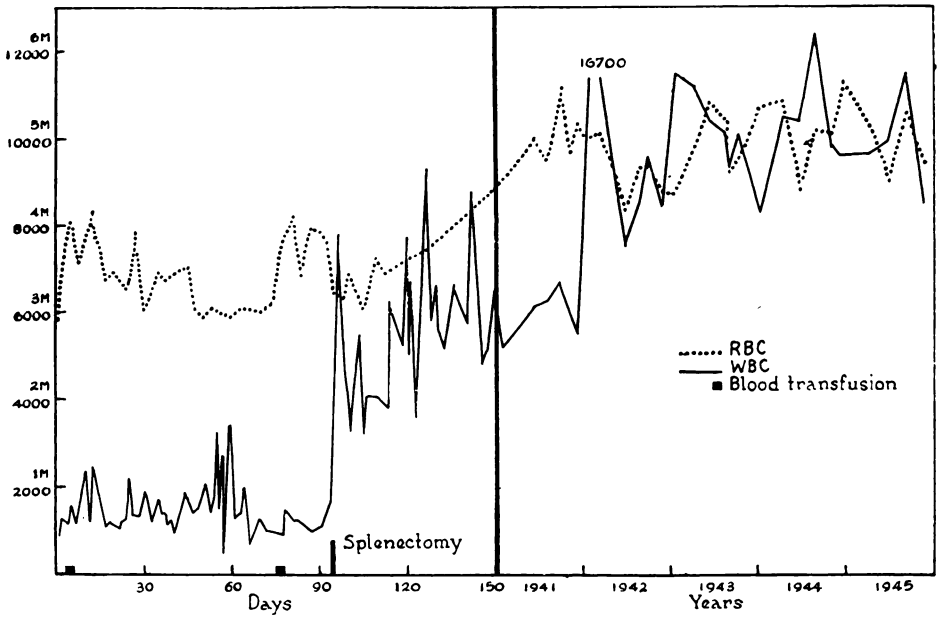

FIG. 1. LEUKOCYTE AND ERYTHROCYTE FLUCTUATION IN CASE 1

The red pulp of the spleen showed cleft-like spaces with widely dilated sinusoids containing erythrocytes and many lymphocytes. Some of the sinusoids appeared to be plugged with large histiocytes. The Billroth cords were prominent and eosinophilic but showed only a very slight increase of connective tissue. Most of them were speckled with lymphocytes and histiocytes. The usual follicles were quite large and widely separated from each other. The lymphoid components of the peripheral portion of the follicles merged indistinctly with the adjacent pulp. Central arterioles were very eccentrically placed. The usual follicle had a very prominent germinal center, composed of large cells with abundant cytoplasm. Minute particles of chromatin debris and blood pigment were visible and an occasional plasma cell was seen. There was no evidence of phagocytosis by histiocytes or other reticulo-endothelial cells observed in the sections.

The patient's postoperative course was uneventful except for a great increase in appetite. She was discharged from the hospital on March 9, 1941, able to walk haltingly without assistance. During the six months following the splenectomy she gained 13.2 kilo. (29 lbs.). Physiotherapy greatly increased the mobility of her joints, and by the end of 1941 she was able again to do her housework. During the last four years she has been able to climb stairs and ride on a bus without assistance. She does her own washing and ironing. The chronic sinusitis appears to have completely disappeared.

On Dec. 5, 1945, approximately five years later, she weighed 54.3 kilo. (115 lbs.). The blood sedi-

mentation rate at this time was 12 mm. (Wintrobe corrected). Examination of the blood revealed R.B.C. 4.71 million, Hb. 13.5 Gm., M.C.V. 95.7 cu. microns, M.C. Hb. 28.7 γγ, M.C.Hb. Conc. 30 per cent, W.B.C. 8,500, mature polymorphonuclears 35 per cent, band forms 12 per cent, eosinophiles 3 per cent, lymphocytes 35 per cent, monocytes 15 per cent. There were 80 erythrocytes with Howell-Jolly bodies per 100 leukocytes. Platelets were 276,000 per cu. mm. and reticulocytes 1.3 per cent. The arthritis had been reduced to a residual state of permanent flexion deformity of both hands and feet with slight limitation of motion in the left elbow. A graphic synopsis of the blood studies is presented in Fig. 1. A differential analysis of sternal marrow cells before and after splenectomy is found in table 1.

TABLE 1.—*Differential Counts of Sternal Marrow Smears (Case 1)*

Splenectomy resulted in a relative increase in more mature forms, a diminution in cells of the erythroid fraction and a pronounced increase in lymphocytes.

	Before splenectomy		1 mo. after splenectomy 2/11/41
	10/9/40	1/11/41	
	%	%	%
Myeloblasts	2.6	1.8	0.8
Promyelocytes	3.8	2.2	2.4
Myelocytes	26.2	17.4	10.8
Metamyelocytes, neutrophilic	17.4	20.0	19.4
Granulocytes, neutrophilic band	8.6	5.8	12.8
Granulocytes, neutrophilic segmented			1.2
Eosinophiles	1.0	1.6	1.8
Basophiles	0.2		0.2
Monoblasts			1.0
Monocytes		1.2	5.6
Lymphocytes	5.8	7.4	30.2
Plasma cells	0.6	0.2	3.6
Proerythroblasts	1.4	2.2	0.2
Basophilic normoblasts	6.2	12.4	0.2
Polychromatophilic normoblasts	10.8	13.8	1.0
Orthochromatic normoblasts	14.0	13.0	7.6
Megakaryocytes			0.2
Histiocytes		0.2	
Unidentified blasts			0.8
Cells in mitosis	1.4	0.8	0.2

Case No. 2. E. E., a white, single female, age 49, was admitted to the Medical Service on Aug. 25, 1941 complaining of inability to care for herself. She was a Christian Scientist and would make no statements regarding pain. Four years prior to admission she began to notice stiffness in her knees, ankles and wrists. Two years later the fingers of both hands became stiff and flexed so that she was unable to continue her occupation as an artist. Since then she had gradually become bedridden and helpless and was brought to the hospital for nursing care.

Physical Examination: Weight 54.5 kilo. (120 lbs.), temperature 99.6, pulse 80, blood pressure 94/62. The patient was unable to sit up without assistance. Moderately severe flexion deformity of all joints of the extremities was present. The hands had the typical appearance of advanced rheumatoid arthritis, with glossy smooth skin and ankylosis. A loud systolic murmur was heard over the entire precordium. The spleen and liver edges were both palpated about 3 cm. below the costal margin. These organs were firm

and smooth. The remainder of the examination was insignificant. There were no enlarged lymph nodes and the skin was not pigmented. Examination of the blood shortly after admission revealed W.B.C. 950, segmented polymorphs 1 per cent, band forms 6 per cent, eosinophiles 2 per cent, basophiles 1 per cent, lymphocytes 83 per cent, monocytes 7 per cent. R.B.C. 3.59 million, Hb. 10.25 Gm., hematocrit 38 per cent, M.C.V. 108 cu. microns, M.C.Hb. 29 γγ, M.C.Hb. Conc. 27 per cent. There were 50 stippled erythrocytes per 100 leukocytes. There were 282,000 platelets and the icterus index was 9.7. Free hydrochloric acid was present in the gastric secretion. Blood culture was negative. Roentgenograms of the hands and knees revealed almost complete loss of joint space as well as mild hypertrophic arthritis. Osteoporosis was present in the bones of the wrists, hands and vertebral column. The urine was normal. Splenic puncture was not attempted because of the relatively small size of the palpable spleen. Sternal marrow aspiration revealed a slightly hyperplastic marrow with a left shift in both the myeloid and erythroid cells (table 2). A low grade fever of 99° to 101° was present almost daily. This patient, because

TABLE 2.—*Differential Count (500 Cells) of a Sternal Marrow Smear before Splenectomy (Case 2)*

	%
Myeloblasts	0.0
Promyelocytes	9.2
Myelocytes, neutrophilic	7.2
Myelocytes, eosinophilic	2.4
Metamyelocytes, neutrophilic	8.4
Metamyelocytes, eosinophilic	5.4
Granulocytes, neutrophilic band	5.2
Granulocytes, neutrophilic segmented	1.2
Eosinophiles	8.4
Basophiles	
Monocytes	0.6
Lymphocytes	12.6
Plasma cells	3.8
Proerythroblasts	0.4
Basophilic normoblasts	3.2
Polychromatophilic normoblasts	23.6
Orthochromatic normoblasts	6.8
Megakaryocytes	0.2
Unidentified cells	1.2

of her religion, was for some time not interested in accepting treatment. After a period of depression she became anxious to submit to any type of therapy. A splenectomy was recommended with the understanding that her advanced arthritis might not be changed but that the blood picture might approach the normal.

On Nov. 10, 1941, splenectomy was performed. Blood was taken from the splenic artery and splenic vein before their ligation. The spleen and two small accessory spleens were removed. The enlarged spleen was adherent in part to its bed. A liver biopsy specimen was removed. Smears of splenic pulp were prepared immediately. They showed as many as 8 to 20 nucleated cells per oil immersion field. Approximately 90 per cent of these cells were lymphocytes. Plasma cells, eosinophiles and a few band and segmented granulocytes were also present. Platelets were always aggregated in groups of about 20 to 80 platelets. Cells readily identified as monocytes were occasionally seen. Many of the reticulo-endothelial cells were very similar to monocytes. An occasional "blast" form with 3 to 5 nucleoli was observed. Typical, large reticulo-endothelial cells were present singly and in groups of 2 to 5 throughout the smears. They accounted for less than half of 1 per cent of all the cells. About half of the adult reticulo-endothelial cells which were observed revealed evidence of phagocytosis and digestion of other cells. The ingested cells were pyknotic and were undergoing lysis, as evidenced by weak and altered staining and loss of structural outline. The remnants of ingested band and segmented granulocytes, erythrocytes, platelets

and lymphocytes were seen. Frequently the type of ingested cell could not be determined and often several different cells were found included in one reticulo-endothelial cell. Section of the splenic tissue revealed prominent follicles and fibrosis of the red pulp. The trabeculae were thin and the Billroth cords thickened and acellular in many places. The sinusoids were outlined clearly in some areas but were very narrow and compressed in others. Plasma cells and lymphocytes were prominent throughout the pulp. The malpighian corpuscles were prominent and had a sharp lymphocytic periphery. The germinal centers were unduly large and active. Many of the cells were pyknotic and mitosis was seen. The sections showed no evidence of phagocytosis by reticulo-endothelial cells. The spleen weighed 525 Gm.

The patient had a stormy postoperative course which was precipitated on the fourth day by a sudden hemorrhage from the incision. She had received 100 mg. of heparin during the day because of the rising platelet count. The wound was slow in healing and on the twenty-second day she developed ascites and ankle edema. The temperature fluctuated between 100° and 101°. On the thirty-seventh day it was necessary to perform an abdominal paracentesis, releasing 7600 cc. of cloudy fluid. The patient expired on the next day. The changes in the blood picture following splenectomy are tabulated in table 3.

TABLE 3.—*Changes in the Blood following Splenectomy (Case 2)*

Date	W.B.C. (per cu. mm.)	Band forms	Mature polys.	Eos.	Lymph.	Mono.	Baso.	Platelets (per cu.mm.)	Howell-Jolly bodies per 100 W.B.C.
	%	%	%	%	%	%	%		
11/7/41	1200	1		8	76	16	2	122,000	0
11/10/41 (before removal of spleen. Patient under general anesthesia)	1500	28	2	2	58	10	0	129,000	6
3 hours after splenectomy	1800	67	10	0	14	9	0	220,000	1
1st post-op. day	8400	not done						269,000	not observed
2nd post-op. day	6500	47	32	2	9	10	0	473,000	2
3rd post-op. day	5500	37	49	2	8	4	0	385,000	6
4th post-op. day	4550	28	52	0	16	4	0	296,000	38
5th post-op. day	5000	28	45	2	17	8	0	424,000	20

An autopsy was performed and the following pertinent findings reported. There were contractures of the thighs and legs, and both legs were edematous. One and a half liters of thick, cloudy fibrino-purulent fluid were found in the abdominal cavity. Heavy fibrinous adhesions were present between the liver and the diaphragm and between the transverse colon and the abdominal wall. The esophagus was dilated and contained large, dilated tortuous vessels. Both lungs were attached to the thoracic wall by old fibrous adhesions. The tracheo-bronchial lymph nodes were enlarged, fused, deeply pigmented and soft. The heart was normal except for slight atheromatosis in the proximal portion of the ascending aorta. The liver weighed 2030 Gm. Its surface was slightly granular, and when cut, the lobules were seen to be surrounded by small white depressions. Microscopic examination of the liver tissue obtained during the splenectomy and at autopsy revealed marked fatty degeneration in the peripheral portions of the lobules and hyperplasia of the peri-portal connective tissue with lymphocytic, eosinophilic and plasma cell infiltration in these areas. The bile canaliculi were dilated. The greatly thickened gallbladder was distended and contained three mixed cholesterol calculi, each about 1½ centimeters in diameter. The portal vein was completely thrombosed at its point of entrance into the liver. Purulent degeneration was present in the center of the thrombus, which was firmly adherent to the lining of the vein. Thrombosis was present in all the intrahepatic branches of the portal vein which could be seen. The splenic vein pedicle was completely thrombosed, and the mesenteric veins supplying the large and the distal portions of the small intestine were almost completely thrombosed. The stomach, intestine, kidney, adrenals, pelvic organs and lymph nodes were essentially normal. Microscopic examination of an abdominal lymph node

revealed indistinct germinal centers composed of small, deeply stained lymphocytes. Sinusoids distended with erythrocytes, lymphocytes and some plasma cells were present.

DISCUSSION

It is quite evident that splenectomy was followed by an increase of the granulocytes in the peripheral blood in both cases. This occurred almost immediately in case 2 but more gradually in case 1. Both patients presented monocytosis before and after splenectomy. Post-splenectomy thrombocytosis was present in each, and case 1 was characterized by a gradual and complete recovery from the anemia.

If the enlarged spleen were phagocytizing cells from the blood stream one would expect a difference in cell counts between blood in the splenic artery and that in the splenic vein. Passage through the spleen should perceptibly change

TABLE 4.—*Comparison between Blood from the Splenic Artery and Splenic Vein (Case 2)*

The blood was obtained immediately before the spleen was excised.

	Splenic artery	Splenic vein
R.B.C. (millions)	4.29	4.12
Hemoglobin (grams)	13.0	13.0
Hematocrit (%)	38	43
M.C.V. (μ^3)	90	104
M.C. Hb. ($\gamma\gamma$)	30	31
M.C. Hb. Conc. (%)	34	30
W.B.C.	11,700	2,600
Myelocytes (%)	1	0
Metamyelocytes, neutrophilic (%)	1	0
Granulocytes, neutrophilic band (%)	9	8
Granulocytes, neutrophilic segmented (%)	1	3
Eosinophiles (%)	6	0
Basophiles (%)	0	0
Monocytes (%)	8	14
Lymphocytes (%)	71	74
Plasma cells (%)	3	1

the character of the blood. In case 2, blood was taken from the splenic artery and the splenic vein just prior to their ligation before excision of the spleen. The leukocyte count in the splenic arterial blood was 11,700, while the count in the splenic venous blood was similar to what had been observed in the peripheral blood prior to the splenectomy, namely 2,600 per cu. mm. Examination of the blood smears verified the difference in the concentration of the leukocytes. Doan has recently reported a similar observation.[16] Table 4 expresses a comparison between the splenic arterial and venous blood. Examination of the differential counts reveals similarity except for a greater left shift and eosinophilia in the arterial blood and a higher percentage of monocytes in the venous blood. If leukocytic phagocytosis occurs in the spleen it would be expected, on the basis of this observation, that it would affect evenly all cell types, with a slight preference for the younger cells. The evidence in this case, that more leukocytes enter than leave the spleen, tends to favor the phagocytic rather than the hormonal theory.

The adherents of the hormonal theory base their belief on several observations, of which the most important is the apparent immaturity and maturation arrest which is seen in marrow smears. The great numbers of erythroblasts and myelocytic cells and, at times, megakaryocytes which are seen crowded in the smears and the paucity of mature or even relatively mature cells lead the observer to a conclusion that maturation arrest is present. If mature cells are present in the marrow and diminished in the blood it is concluded that there is faulty emission of cells from the marrow. Histological evidence of cellular phagocytosis in the spleen is seldom sufficient to explain the hyperplasia in the marrow. A more convincing argument depends upon the observation that after splenectomy the number of blood cells rises slowly over a period of days and sometimes weeks, according to a pattern of escape from maturation arrest. If the spleen were merely phagocytizing, one would expect a very abrupt increase in cells in the blood after splenectomy. Then, too, the phagocytic theory fails to explain the presence of old segmented granulocytes and the absence of metamyelocytes and myelocytes when peripheral leukopenia is present. The opposite would be expected. It is difficult to believe that, with a leukocyte count of 850 in the presence of a very hyperplastic marrow, metamyelocytes would be absent from the peripheral blood if the spleen were removing great numbers of leukocytes. A marrow thus strained to the limit of its productive capacity would pour immature cells into the blood in great profusion and one would expect them to predominate in the blood residue.

The experiments of Bock and Frenzel[17] and of Jombres[18] may eventually help explain the phenomenon. The former investigators ligated the splenic vein and the gastric coronary veins in rabbits in such a way that the venous outflow from the spleen passed into the esophageal veins and the superior vena cava by way of the left gastro-epiploic vein and a collateral circulation in the stomach. This double ligation prevented blood which left the spleen from passing through the liver. The rabbits developed the "hypersplenic" syndrome. Jombres performed essentially the same experiment and observed that the femoral marrow became hyperplastic several weeks after ligation. It is possible that an essential factor in the mechanism of "hypersplenism" is a retardation of blood flow through the spleen. Bock and Frenzel and Jombres adhere strictly to the hormonal theory of hypersplenic suppression of the marrow and propose that the liver enters into the hormonal mechanism inasmuch as their ligations effectively prevent splenic venous blood from passing through the liver.

The answer to the problem of "hypersplenism" may eventually be found in a combination of the hormonal and phagocytic theories. The evidence now available supports, in part, both sides. Thus "hypersplenism" may well have a complex origin.

SUMMARY AND CONCLUSION

Two cases of Still-Chauffard-Felty syndrome treated by splenectomy are presented. One case has survived five years with complete hematologic restitution and definite improvement in the arthritis. The second case expired six weeks after

splenectomy. Autopsy revealed portal vein thrombosis (pylephlebitis). Both cases exhibited the blood manifestations associated with "hypersplenism." In both cases splenectomy resulted in a return of the peripheral blood picture to relative normality.

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