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Circulatory Dynamics of the Spleen

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Summary

Circulatory dynamics are examined in terms of the open and closed circulation, pathologic changes in blood dyscrasia and portal hypertension, and the rationale of circulatory control (ischemic therapy) in treatment of hypersplenism.

A. General Considerations

As a major component of the reticuloendothelial system, and as the largest lymphopoietic organ in the general circulation, the adult human spleen receives a sizable volume of blood (> 250 liters) every 24 hours. Although numerous minor variations exist in the anatomical arrangement of the splenic blood supply, the predominant pattern consists of a solitary artery arising from the celiac axis that passes along the superior surface of the pancreas in gentle twists or tight coils before bifurcating or trifurcating near the splenic hilum (1). From there, polar arteries segmentally supply discrete intrasplenic compartments (Fig. 1). Subsidiary auxiliary sources originate from peripancreatic and perigastric arteries with splenic venous efflux contributing 10–20% to portal blood flow (2). Because venous valves are rudimentary or lacking altogether in the portal system, hydrostatic pressure in splenic venous blood is virtually identical to that in the portal vein (~8–12 mmHg) and freely transmitted to the splenic pulp. Whereas the topography of the extrasplenic circulation has been clearly defined, the nature of splenic microcirculatory dynamics remains vigorously contested.

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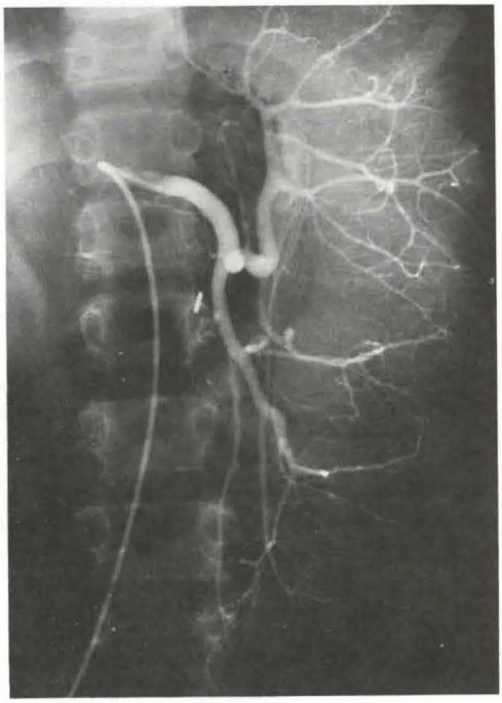
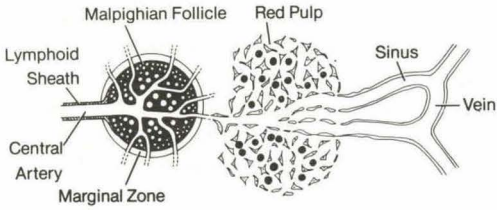


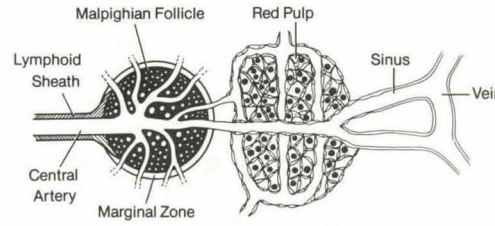
Fig. 1 Superselective splenic arteriogram in a 7 year old boy with histiocytosis-x and an enlarged spleen. Note the segmental distribution of the splenic arterial circulation with little or no collateralization among compartments

For more than 100 years, debate has raged over whether the intermediary circulation of the spleen is "open" or "closed", that is, whether arterial capillaries open freely into the spongy red pulp from which blood elements are squeezed back into venous sinuses (3), or alternatively arterial capillaries com-



Intermediary Circulation of the Normal Spleen

Fig. 2 Schematic diagram illustrating the "open" nature of the intermediate circulation of the human spleen. Although affected by environmental conditions (e.g. anesthesia, anoxemia), the vast bulk of splenic arterial blood after supplying lymphoid tissue and passing through the marginal zone "opens" into the spongy network of the red pulp. In these splenic cords, cellular traffic intensifies as blood elements are pushed and squeezed forward into venous sinuses through large interendothelial gaps (compare with Fig. 3)



Intermediary Circulation of the Spleen in Portal Hypertension and Certain Blood Dyscrasias

Fig. 3 Schematic diagram demonstrating the "closed" nature of the intermediate circulation of the human spleen as seen in pathologic states. Disorders characterized by white pulp hypersplasia (e.g. myeloid metaplasia, chronic lymphocytic leukemia) and/or reticuloendothelial proliferation (e.g. hepatic cirrhosis) are associated with increased blood flow and progressive deposition of reticulum and collagen fibers in the meshwork stroma. As endothelialization and fibrosis matures, blood flow from central arteries to venous sinuses is more direct (i.e. closed), and cellular elements in the red pulp are increasingly trapped and "concentrated". Although overall splenic blood flow is accelerated and streamlined, that in the red pulp is progressively "congested" and stagnant. Splenomegaly and secondary hypersplenism are clinical manifestations of this pathologic process

municate through intact endothelial lined channels (hence "closed") with draining venous sinuses and from which blood elements enter red pulp via interendothelial gaps as elsewhere in the body (4).

Although this issue is far from settled, it seems reasonable that both mechanisms operate depending on external conditions (e.g. temperature, anesthesia, operative manipulation), the nature of the spleen itself (e.g. normal or diseased) and the species studied (e.g. human, rabbit, mouse). From intrasplenic distribution of tiny rigid microspheres (0.5–2.5 μm) injected intravenously into rabbit spleen (a mammalian organ that resembles microscopically human spleen) and dissection scanning electron microscopy of human spleen, it has been shown that in the resting, unanesthetized subject the vast bulk of splenic microcirculatory flow opens directly into red pulp while only a small fraction crosses directly into sinuses and splenic venous blood (5, 6) (Fig. 2). This interrelationship varies considerably, however, in pathologic states (e.g. hemolytic anemia, fibrocongestive splenomegaly) (7, 8) and becomes a critical factor not only in modulating splenic immunity but also in regulation of portal pressure and flow.

Because the general architecture of the spleen resembles a loose honeycomb, the rate of cellular migration through the splenic meshwork (i.e. red pulp) is generally slow*. The open spongy nature of the cords is ideally suited for sequestering and destroying senescent or deformed red blood cells, and this activity is a prime function of the normal spleen. In disorders characterized by increased cellular traffic in the cords, heightened red cell fragility, or greater impedance to splenic venous flow, intense red pulp congestion supervenes.

*This unusual feature does not mean necessarily that *total* splenic blood flow is sluggish. A narrow waterway emptying into a wide lake may undergo a sharp reduction in velocity in conformity with the changing dimension in cross-sectional area. Unless, however, downstream obstruction to runoff from the lake develops, volume flow overall is maintained.

In the Malpighian bodies of the white pulp, capillary flow is more direct, and during immunostimulation, these lymphoid follicles enlarge and total splenic blood flow increases. This latter response exemplifies the work hypertrophy concept of splenic enlargement wherein circulating particulates or antigens stimulate splenic cellular reactivity (9) often with a rise in blood flow. In some circumstances these responses are accompanied by alterations in the splenic reticulum matrix, and blood elements in the interstices of the cords thereby become increasingly trapped. At this stage healthy red cells as well as other blood elements are prematurely destroyed. Indeed, when cellular elements are very tightly clustered as in sickle cell anemia and chronic myelogeneous leukemia, blood flow in the cords becomes precariously impaired. As inadequate oxygenation develops and persists, frank segmental or total infarction ensues sometimes with spontaneous rupture of the spleen.

B. Pathologic States

1. Blood Dyscrasia

In many disorders of circulating blood elements, a derangement in splenic activity coexists. In leukemia, myeloma, lymphoma and other primary white cell diseases, enlargement of Malpighian corpuscles with cellular reactivity and erythrophagocytosis within the cords is so common that splenectomy is often performed either to stage the extent of malignant spread or to facilitate intensive cytotoxic therapy. Although neoplastic spleens are usually enlarged and sometimes immense, hemodynamic consequences are infrequent except for rare instances of spontaneous arterial thrombosis with splenic infarction and abscess formation, or conversely, profoundly hyperdynamic blood flow associated with portal hypertension (vide infra). In contrast to pathologic conditions of white blood cells, splenic circulatory dynamics play a key role in red cell and platelet dysfunction. For example, in congenital hemolytic anemia such as sickle cell disease, thalassemia, spherocytosis or pyruvate-kinase deficiency, biophysical defects in the hemoglobin molecule or cell membrane render the erythrocyte especially sensitive to splenic sequestration and destruction. Because these patients commonly require frequent blood transfusions, a combination of iron overloading and red cell breakdown favors development of splenomegaly. As cellular traffic increases, the red pulp becomes progressively more congested and a gradual shift develops away from an "open" to "closed" circulation. Despite the sluggish flow in the cords, however, splenic blood flow through central arteries emptying directly into venous sinuses may remain rapid. Nonetheless, in the absence of rising resistance downstream, splenic venous pressure is minimally affected (10, 11). As time elapses, white blood cells and platelets are also entrapped and destroyed in the densely packed cords. In this way secondary hypersplenism may further complicate an underlying hemolytic anemia.

Although a wide variety of myelo- and lymphoproliferative disorders are secondarily associated with splenic enlargement and thrombocytopenia, a primary deficiency in platelets is ordinarily traceable to a disturbance in autoimmunity. Coating of thrombocytes by circulating globulins, some of which are manufactured in the spleen's lymphoid network, renders platelets highly susceptible to splenic pooling and premature destruction. Yet surprisingly, splenic enlargement in this syndrome is minimal although the spleen has a dark or purple color. Microscopically, in addition to intense red pulp congestion the splenic follicle exhibits prominent germinal centers (12).

2. Portal Hypertension

In patients with portal hypertension, bleeding esophageal varices, chronic ascites and enlargement of the spleen compose a well known clinical triad. Despite the close association between splenomegaly and elevated portal pressure, however, the pathogenic link between the two remains uncertain. Splenomegaly is ordinarily viewed as the end result of passive congestion transmitted backward through the portal system from increased resistance to flow of splenic or portal venous blood. Yet splenic size is quite variable in this disorder and, morover, fails to correlate with the level of portal pressure (13, 14), degree of obstruc-

tion to portal or splenic venous flow (13, 15–17), age of the patient (13, 18) or, when present, the severity of gastrointestinal hemorrhage (13, 18). In liver disease, particularly hepatic cirrhosis, spleen size is also unrelated to the extent of hepatic fibrosis (13, 18) or to the duration and severity of hepatocyte dysfunction (19). Furthermore, in patients with cirrhosis oxygen saturation of splenic venous blood is usually greater than 90 % suggesting that total splenic blood flow is not slowed (10, 20). Even in experimental animals prolonged obstruction to the portal or splenic vein imparts only a slight permanent enlargement to the spleen (20–22). On the other hand, in clinical portal hypertension the spleen is not only at times dramatically enlarged, but also characteristically displays a dense fibrotic matrix, intense red pulp congestion, often in conjunction with prominent histiocytic and reticuloendothelial proliferation (8, 23) (Fig. 3). These features are commonly accompanied by a greatly increased splenic blood flow rate (24). In fact, in patients with hepatic cirrhosis the degree of splenic enlargement correlates best with the magnitude of splenic arterial flow, not with the level of portal pressure! (10, 25). Examination of the pathogenesis of splenomegaly in portal hypertension seemingly favors a hemodynamic shift from a generally "open" to a more "closed" type of microcirculation. As splenic scaffolding becomes fibrotic and inelastic (26) and as cellular traffic in the cords more dense, the circulation rate in the red pulp stagnates. A variety of secondary blood cytopenias appears clinically. Conversely, with development of reticuloendothelial hyperplasia and fibrosis, blood flow through the spleen is directed more rapidly into venous sinuses, and the effect is to accelerate the central intermediate circulation. In this way, the enlarged spleen of Banti's syndrome comes to resemble morphologically and functionally that of other blood dyscrasias associated with splenic "work hypertrophy". Thus, hyperdynamic splenic blood flow is not only characteristic of cirrhosis with secondary hypersplenism, but is also typical of other white cell and reticuloendothelial proliferative syndromes with prominent splenomegaly such as myeloid metaplasia (27, 28) (Figs. 4, 5), osteopetrosis (29) and certain lipoidoses (30, 31). These disorders are also complicated by portal hypertension and bleeding esophageal varices when hyperdynamic splenic blood flow encounters heightened resistance to portal flow from superimposed venous thrombosis, liver fibrosis, hepatonodular transformation or hepatic infiltration with histiocytes or Gaucher's cells. Splenic enlargement is also a characteristic feature of splenic congenital vascular malformations, and in these conditions rapid splenic blood flow may contribute to the development of portal hypertension (22, 32).

From the foregoing analysis it seems reasonable that splenomegaly in portal hypertension primarily relates to cellular reactivity and increased blood flow (active congestion) and only in part to passive congestion from increased resistance to splenic venous outflow. On the other hand, increased splenic pulp pressure in most patients is attributable predominantly to elevated venous resistance, but also in part and on occasion to a major extent, to hyperdynamic splenic inflow. Finally, hyperfunction of the spleen as manifest by peripheral cytopenia is traceable primarily to intense red pulp congestion and pooling of blood elements in thickened cords. When splenic derangements are longstanding the matrix becomes densely fibrotic, unyielding and rigid (like a cirrhotic liver) and later reversal of red pulp congestion with reversion to an open circulation highly unlikely. At this stage portal decompression by total or segmental venous shunt generally fails to decrease spleen size, relieve cord congestion or improve secondary hypersplenism. If, however, reticulum deposition is still immature and therefore potentially resorbable then these features may improve after reduction of pulp pressure by these operative maneuvers. This explanation probably accounts for the variable response of secondary hypersplenism to portal decompression (34). In other instances, however, thrombocytopenia accompanying hepatic cirrhosis and its "improvement" following portasystemic shunt is improperly attributed to reduction in splenic hyperfunction rather than forced withdrawal from chronic ethanolism, a potent inhibitor of marrow megakaryocyte production.

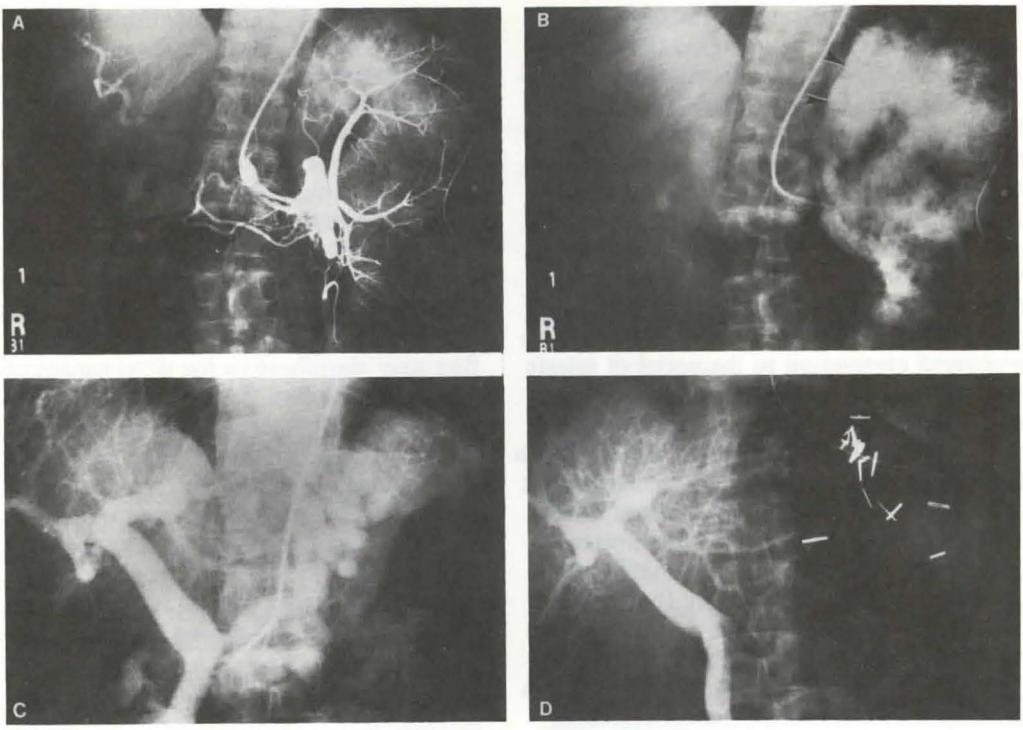


Fig. 4 Splenic circulatory dynamics in a 67 year old woman with chronic myelogenous leukemia and numerous episodes of bleeding from esophagogastric varices. Arterioportograms show an enlarged splenic artery (A) which at operation measured 15 mm and yielded a blood flow rate of 2500 ml/min using a non-cannulating electromagnetic flow meter (the arteriographic image appears smaller because of partial dissection by the catheter). The venous phase of the superselective splenic arterial (B) and selective superior mesenteric arterial injection (C) both show prominent variceal filling (arrows in B). After splenectomy (weight approximately 2 kg) and transabdominal ligation of huge varices (many of which were as large as 2 cm) operative portography (via a jejunal venous tributary) showed absence of esophagogastric variceal filling (D). Portal pressure was unaffected remaining at 29–31 cm saline before and after splenectomy (mean arterial pressure –90 to 100 mmHg). Except for persistent white cell counts of 30–50,000/mm^3 she remains well

Liver cell dysfunction and impaired transhepatic portal blood flow are both potent stimuli to spleen growth. Splenic remnants implanted either into the omentum or peritoneal cavity (portal bed) or subcutaneous pockets (systemic bed) enlarge comparably after poisoning of the liver with carbon tetrachloride (35) or induction of hepatocellular damage by experimental schistosomiasis (36) or common bile duct ligation (37). These data taken together with known abundance of antigens normally continuously emanating from the intestinal tract suggest that in portal hypertension syndromes, circulating glycolipid-protein complexes that commonly escape liver trapping function to immunostimulate the spleen. The subsequent response in splenic cellular activity promotes congestion of the red pulp, a secondary rise in splenic blood flow, progressive thickening of the trabecular framework and a gradual shifting from an open to closed microcirculation. Ultimately, hyperdynamic splenic flow (analogous to a physiologic arteriovenous shunt) in conjunction with unrestrained mesenteric blood flow and increased portal venous resistance promotes marked por-

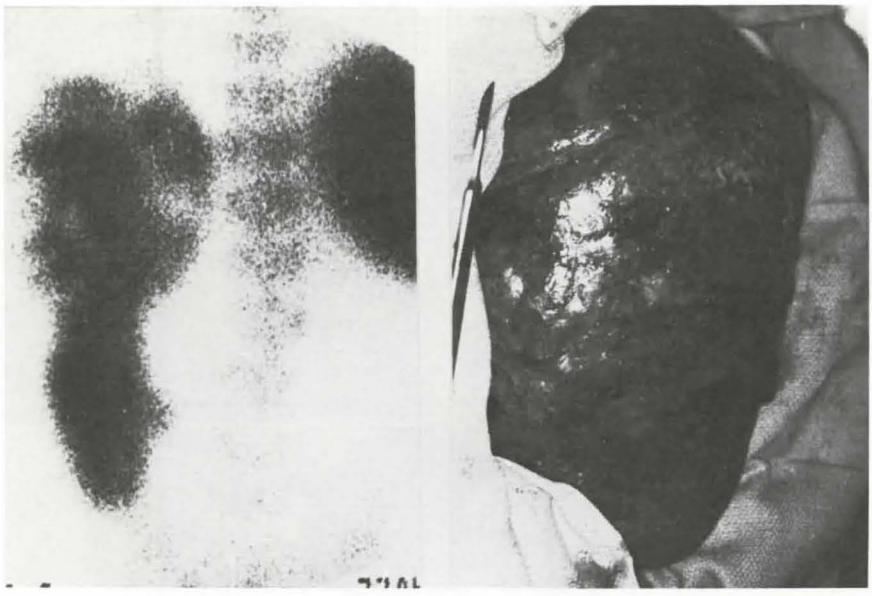


Fig. 5 Splenic posterior scintigraphy (left) and operative photograph (right) in patient described in Fig. 4, demonstrating marked splenomegaly with numerous filling defects consistent with multiple intrasplenic infarcts

tal hypertension and with it the familiar complications of varix hemorrhage, ascites and secondary hypersplenism. In some instances where obstruction to venous flow is limited to the splenic vein (so-called sinistral or left-sided portal hypertension) or occasionally where hyperdynamic splenic flow is a major contributor to the development of high portal pressure, splenectomy alone, preferably in conjunction with transabdominal ligation of gastroesophageal varices, suffices as treatment (38).

C. Circulatory Control

1. Theoretical Considerations

Although increased susceptibility of the asplenic individual to overwhelming bacteremia or parasitemia has been suggested for many years (39, 40), it is only in the last decade that some idea of the magnitude of this risk has been realized (41). As a result a major shift in attitude toward splenectomy has taken place and a number of "salvage" alternatives proposed for management of splenic injury and hyperfunction (see Preservation of the Spleen). Included among these is circulatory control or regulation of splenic activity by manipulation of blood flow. Conceptually, restriction of arterial inflow with ischemia and partial infarction of the spleen reduces hyperfunction while retaining some viable splenic tissue.

2. Ischemic Therapy

Before total splenectomy became "standard" treatment for symptomatic splenomegaly and life-threatening traumatic injury, a number of lesser operations were advocated including splenic artery ligation (42). Despite sporadic enthuasiasm for this latter procedure, later disenchantment with the long-term clinical outcome (43, 44), and improved anesthesia and operative skills in performing splenectomy led to general abandonment of splenic artery ligation as primary treatment. Review of the literature case presentations revealed, however, considerable variation in technique and

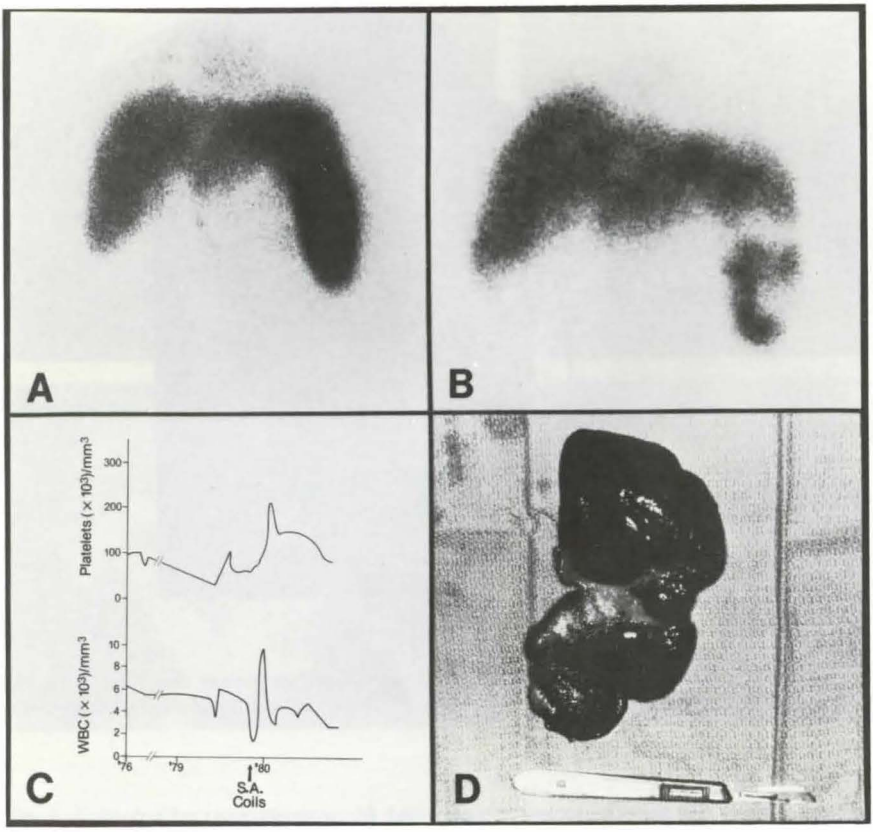


Fig. 6 Splenic scintiscans with Tc99m sulfacolloid in a 61 year old woman with hepatic cirrhosis before (A) and two months after (B) transcatheter occlusion of the distal splenic artery using multiple steel coils for relief of painful, tender splenomegaly and hypersplenism and amelioration of numerous small gastric bleeds with transient encephalopathy. Note the filling defects in the followup scintiscan compatible with large foci of infarction, the appearance of which resembles the resected spleen nearly 11 months later (D). While this maneuver initially improved the peripheral blood picture (C) and portal circulatory dynamics (Fig. 1), the effect was short-lived and after 11 months gastric bleeding with encephalopathy, leukopenia and thrombocytopenia recurred (reprinted from the Brit. J. Surg.) (49)

particularly the site of ligation, that is, anywhere from just beyond takeoff from the celiac axis to branching near the splenic hilus. Moreover, in an era before hepatosplenic scintigraphy and selective arteriography were available, documentation and followup of interruption in blood flow and changes in spleen size were largely subjective.

Based on shifts in splenic circulatory dynamics accompanying portal hypertension syndromes (10, 11, 24, 45) and extensive experimentation establishing the safety of splenic artery ligation (46, 47), we reexamined the utility of splenic artery ligation adjacent to the hilum, in conjunction with coronary vein(s) ligation in selected patients with hepatic cirrhosis (46). Specifically choosing those individuals with prominent splenomegaly, notably hyperdynamic splenic blood flow and often secondary hypersplenism, we sharply lowered the splenic contribution to portal flow and pressure and thereby decompressed the gastrosplenic (i.e. lesser splanchnic) circuit. Moreover, because functioning portasystemic venous collaterals

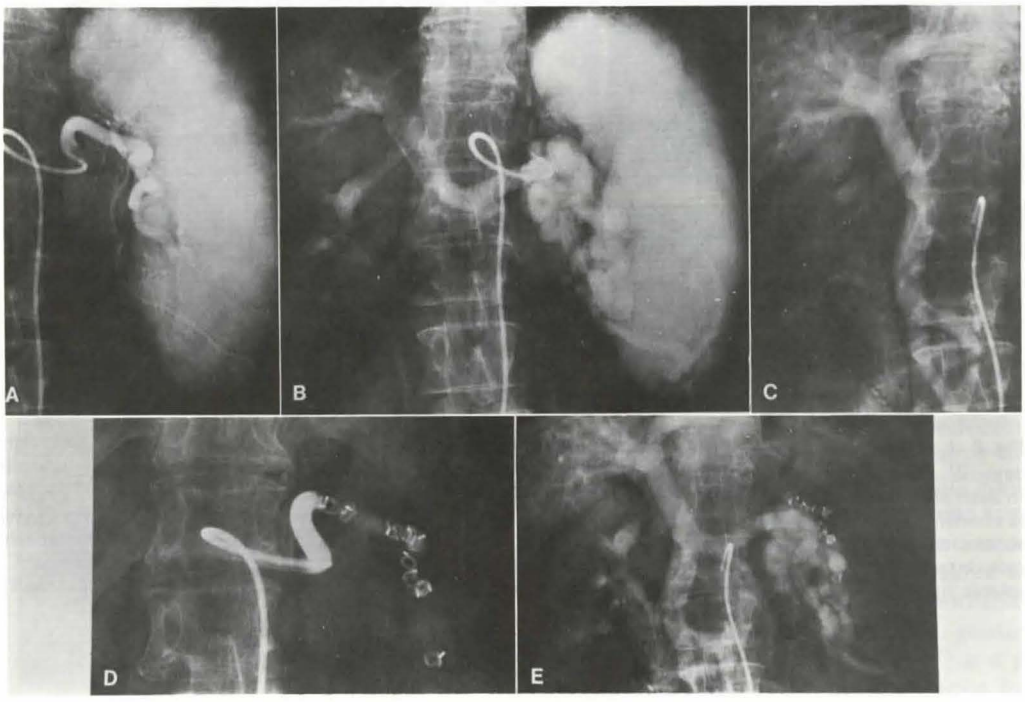


Fig. 7 Superselective splenic and selective superior mesenteric arterioportography in patient described in Fig. 6, before (A, B, C) and immediately after (D, E)transcatheter occlusion of the distal splenic artery with multiple steel coils. Note that interruption of the main splenic circulation (D) altered mesenteric-portal flow from exclusively hepatopetal (C) to partial hepatofugal decompression into the splenic venous system (E) as splenic venous flow shifted into a portal outflow tract from purely an inflow tract (B). (Reprinted from Brit. J. Surg.) (49)

around the splenic pedicle were preserved (in contrast to splenectomy) and no longer draining hyperdynamic splenic flow, these auxiliary channels were converted into an alternative escape route for mesenteric venous (i.e. greater splanchnic) blood entering the portal system under high pressure. A third benefit was partial relief of intense intrasplenic congestion with subsequent improvement in peripheral blood counts. Similar observations were described by *Hastbacka* (48) who advocated splenic artery ligation after transposition of the spleen into the left chest for control of portal hypertension (Turunen's operation).

Although initial hemodynamic and hematologic responses were encouraging, reconstitution of splenic arterial flow via pancreatic, gastric and enteric collaterals with recrudescence of signs and symptoms were disappointing (46). Later, to avoid laparotomy and to minimize revascularization we occluded the splenic artery over a longer segment via superselective retrograde transfemoral arterial catheterization of the splenic artery and insertion of multiple steel coils (49). Although initially effective, this method, too, was only of transient benefit (Fig. 6 and Fig. 7).

A similar experience was encountered in management of hypersplenism associated with congenital hemolytic anemia (50). Here, initial improvement in blood dyscrasia(s) was ultimately thwarted by continued "work stimulation" from defective erythrocytes. Gradually, splenomegaly returned, and a recurrence of hemolytic anemia prompted total splenectomy 4–6 years later (Fig. 8). Ironically, however, the

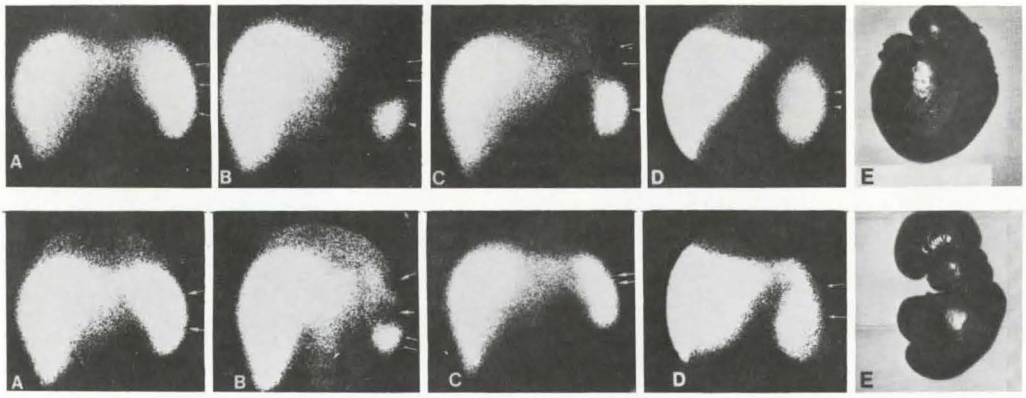


Fig. 8 Liver-spleen scintigram (A–D) with 99mTc sulfacolloid in 6 year old twin brothers before (A), eight days (B), 16 months (C) and 51 months (D) after ligation of the splenic artery for hereditary spherocytosis. In each child because of a slow upward trend in the reticulocyte count and gradual enlargement of the splenic remnant over the ensuing 4 1/2 years, splenectomy was performed at 12 years of age. Photographs of resected specimens (E) confirm notable enlargement of the remaining fragments where circulation was left anatomically intact. Presumably with continued work stimulation (fragile spherocytes) hyperplasia of the remnant splenic tissue recurred with recrudescence of a hemolytic state. After splenectomy each child remains well

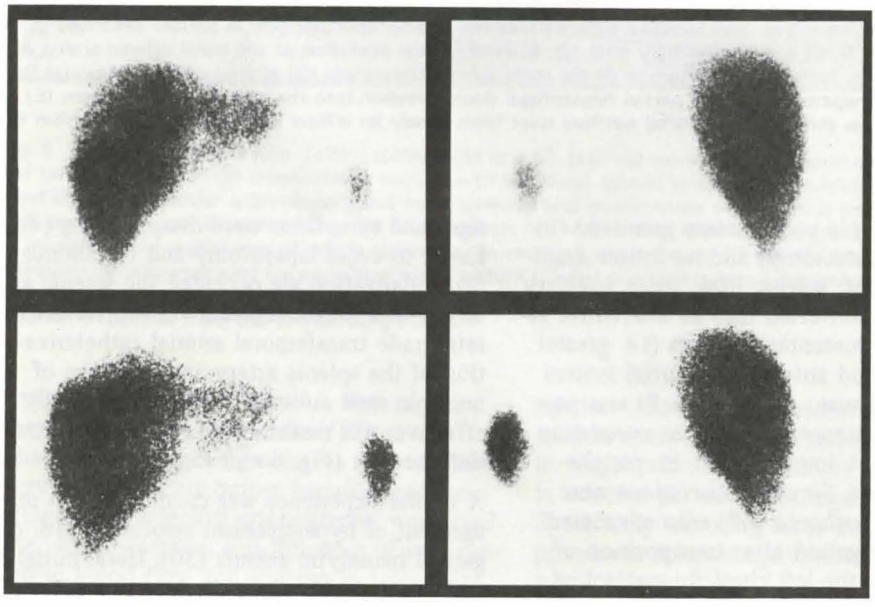


Fig. 9 Anterior (left) and posterior (right) splenic scintigraphy (^{99m}Tc sulfacolloid), 10 days (above) and 2 months after (below) ligation of the upper pole branch of the splenic artery for control of splenic hemorrhage from traumatic rupture. Note gradual intensification of splenic reticuloendothelial radionuclide trapping (? improved blood flow or regeneration) with preservation of a sizable splenic fragment

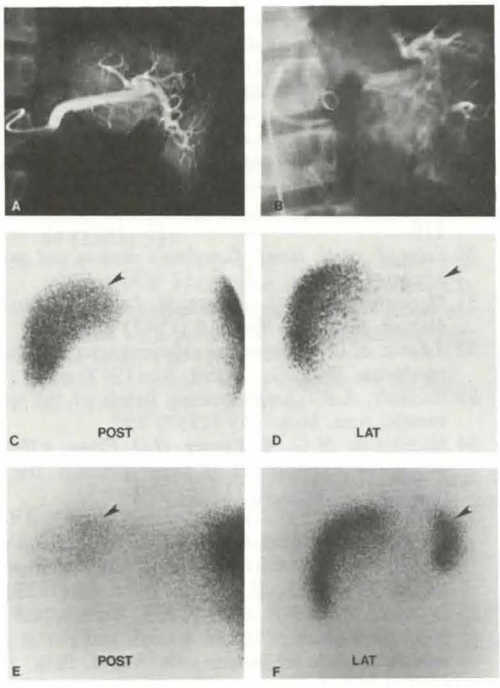


Fig. 10 Superselective splenic arteriography and radionuclide splenic scintiscan (99mTc sulfacolloid) in a 16 year old boy with chronic renal disease before (A, C) and after (B, D, E, F) transcatheter insertion of multiple gelatin sponge plugs into the splenic artery for reduction of splenic function prior to allotransplantation. After embolization there was marked reduction in vascular perfusion with truncated arteries and loculation of contrast material consistent with poor perfusion and injury (B). Although no splenic activity was seen in 10 days (D), repeat scintiscan at seven months showed a sizable splenic fragment (E, F). Posterior view (C, E): lateral view (D, F). After splenic ischemic therapy there was a prompt rise in both peripheral leukopenia (~ 3000 per mm^3) and mild thrombocytopenia (140,000 per mm^3) stabilizing around 8800 and 250,000 per mm^3, respectively. Despite large doses of prednisone and azathiaprine and local transplant external irradiation subsequently to overcome rejection crisis the peripheral blood elements remain in a normal range and he continues to do well 1 1/2 years postembolization. Howell-Jolly bodies are not seen on the peripheral blood smear (reprinted from Brit. J. Surg.) (49)

drawbacks of splenic artery ligation in management of hypersplenism have demonstrated its value for treatment of splenic injury (51, 52). By removing the major jet of pressure supplying the injured spleen, ligation of the splenic artery safely and effectively aborts serious parenchymal hemorrhage while permitting adequate time for return of splenic function (Fig. 9).

This clinical experience corroborates that interruption of extrasplenic arteries is only temporary and not definitive treatment of hypersplenism (53). On the other hand, in view of the desirability of retaining protective function of the spleen, the concept of achieving eusplenism or mild hyposplenism rather than asplenism by graded reduction in functional splenic mass through ischemia remains appealing (see Preservation of the Spleen). Some success in this regard has now been realized using transcatheter embolization with absorbable and nonabsorbable particulates (e.g. gelatin or ivalon sponge or fine steel coils). While a potential risk exists of intrasplenic abscess formation (54), recent patient experience using broad-spectrum antibiotic coverage and strict asepsis suggests that "controlled" splenic infarction with alleviation of peripheral cytopenia along with some preservation of remnant spleen is feasible (55, 56) (Fig. 10). Recurrence of splenic hyperfunction may, if desired, be managed by repeat embolization.

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