

## Preservation of the Spleen

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*"Beside your stomach may be seen  
A pulpy organ called the spleen  
The body seems to perk without it  
But, since its role is still in doubt, it  
Is prudent on the part of man  
To keep it in him if he can . . ." (1)*

### Summary

Because the spleen can no longer be considered readily dispensable, a variety of alternatives to total splenectomy (splenic repair, partial resection, auto-transplantation, ischemic therapy, reticuloendothelial blockade and irradiation) have been developed to preserve functioning remnants in trauma and hypersplenism. It remains unclear how much spleen adequately protects against OPSI or under persistent workload stimulus leads to recurrence of hypersplenism

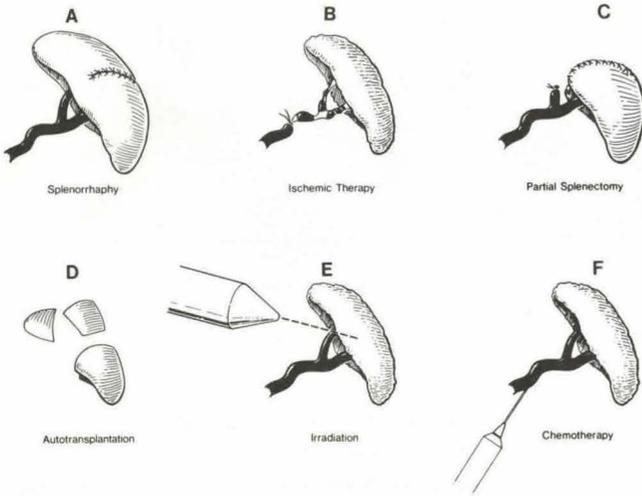
Growing recognition of the risk of overwhelming sepsis after splenectomy (OPSI) and shortcomings of measures to prevent or treat this complication have generated widespread enthusiasm for retaining some splenic tissue. These attempts at preservation (Fig. 1) carry not only important practical implications but also provide insight into what exactly the spleen does and how its functions relate to blood flow, workload, mass, resident cell populations, the rest of the reticuloendothelial (RE) system, and intercurrent disease.

Because the spleen was long considered readily dispensable, total splenectomy gradually evolved during the past 50 years as the treatment of choice for injury and symptomatic

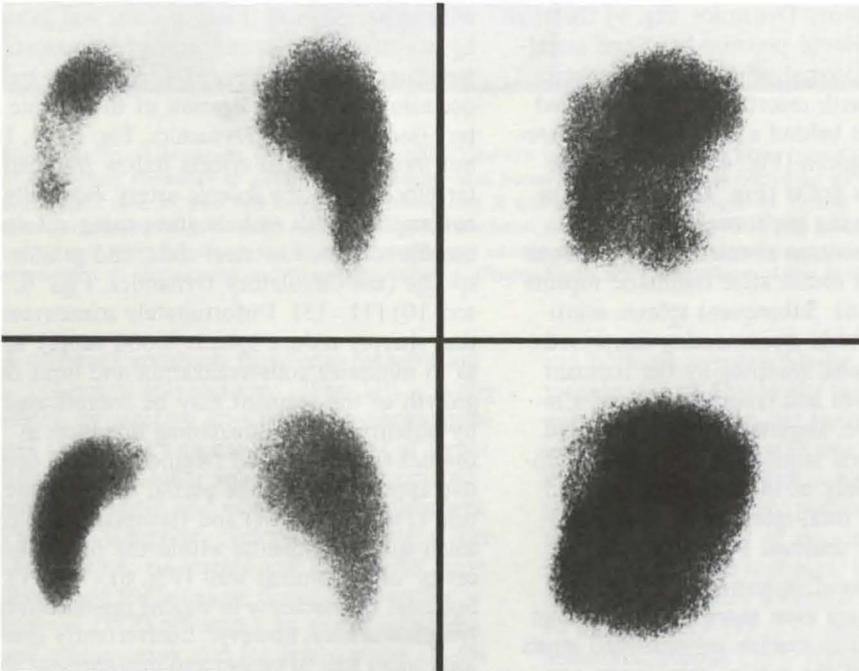
hyperfunction. Historically, less radical procedures such as incision of the spleen (splenotomy), repair (splenorrhaphy), fixation (splenopexy) and partial resection enjoyed sporadic success most notably for management of trauma and fibrocongestive splenomegaly associated with portal hypertension (Banti's syndrome). But as operative technique and anesthetic safety advanced, these options were progressively shunted into the background. Indeed, it became almost axiomatic that splenic repair and reconstruction were unthinkable even with minor injury, and non-resective operations quickly faded from the surgical scene. Now, with increasing recognition of the spleen's role in host defense against infection, these alternative procedures are coming back into favor (2). Ultimately, for acceptance in the therapeutic armamentarium, splenic preservation must prove as safe as splenectomy while minimizing the risk of fulminant sepsis and at the same time controlling symptomatic hypersplenism.

After blunt trauma, careful observation is gradually replacing "routine" splenectomy in children with injured spleens, and more recently this approach has been cautiously extended to adults (Fig. 2). If unstable vital signs, deteriorating abdominal findings, and declining blood hematocrit dictate early operation and a ruptured spleen is confirmed at laparotomy,

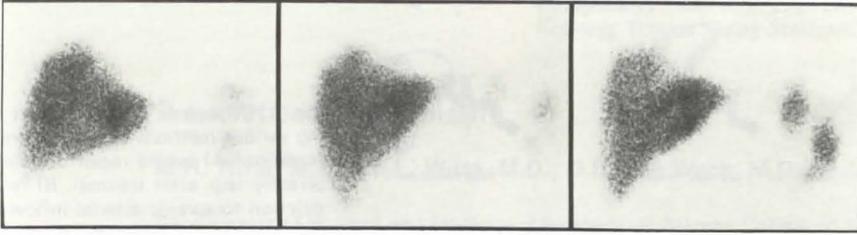
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**Fig. 1** Schematic diagram depicting various methods of splenic preservation: A) suture repair or splenorrhaphy (e.g. after trauma), B) restriction to splenic arterial inflow (ischemic therapy or circulatory control), C) partial resection leaving the remnant in situ with vascular supply intact, D) implantation of splenic fragments in the peritoneal cavity or subcutaneous tissue (autotransplantation), E) irradiation, F) chemical splenectomy through various antimetabolic-alkylating agents or particulate reticuloendothelial blockers



**Fig. 2** Posterior (left) and left anterior oblique views (right) of splenic scintiscans ( $^{99m}\text{Tc}$  sulphacolloid) within a few hours (upper) and 4 weeks after (lower) trauma to the spleen from a high speed motor vehicle accident. Note the "filling in" of defects as splenic repair proceeds. Treatment was non-operative

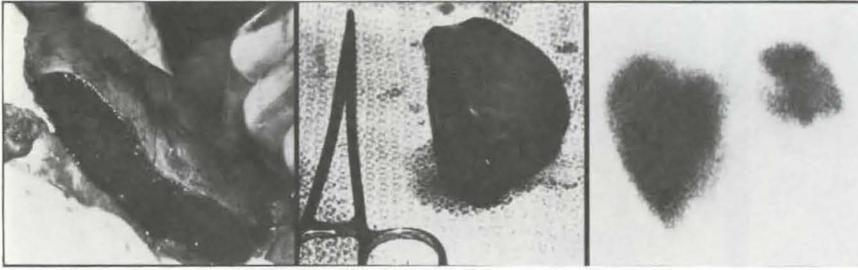


**Fig. 3** Serial anterior views of splenic scintiscans (99mTc sulphacolloid) one week (left), four weeks (middle) and 12 weeks (right) after omental wrapping and splenorrhaphy for splenic disruption following a motor vehicle accident. Note gradual improvement in the splenic scintiscan

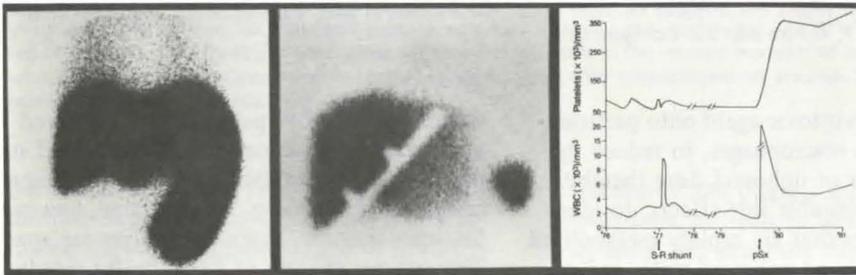
the entire spleen may not need removal. Simple tamponade, topical application of thrombogenic agents (e.g. microcrystalline collagen) and suture repair (Fig. 1A and 3) often control minor bleeding. Because splenic blood flow is segmental in distribution and collateralization rich via the celiac and superior mesenteric arteries, the splenic artery may be ligated preferably close to the hilum (Fig. 1B and see Circulatory Dynamics, Fig. 9) thereby lowering the arterial pressure head and arresting bleeding. Alternatively, partial splenectomy (Fig. 1C) with resection of the pulpified fragment leaves behind a remnant of architecturally intact spleen (Fig. 4) (3, 4). Splenic fragments (free grafts (Fig. 1D) too, may be implanted into the peritoneal cavity or wrapped in omentum simulating spontaneous autotransplants found after traumatic rupture (splenosis) (5, 6). Subsequent splenic scintiscans are helpful in documenting continued reticuloendothelial trapping by the remnant as well as growth and reconstitution of a repaired, ischemic, amputated or transplanted fragment. Several large clinical series now document the safety of these alternatives, and the number of total splenectomies for trauma has sharply declined (4, 7, 8).

On the other hand, in patients with hypersplenism, who are even more vulnerable than injured patients to sudden uncontrolled sepsis after removal of the spleen, splenic preservation has received scant attention largely because of concern over recurrent hyperfunction. Theoretically, restriction of arterial inflow (synonyms include "ischemic therapy",

"circulatory control" or "induced splenic angina") limits splenic function and thereby ability to respond to a particulate workload. During the past decade it has been clearly documented that marked restriction to splenic blood flow reduces splenic mass (visualized by reticuloendothelial uptake on splenic scintiscan) and initially raises one or more depressed cellular elements in peripheral blood associated with hypersplenism. Early success was gained by selective catheter infusion of vasoconstrictor drugs (e.g. vasopressin), intraarterial balloon occlusion, and distal ligation of the splenic artery (see Circulatory Dynamics, Fig. 8) (9, 10), but more prolonged effects follow transcatheter blockage of the splenic artery especially in conjunction with embolization using autologous blood clot, fine steel coils, and gelatin sponge (see Circulatory Dynamics, Figs. 6, 7 and 10) (11–13). Unfortunately maneuvers that sharply reduce splenic blood supply so as to minimize collateralization and limit regrowth of the segment may be complicated by potentially life-threatening infection in the ischemic, infarcted fragment. Other operative approaches include partial splenic resection (Fig. 5) (13, 14) and transplantation of small splenic remnants within the peritoneal cavity or abdominal wall (Fig. 6) (15–17). Subtotal splenectomy in staging operations for lymphoma may, however, inadvertently overlook small foci of cancer and misrepresent the true extent of tumor progression (18). Although splenic irradiation (Fig. 1E) temporarily also reduces splenomegaly, it has been generally ineffective in controlling hypersplenism (19).



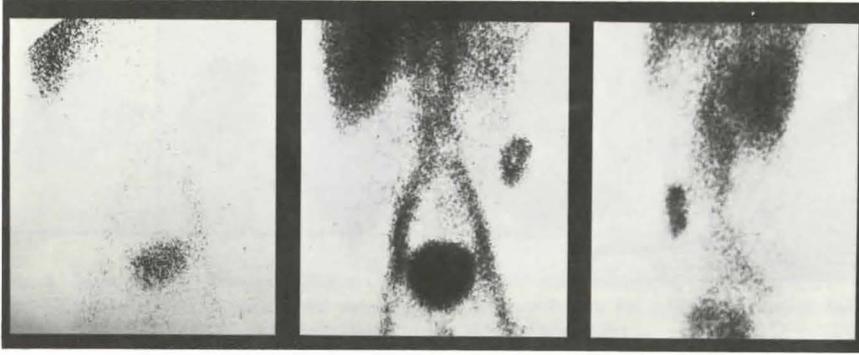
**Fig. 4** Large splenic remnant left in situ (left) after resection of pulpified fragment of spleen (middle) in a young man following an automobile collision. A substantial splenic remnant (right) is visible on  $^{99m}\text{Tc}$  sulphacolloid scintiscan 3 months later



**Fig. 5** Splenic scintiscans ( $^{99m}\text{Tc}$  sulphacolloid) before (left) and 6 months after (middle) partial resection of the spleen for relief of painful splenomegaly and hypersplenism following occlusion of a distal splenorenal shunt (SR) in a 12 year old boy with histiocytosis X and portal hypertension. At 12 and 24 months the splenic remnant on scintiscan was unchanged. Peripheral white blood cell (WBC) and platelet counts (right) before and after SR shunt for bleeding esophageal varices and subsequent splenectomy, showing eventual improvement of leukopenia and thrombocytopenia. (Reproduced with permission of the Brit. J. of Surg.) (13)

A different approach to splenic preservation – “chemical splenectomy” (Fig. 1F) – is suggested by salutary effects of immunosuppressive (cytotoxic) agents in treatment of hypersplenism and other splenopathies associated with neoplastic and non-neoplastic disorders. Thus, azathioprine, cyclophosphamide, 6-mercaptopurine, vincristine and vinblastine, have been tried for immune thrombocytopenic purpura (ITP) refractory to glucocorticoids and splenectomy and for low platelet counts accompanying disseminated lupus erythematosus, lymphoma, leukemia, carcinoma and bone marrow aplasia. Circulating antibodies to platelets or abnormalities in cell-mediated immunity are implicated in these disorders,

and both are suppressible by these potent cytotoxic agents. Among the various mechanisms proposed to explain the beneficial clinical response, interference with macrophage function leading to impaired destruction of sensitized platelets is particularly germane. For example, to enhance delivery of vincristine or vinblastine to impede macrophages, the ability of platelets to bind vinca alkaloids has been exploited in refractory ITP (20) and in autoimmune hemolytic anemia (21). While the long-term efficacy of this particular treatment is unclear, the concept of using a particulate vehicle for targeted delivery of cytotoxic agents to hyperfunctioning macrophages is intriguing. What is needed now are ways to enhance loading or



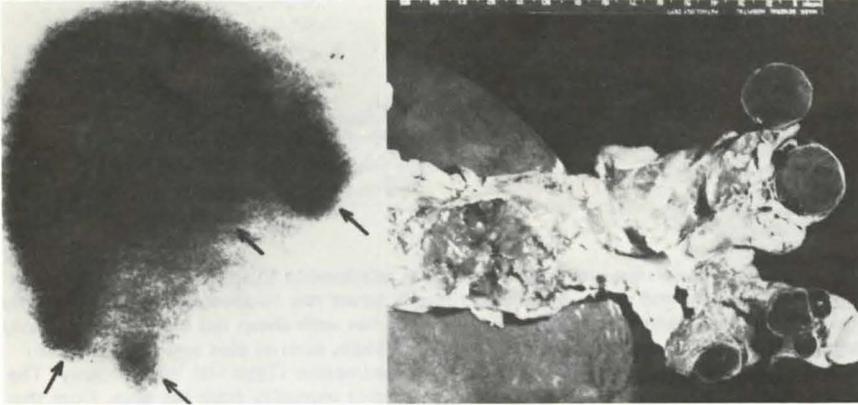
**Fig. 6** Serial splenic scintiscans (technetium labelled heat-damaged red blood cells) in young boy with idiopathic thrombocytopenic purpura failing to visualize immediately after (left) but revealing a substantial splenic fragment 2 years after (middle, right) autotransplantation in the abdominal subcutaneous tissue. Lateral view (right) shows the palpable remnant under the abdominal wall. Platelet count is  $335,000/\text{mm}^3$  (Courtesy of Drs. P. Crowe and J.J. Corrigan, Jr.)

binding of the cytotoxic agent onto particles targeted for the macrophages, to reduce the circulating levels of unbound drug thereby minimizing undesirable side effects, to identify drug analogs that are rapidly metabolized and eliminated in an unbound state, and to deliver high concentrations of the particle selectively into reticuloendothelial organs. Where the underlying disorder is thought to reside primarily in the spleen, loading of bleomycin onto red blood cells (22) and selective splenic arterial infusion of particle-bound cytotoxic agents (as previously for unbound cytotoxic agents in chronic granulocytic leukemia or  $^{90}\text{yttrium}$  microspheres in malignant lymphoma) (23) hold promise for the future. Reticuloendothelial blockade probably also underlies amelioration of refractory ITP with high-dose intravenous polyvalent intact immunoglobulin (24), which presumably interferes with phagocyte-Fc receptor-mediated immune clearance by the spleen. High dose long-term corticosteroid therapy may also exert therapeutic benefit in these derangements by impairing splenic phagocytosis.

Several decades ago, ethyl palmitate (Ethpalm), an esterified long-chain fatty acid, was shown to profoundly inhibit the ability of sessile cells to remove particulate matter from the bloodstream (25). In mice, a colloidal

suspension of ethyl palmitate administered intravenously produces rapid and marked suppression of phagocytic function and widespread necrosis of the spleen. By and large, however, the bone marrow, thymus and liver are spared. This curious affinity of Ethpalm for splenic macrophages suggests regional differences in RE function or possible metabolism ("detoxification") in the liver. While applicability to patients is as yet undefined, this substance may be potentially useful when administered via superselective splenic arterial infusion in patients with life-threatening peripheral cytopenias.

Despite mounting evidence of advantages to possessing a spleen and growing clinical application of various methods of splenic preservation, it is unclear how much spleen is needed. On the one hand, the rarity of OPSI and the frequency of functional splenosis in patients splenectomized for trauma have prompted speculation that small splenuli (so-called "born again spleens") (Fig. 7a) restore host resistance to infection (26–28). On the other hand, fulminant pneumococcal septicemia and death have occurred in patients following splenectomy for blunt injury despite large ectopic splenic fragments and innumerable minute splenic nodules (splenosis) found at autopsy (Fig. 7b) (29, 30). Similarly, patients with small or hy-



**Fig. 7** Extensive splenosis (arrows) visualized on hepatosplenic scintiscan (left) in a healthy 15 year old boy 8 years after splenectomy for traumatic rupture, who also showed a low percentage (0.8%) of pitted circulating red blood cells. This finding is contrasted with similar splenosis in the retroperitoneum of another patient (right) who succumbed to fulminant pneumococcal sepsis 10 years after splenectomy for trauma. (Reproduced with permission of New Engl.J.Med.) (28, 20).

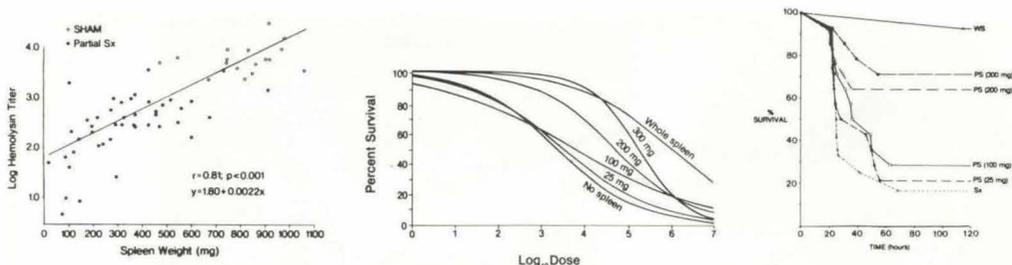
poofunctioning spleens from sickle cell anemia, ulcerative colitis, sarcoid infiltration and following thorotrast administration or splenic irradiation have also succumbed to pneumococcal sepsis (see Clinical Disorders of Splenic Function). Together, these findings suggest that small or severely hypofunctioning splenic remnants cannot be relied upon to protect against the spectrum of sudden and fulminant infections characteristic of the asplenic state (see Overwhelming Postsplenectomy Infection: OPSI).

Experimental autotransplantation of splenic fragments has been reported by some to protect (31–33) and by others to offer little or no protection against intravenous live pneumococcal challenge (34). These implants, which closely resemble clinical splenosis, first undergo central necrosis but over the ensuing 6–12 weeks gradually enlarge emerging as splenuli histologically resembling an intact spleen (35). Moreover, they take up radiocolloid and trap damaged red blood cells. Blood supply, however, derives from penetration of the capsule rather than hilar arteries and in the absence of an abnormal workload (e.g. liver injury or circulating particulate antigen), regrowth is unpredictable, limited to

a fraction of the original spleen size and cell populations, difficult to quantify for multiple fragments, and gradually declines with advancing age.

While these ectopic implants have been reported to retard *Bartonella* infestation (36), restore gamma leukophilic opsonin levels (37) produce antibodies to particulate antigen (38) as well as reduce the number of pitted red blood cells (26), the bulk of evidence indicates that they do not provide adequate protection against pneumococcal septicemia.

In a rat model of incremental partial splenic resection permitting early and quantitative determination of remnant function over a precisely graded range of mass, both early antibody production to intravenous particulate antigen (sheep red blood cells) (Fig. 8a) (39) and LD<sub>50</sub> after intravenous pneumococcal challenge (Fig. 8b) (40) vary directly with residual splenic mass. In these experiments, remnant spleens of less than one-third the original spleen size fail to improve host survival over the spleenless state. Furthermore, in rats depleted of complement by parenteral cobra venom factor, a substantial splenic mass (approximately one-third to one-half normal)



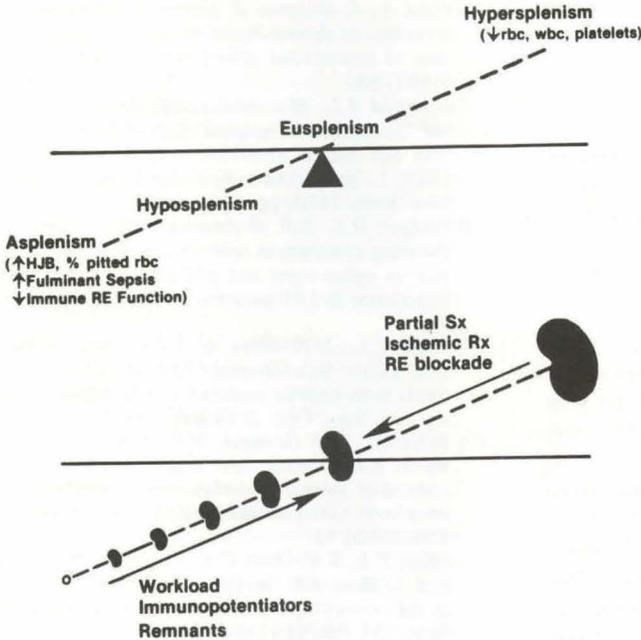
**Fig. 8** Demonstration that various splenic functions bear a close relationship to splenic mass. Left, direct relationship between splenic weight and serum hemolysin titers in intact rats (sham-operated) and rats after partial splenectomy (Sx) following intravenous challenge 5 days earlier with sheep red blood cells. Hemolysin activity in totally splenectomized rats was barely detectable. Middle, survival plot and LD<sub>50</sub> in adult rats with varying size spleens after administration of virulent *S. pneumoniae* (Type III) intravenously. The model represents a form of the generalized logistic equation to predict mortality from log dose. Note that the smaller the remnant spleen mass left in situ the lower the LD<sub>50</sub>. Right, survival rates of rats challenged with low dose *S. pneumoniae* (Type III) (10<sup>2</sup> bacteria) 24 hours after complement depletion with cobra venom factor. A substantial protective advantage was offered by partial spleens (PS) of greater than 200 mg left in situ (approximately one-third whole spleen (WS) weight). (Reproduced with permission of Surgery, J. of Surg. Res. and J. Inf. Dis.) (39–41)

is needed to restore host resistance in this highly susceptible state (Fig. 8c) (41). Sophisticated statistical analysis by failure-time modelling of the experimental data (42) indicates, however, that even a small remnant left in situ has some small protective value but large remnants provide an exponential increase in host resistance. No significant protection is provided by ectopic remnants, either single or multiple, in this highly sensitive bioassay system.

Because “born-again spleens” rarely achieve the critical threshold of substantial protection provided by the splenic remnant with intact blood supply and architecture, their ability to protect against OPSI remains in doubt as does the efficacy of attempts at splenic preservation which leave behind small remnants of insufficient functioning cell density. While deaths from fulminant sepsis have occurred in patients with extensive spontaneous splenosis, long-term follow-up of patients with splenic preservation carried out by a variety of techniques for trauma and particularly for hypersplenism is still limited. Accordingly, meaningful population studies to examine changes in incidence of OPSI are not yet possible, and experimental studies remain the main source of information about survival

value of different methods of splenic preservation.

In contrast to individuals undergoing splenectomy for injury where “the more spleen the better”, in patients with hypersplenism, retention of a splenic fragment for immune protection raises the spectre of eventual recurrence of splenic hyperfunction. In a sense, the phenomenon of hypersplenism and associated splenomegaly is an appropriate reaction of splenic RE tissue to an abnormal stimulus or “workload” (e.g. increased numbers of defective red blood cells, abnormal lipids or foreign particulate antigens) (35). As treatment directed at eliminating or reducing the excessive workload, enhancing hepatic function, or improving a stagnant congested splenic intermediary circulation is difficult or impossible, the spleen is usually removed despite the even greater risk of OPSI in patients with diseased compared to normal spleens. Although recurrence of hypersplenism has occasionally been reported with a small accessory spleen, the frequency of such relapses and the time period for recurrence are both unclear and open to reinterpretation (43). Most presumed recurrences from accessory spleens have been associated with ITP (a special disorder characterized by a normal size spleen, circulating antiplatelet antibodies, spontaneous remissions,



**Fig. 9** Titering of splenic function through manipulation of splenic mass. While a fine line exists between susceptibility to fulminant sepsis (hyposplenism and asplenism) on the one hand and recurrent hypersplenism on the other, splenic mass and function can be titrated by a variety of preservation techniques (partial splenectomy, ischemic therapy, RE blockade). Conversely, splenic mass and function can also be “boosted” by increasing workload, immunopotentiating agents, and splenic remnants to attain eusplenism — the ideal balance of splenic immunologic and hematologic function (see text for expansion of these concepts, HJB = Howell-Jolly bodies)

and recurrence even in the absence of detectable splenic tissue), and even the favorable response to accessory splenectomy reported by some in ITP has been disputed (44). In the few instances of recurrent anemia from accessory spleens in hereditary spherocytosis, the original diagnosis has been questioned. Besides, accessory spleens are detected on occasion in this disorder without reappearance of reticulocytosis and anemia. Nonetheless, there is little doubt that if a substantial remnant is left behind in situ, as after splenic arterial ligation where collateralization continues and workload of abnormal red cells persists, re-growth of the remaining spleen to greater than normal size takes place with recrudescence of splenic hyperfunction (see *Circulatory Dynamics*, Fig. 8 and *Clinical Disorders of Splenic Function*, Fig. 2) (10, 13).

Despite these limitations, it is likely that the goal of “titering” splenic function through manipulation of splenic mass is attainable (Fig. 9). While one may tread a fine line

between susceptibility to fulminant sepsis on the one hand and recurrent hypersplenism on the other, splenic mass can be reduced gradually by a variety of preservation techniques already described; conversely, splenic function can also be “boosted” in several ways. For example, immunopotentiators such as vaccines prepared from anaerobic coryneform bacteria stimulate the normal spleen (and even the rudimentary spleen of immunodeficient CBA-N mice) to enlarge several-fold and provide “supernormal” resistance against bacterial, viral and protozoan infestations as well as certain neoplasms (45). Thus, while preservation of maximal splenic tissue may be desirable after trauma, careful “titration” of mass in hypersplenism to optimize the balance between immunologic protection and hematologic remission is appropriate. Splenic remnants may be “boosted” by stimulation from particulate antigen or immunopotentiating agents, recruitment of new blood supply to ischemic remnants (e.g. wrapping in omentum), auxiliary implantation of subcutaneous and omental

autografts preserved in a frozen state, injection of spleen cells, and ultimately by selectively replacing identifiable splenic immune "protective factors" (e.g. with cryoprecipitate). More precise control and tailoring of remnant mass and function will likely follow greater elucidation of specific spleen cell populations (e.g. macrophages, T and B lymphocytes) and subpopulations and their participation in the spleen's pitting and culling functions, filtering capacity, and antibody production.

From this brief analysis, it is apparent that a wide array of preservation techniques are now feasible. While the technical aspects are relatively simple, straightforward, and safe, major unanswered questions remain about the long-term value of these remnants in terms of protection from sepsis and, in hypersplenism, risk of recrudescence hyperfunction. Nonetheless, the potential benefit of defining critical splenic mass, relating it to vascular supply, architecture, and cell populations, and determining the best way to attain and maintain this mass, is great, especially for young children, immunosuppressed patients such as renal transplant recipients, and those with blood dyscrasias, where asplenism carries a particularly high risk of OPSI (see Overwhelming Postsplenectomy Infection). Titering splenic function upward and downward to attain the ideal of eusplenism — the optimal balance of the spleen's many and complex functions — represents the real challenge of the future. In this context, "the salvaged spleen or splenic remnant is a far greater trophy . . . than the spleen in the pathologist's hands" (46).

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