

## Clinical Disorders of Splenic Function: The Spectrum from Asplenism to Hypersplenism

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### Summary

Pathophysiology, clinical manifestations and treatment of splenic disorders are viewed in terms of the broad spectrum of function ranging from asplenism through hypersplenism.

Mention of the spleen usually conjures up in the clinician's mind the image of hypersplenism, the associated life-threatening peripheral cytopenias, and striking long lasting benefit from splenectomy. It is now well recognized, however, that absence or atrophy of the spleen, once thought merely to induce a cosmetic defect in the red blood cell but otherwise compatible with long life, notably enhances susceptibility to death from sudden overwhelming sepsis. Thus, syndromes of both deficiency and excess — asplenism, hyposplenism, and hypersplenism — can be viewed in terms of a continuous spectrum of certain well defined and other more elusive functions of the spleen (1-3).

### *Deficient splenic function: Asplenism and hyposplenism*

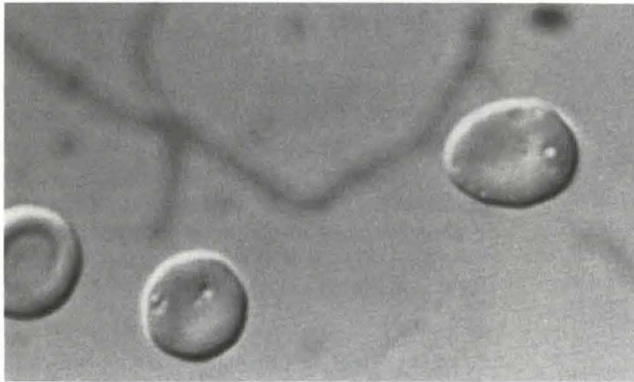
Splenic function is partially or completely reduced in a variety of congenital and acquired disorders (Table) (2-5). Congenital absence or hypoplasia of the spleen may go undetected unless death supervenes from coexistent cardiopulmonary dysfunction or overwhelming infection (4, 6-8). In patients with sickle cell disease, functional hyposplenism arises when crescent-shaped red cells clog the spleen's

microcirculation and block arterial inflow (9, 10). Though reversible early in life by transfusing normal red cells, this transient loss of splenic function eventually progresses to permanent splenic infarction, fibrosis and atrophy, giving rise to the term "autosplenectomy." More sudden vascular occlusion, brought on by arterial embolization (e.g. from a cardiac mural thrombus), periarteriolar infiltration in chronic myelogenous leukemia, or splenic vein thrombosis, also produces signs of autosplenectomy though loss of organ function is rarely total or permanent. While the etiology of hyposplenism in a variety of intestinal malabsorption syndromes remains a mystery, the return of splenic function after successful treatment of the underlying disease in some patients is intriguing (3).

In general, the hyposplenic state is more readily detected by hematologic than immunologic methods. The hallmark of the asplenic state is the appearance of Howell-Jolly bodies, small intraerythrocytic inclusions ordinarily removed by the spleen's pitting and culling process (11). However, since Howell-Jolly bodies are only present in peripheral blood when splenic function is virtually absent, a more useful marker for relative hyposplenism is the development of craters or "pits" in red cells viewed under interference-phase contrast (Normarski) microscopy (12) (Fig. 1). Determined as a percentage of total erythrocytes, the number of cratered cells is inversely related to splenic function, ranging from 40-50% in asplenic patients to

**Table** Disorders of splenic function

<i>Hypersplenism</i>	<i>Hyposplenism</i>
A. Work Hypertrophy	A. Congenital absence/hypoplasia
1. Gaucher's Disease	B. Splenectomy
2. Liver disease	C. Splenic arterial occlusion (iatrogenic)
3. Inherited hemolytic anemia	D. Splenic arterial or venous thrombosis
a. red cell membrane disorder (e.g. spherocytosis)	E. Splenic atrophy
b. hemoglobinopathies (e.g. thalassemia)	1. Sickle cell disease
c. red cell metabolic disorder (e.g. pyruvate-kinase deficiency)	2. Celiac disease
4. Autoimmune cytopenias	3. Dermatitis herpetiformis
a. hemolytic anemia	4. Ulcerative colitis
b. thrombocytopenia	5. Hyperthyroidism
c. neutropenia (Felty's syndrome)	6. Thrombocythemia
B. Congestion or increased pooling	7. Thorium dioxide-induced
1. Cirrhosis with portal hypertension	8. Systemic lupus erythematosus
2. Thrombosis of hepatic, portal and/or splenic vein(s)	



**Fig. 1** High power (1000x) interference phase photomicrograph of red blood cells from a splenectomized patient, demonstrating surface membrane "pits" or "craters" characteristic of the asplenic state

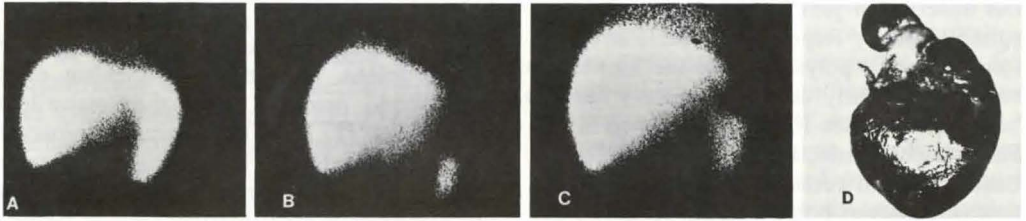
less than 5% in eusplenic adults. This test provides a semiquantitative, noninvasive estimate of splenic function but requires sophisticated optics not routinely available.

Because postsplenectomy changes in peripheral blood cell counts vary with cell type, postoperative interval and underlying disease, these hematologic indices provide little additional assistance in detecting hyposplenism and asplenism. The granulocytosis which follows splenectomy is transient, resolving after

several weeks, whereas lymphocytosis and monocytosis persist, suggesting that the normal spleen selectively removes lymphocytes and monocytes. Thrombocytosis occasionally reaches alarming levels immediately postsplenectomy but platelet counts usually return to normal within two weeks unless the patient has ongoing hemolysis, sideroblastic anemia with active bone marrow, or underlying myeloproliferative disease.

Radionuclide studies including Tc-99m sulfur-





**Fig. 2** Liver-spleen scintigram with  $^{99m}\text{Tc}$  sulfur-colloid, a, b, and c, and gross photograph, d, in a four year old girl with pyruvate-kinase deficient hemolytic anemia before, A, five days, B, and three months, C, after ligation of the splenic artery. Whereas the upper portion of the spleen remained atrophic, the lower pole splenic remnant ultimately (39 months) enlarged dramatically, D, associated with increasing transfusion requirements necessitating splenectomy (Reprinted from Surg., Gyn., Obst.) (15)

colloid or Tc- $^{99m}$ -tagged heat-treated red blood cells, provide insight into splenic vascularity, volume, and localization function in patients with small spleens. Taken together with the observation of Howell-Jolly bodies or increased numbers of cratered red blood cells, a scan displaying diminished radiolabel uptake by the spleen confirms the diagnosis of hyposplenism.

Despite these criteria, the relationship between splenic hematologic function and mass (as evidenced by scintiscan or other imaging technique, laparotomy or autopsy) is not straightforward. The spleen may be normal in size or even enlarged yet hypofunctioning (so-called functional hypo- or asplenia) in sarcoidosis, light chain myeloma, sickle cell anemia in crisis, acute leukemia, multiple myeloma, immunoblastic lymphoma, and amyloidosis or after high dose corticosteroid therapy (2, 3). The personal experience (W. H.C.) of two patients in this regard is particularly noteworthy (2). In one with hyposplenism and bone marrow hypoplasia associated with Fanconi's syndrome, Howell-Jolly bodies but not siderocytes were present in peripheral blood smears. Splenectomy, which yielded a 16 gram spleen, was followed by the appearance of 4 percent siderocytosis, suggesting that this weight of tissue (compared to the normal 150–200 g) was sufficient to suppress siderocytes but not Howell-Jolly bodies. In the other, a 45 year old male with hereditary spherocytosis, splenosis was iatrogenically induced by implanting subcu-

taneously 2 grams of tissue cored from the extirpated spleen. When removed five years later the mass still weighed 2 g and neither anemia nor reticulocytosis had recurred. Even 100 g of spleen left behind in spherocytosis did not produce recrudescence of anemia or reticulocytosis.

Contrary to prevailing medical dogma, there is little objective evidence to incriminate accessory or "born again" splenic tissue when hematologic relapse follows splenectomy for blood dyscrasia (13). The role of small accessory spleens in recurrent anemia of hereditary spherocytosis or thrombocytopenia of idiopathic thrombocytopenic purpura (ITP) has been disputed, either because the original diagnosis was questioned or because remission after accessory splenectomy was only transient. On the other hand, in children undergoing splenic artery ligation to manage hereditary spherocytosis or pyruvate kinase deficiency, a large splenic remnant left in situ is capable of substantial regeneration after extensive spontaneous arterial revascularization and under continued stimulus of fragile spherocytes (14). Documented on splenic scintiscan and at reoperation, regrowth in this setting may be accompanied by resurgent reticulocytosis, progressive anemia and increased transfusion requirement (Fig. 2). (See also Circulatory Dynamics, Fig. 8).

The asplenic state is also characterized immunologically by prolonged clearance and delayed antibody production after intraven-

ous injection of particulate antigen (16). Impaired antibody response to soluble antigen (pneumococcal polysaccharide vaccine) injected intramuscularly or subcutaneously has also been observed (see Role of the Spleen in Pneumococcal Infection). Lack of a safe particulate antigen currently available for human testing, however, poses a major barrier to evaluating and manipulating splenic immunologic function in patients with hyposplenism.

Although information is limited, evidence suggests that patients with congenital or acquired hyposplenism share not only hematologic but also immunologic features of resected counterparts. Patients with sickle-cell disease develop Howell-Jolly bodies, cratered red cells, failure of splenic visualization on Tc-99m scan, impaired response to pneumococcal vaccine, and increased susceptibility to overwhelming infection. Similar findings have been observed in patients with intestinal sprue, congenital asplenia and congenital splenic hypoplasia (2, 3).

The minimum splenic mass needed to protect against infection is not clear from scattered reports in patients. Among otherwise normal splenectomized adults who develop OPSI (see Overwhelming Postsplenectomy Infection), autopsy-proven splenules, splenosis, or accessory spleens occur with disturbing frequency. There is little doubt that patients with as much as 25–50 grams of remnant spleen (12 to 30% normal spleen weight) can succumb to postsplenectomy sepsis.

Thus, though the spleen performs a variety of hematologic and immunologic functions and many conditions associated with diminished spleen mass have been identified, the precise relationship between spleen size (big or small) and function is still unclear in part because tools for studying the problem clinically are crude, inexact, or unavailable. Until a particulate antigen is developed for intravenous injection in patients, the burden of investigation will likely continue to rest on experimental simulations of hyposplenism (see Experimental Models).

#### *Excessive splenic function: Hypersplenism*

Splenomegaly refers to anatomic enlargement of the spleen. The term hypersplenism, on the other hand, describes states of excessive splenic function (1, 17–20). Classically, hypersplenism is manifested by the association of anemia, leukopenia and/or thrombocytopenia, normal to hyperplastic bone marrow cellular elements, usually splenomegaly and the disappearance of the cytopenia(s) following splenectomy. In patients with hypersplenism, intravenous injection of radiolabelled red cells, white cells, or platelets often confirms shortened intravascular lifespan and increased intrasplenic sequestration of these elements.

Several different pathogenetic mechanisms may be involved (Table). The major one is work hypertrophy from destruction of abnormal blood cells or immune stimulation, phenomena which likely reflect splenic reticuloendothelial reactivity to an abnormal stimulus or workload. Often the endogenous workload is readily identifiable (e.g. abnormal red blood cells in hereditary spherocytosis and pyruvate kinase deficiency, or deranged cerebroside in Gaucher's disease). In other disorders (e.g. Hodgkin's disease or non-Hodgkin's lymphoma) an increased workload of foreign antigen has been postulated but not demonstrated. In experimental animals the spleen enlarges with nonselective overshoot of sequestering activity in conjunction with pancytopenia after exogenous administration of colloidal polymers or macromolecules (see Experimental Models).

Moreover, reciprocity between the spleen and liver in sharing a fixed workload is well recognized. For example, when hepatic fixed macrophage function is reduced as in cirrhosis, there is a concomitant increase in splenic reticuloendothelial (RE) activity. Experimentally, hepatic RE and regenerative capacity increase following splenectomy, whereas spleen size increases following partial hepatic resection. However, other factors in addition to work hypertrophy, including congestion, myeloproliferation and neoplastic infiltration, may contribute to splenomegaly in liver disease at times resulting in hypersplenism.



Whatever the underlying disorder, hypersplenic cytopenias can be classified as the result of one of three processes: excessive splenic sequestration without destruction; excessive splenic destruction; or intrasplenic production of antibody hastening splenic or extrasplenic destruction of circulating cells (1, 3). Many instances of "hypersplenic anemia" involve more than one process. Thus, while a normal spleen of 150 g contains only 20 ml of red cells, a spleen enlarged by the stimulus of abnormal cells or circulating antigens may store as much as 10 to 25% of total erythrocyte mass (1). When red cell membrane, hemoglobin or metabolic defects predominate, as in hereditary spherocytosis, sickle cell anemia, thalassemia, or pyruvate kinase deficiency, irreversible cell destruction also takes place. In the example of autoimmune anemias, the spleen produces antibody which binds red cell surface antigens, thereby opsonizing circulating red cells. Depending on the type of antibody (IgM or IgG), the number of antibody molecules per red cell, and the presence or absence of complement fixation, antibody-coated cells are quickly removed, engulfed and destroyed by either the spleen or liver. As with bloodborne pneumococci (see Role of the Spleen in Pneumococcal Infection), weak or incomplete opsonization favors splenic uptake, whereas strong or complete opsonization favors capture by the liver. Accordingly, successful treatment of autoimmune hemolytic anemia by splenectomy hinges on the relative splenic contribution not only to autoantibody synthesis but also to total red cell destruction. Alternatively, corticosteroids may prolong survival of antibody-sensitized erythrocytes by decreasing antibody production or impairing RE clearance and phagocytosis. Similarly, "hypersplenic thrombocytopenia" may arise from excessive intrasplenic platelet sequestration, premature destruction of circulating platelets, a combination of both, or primary production of antiplatelet antibody. These disorders include immune thrombocytopenic purpura (where antibody and the spleen collaborate to destroy circulating platelets) and secondary hypersplenic thrombocytopenia from a variety of other causes.

Whereas splenectomy in secondary disorders is extremely successful in correcting thrombocytopenia, postsplenectomy resolution is less frequent in ITP, where a significant source of antiplatelet antibody and RE entrapment may be extrasplenic. As in immune hemolytic anemias, corticosteroids may retard antibody production or RE clearance of antibody-coated platelets.

"Hypersplenic leukopenia" includes both primary and secondary disorders, but the underlying pathophysiology is poorly understood. In some instances IgG antibody is directed against the granulocyte cell surface, as in platelet and erythrocyte autoimmunity, and destruction takes place either within the RE system or in the microvasculature as neutrophils activated by IgG fixation become sticky and marginate in peripheral capillaries. In other instances, hypersplenic pancytopenia may coexist with an aregenerative bone marrow, which may arise from an acute exacerbation of "humoral" dysfunction of the spleen. Treatment with splenectomy is often unsuccessful, and recurrent infections are frequently associated with ongoing neutropenia.

While the hematologic manifestations of hypersplenism have received widespread attention, it is unclear whether immunologic reactivity of hyperfunctioning spleens is likewise "supernormal" or whether immunologic activity is blocked when the spleen is preoccupied with an increased hematologic workload. Again, lack of a particulate antigen safe for intravenous injection in patients has sharply limited inquiry in this area.

#### *Normal splenic function: Eusplenism*

As the clinical manifestations of splenic "excess" and "deficiency" become clearer and the spleen's functions more amenable to quantitation, the concept of optimal splenic function (eusplenism) is gradually emerging. Both excessive and deficient function represent clinical disturbances which may need to be brought under careful control.

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