Hyposplenism—a review

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The term 'hyposplenism' was introduced by Eppinger [1] to describe the condition that develops after splenectomy, and was adopted subsequently to describe the effects of impaired splenic function, whatever the aetiology [2,3]. The main functions of the spleen are concerned with the formed elements of the blood and immunity, but traditionally hyposplenism has been detected by haematological rather than by immunological methods. The conventional hallmark of the gross hyposplenic state is the presence, in the peripheral blood film, of Howell-Jolly bodies, intra-erythrocytic inclusions consisting of nuclear remnants.

This review highlights the non-surgical causes of hyposplenism, examines the possible mechanisms leading to impaired splenic function, emphasises the clinical sequelae of hyposplenism and considers practical aspects of the management of hyposplenism.

Causes of hyposplenism

Hyposplenism is most commonly due to splenectomy, the indications for which have been reviewed recently [4], but it may also result from agenesis or atrophy of the spleen, or may be 'functional'. The concept of functional hyposplenism arose from the observations that Howell-Jolly bodies can occur in the peripheral blood of patients whose spleens are of normal size or enlarged [5] and that in some conditions the haematological features are transient, suggesting that hyposplenism may be reversible [6].

A wide variety of disorders has been associated with hyposplenism (Table 1). In some of these conditions the mechanism is apparent. In sickle cell disease and essential thrombocythaemia, repeated infarction leading to atrophy of the spleen is implicated. Damage following the radio-contrast agent Thorotrast or external irradiation may cause hyposplenism. In amyloidosis the spleen is infiltrated and its normal structure and function are destroyed. High levels of circulating immune complexes may block splenic reticuloendothelial function in rheumatoid arthritis and systemic lupus erythematosus. Intestinal diseases are among the conditions most frequently reported in association with hyposplenism and, in the UK, if a hyposplenic blood film is discovered unexpectedly on routine haematological screening, the diagnosis is likely to be asymptomatic coeliac disease [32,33]. Despite much interest, the mechanism leading to hyposplenism in coeliac disease remains obscure, but the degree of hyposplenism appears to be related to the state of the jejunal mucosa, and splenic function may improve after withdrawal of gluten from the diet. However, in some patients there is irreversible loss of splenic function consequent on atrophy of the spleen [34,35]. Could reticuloendothelial

Table 1. Diseases in which hyposplenism may occur.

		Ref. No.
Congenital:	Congenital asplenia	7
	1. Ivemark's syndrome	
	2. Isolated anomaly	
	Congenital cyanotic heart disease	8
Haematological:	Sickle cell disease	5
	Essential thrombocythaemia	9
	Fanconi's syndrome	10
Autoimmune:	Systemic lupus erythematosus	11
	Glomerulonephritis/vasculitis	6
	Rheumatoid arthritis	12
	Hashimoto's disease	13
	Graves' disease	14
Intestinal:	Coeliac disease	15
	Dermatitis herpetiformis	16
	Ulcerative colitis	17
	Crohn's disease	17
	Tropical sprue	18
	Whipple's disease	19
	Intestinal lymphangiectasia	20
	Chronic ulcerative jejunitis	21
Miscellaneous:	Splenic irradiation	
	1. External	22
	2. Thorotrast	23
	Amyloidosis	24
	Sarcoidosis	25
	Sezary's syndrome	26
	Chronic active hepatitis	27
	Thrombosis	
	1. Splenic artery	28
	2. Splenic vein	28
	Graft-versus-host disease	29
	Immunodeficiency	30
	Hypopituitarism	31

blockade by high levels of circulating immune complexes, resulting from passage of antigens across the abnormal jejunal mucosa, be the explanation for hyposplenism in coeliac disease? The levels of immune complexes are increased in untreated coeliac disease, and fall following the introduction of a gluten-free diet [36], but hyposplenism has not been observed in children with coeliac disease despite high levels of circulating immune complexes [37], and Bullen *et al.* [38] found no difference in the levels of immune complexes between patients with or without hyposplenism. By analogy with animal models, in which lymphocyte depletion following drainage of the thoracic duct led to changes in the spleen similar to those observed in splenic atrophy [39], Bullen and Losowsky [40] proposed that hyposplenism in coeliac disease might result from loss of lymphocytes into the gut, and Corazza and Gasbarrini [41] pointed out that enteric loss of lymphocytes is common to those gastrointestinal conditions associated with hyposplenism.

Clinical sequelae

Infection

Overwhelming infection is now a well-known complication of splenectomy and, although the risk is greatest in children and within the first few years following operation, there is no doubt that patients of any age are at risk throughout their lives. The risk is least following splenectomy for trauma and increases when the spleen is removed because of disease [42]. Less well recognised is the fact that non-surgical hyposplenism may be complicated by severe infection (Table 2). Hyposplenism is characteristically associated with pneumococcal infection. The illness is usually abrupt in onset and follows a fulminant course. Severe infection with other bacteria, in particular *H. influenzae* and meningococcus, is well documented and overwhelming infection with organisms not usually pathogenic in man has been seen in hyposplenic subjects [55-57]. In addition to bacterial infections, malaria and babesiosis appear to be more common in asplenic subjects [58,59] and there have been reports that some viral infections may be more frequent and severe after splenectomy [60,61].

The increased risk of infection associated with hyposplenism results from a number of factors. Loss or reduction of splenic reticuloendothelial function is important because, in the non-immune subject, the spleen assumes the major role in clearing bacteria from the circulation and, irrespective of immune status, the spleen has a higher capacity for uptake per unit weight than the liver [62]. Furthermore, there is evidence that the function of alveolar macrophages and hepatic Kupffer cells is impaired after splenectomy [63-65], which suggests that the spleen may have a necessary role in the normal phagocytic activity of reticuloendothelial cells. *In vitro* phagocytosis and chemotaxis of polymorph neutrophils are impaired in the presence of serum from splenectomised subjects [66], which may be due to low levels of IgM, properdin and tuftsin, that act as opsonins [67]. Finally, hyposplenism results in defective antibody responses, particularly to antigens administered intravenously. The primary antibody response is depressed and the secondary response is also abnormal, with impairment of the normal switching of IgM to IgG production [68,69]. It appears that absence of the spleen causes a long-lasting B-cell defect, characterised by a limited capacity of circulating B-cells to differentiate into antibody secreting cells [70-72].

Autoimmune phenomena

Splenic atrophy is associated with a high incidence of autoantibodies and autoimmune disease [33,73] and several groups have found an increased frequency of autoantibodies in splenectomised subjects [74-76]. Robertson and his colleagues [76], who studied patients before and after splenectomy, observed the development of autoantibodies within a few months of the operation. The expression of these autoimmune phenomena may be due to an imbalance in immunoregulatory cells. The spleen is a rich source of suppressor T-cells [77], which are believed to be important in regulating immune responses, and splenectomy results in impaired suppressor cell activity in the peripheral blood [78,79].

Table 2. Severe infection complicating non-surgical hyposplenism.

Organism	Aetiology of hyposplenism	Ref. No.
Pneumococcus	Congenital asplenia	43
Pneumococcus	Hereditary splenic hypoplasia	44
H. influenzae		
Pneumococcus	Congenital asplenia	7
Pneumococcus	Idiopathic splenic atrophy	45
Pneumococcus	Idiopathic splenic atrophy	46
Pneumococcus	'Ischaemic' atrophy	47
Pneumococcus	Splenic infarction	48
Pneumococcus	Sickle cell disease	49
Pneumococcus	Splenic atrophy in Still's disease	50
Pneumococcus	Splenic atrophy and SLE	11
Salmonella	Splenic atrophy and SLE	51
Pneumococcus	Sarcoid infiltration	25
Pneumococcus	Splenic atrophy and ulcerative colitis	52
Pneumococcus	Hyposplenism in ulcerative colitis	17
clinical picture of Gram negative shock and DIC* (no organism)		
Pneumococcus	Splenic atrophy in coeliac disease	53
Meningococcus	Hyposplenism in coeliac disease	54
Pneumococcus	Splenic atrophy after Thorotrast	23
Pneumococcus	Splenic atrophy following irradiation	22

*Disseminated intravascular coagulation

Thrombosis

Rosenthal [80] was the first to draw attention to venous thrombosis complicating splenectomy. Subsequently, there have been a number of case reports confirming the association. These have been reviewed critically by Dawson *et al.* [81] who point out imperfections in the information. The data have usually been collected regardless of the disorder for which splenectomy was performed, and both benign and malignant disorders, in which the incidence of deep vein thrombosis might be expected to differ, have been included. Most studies are retrospective and the methods for detection of venous thrombosis have varied from clinical signs to venography and isotope techniques. Finally, the majority of studies have not included an appropriate or adequately described control group. In the studies by Dawson *et al.* [81] and Butler *et al.* [82], which avoided most of the above criticisms, no significant increase in deep vein thrombosis was observed after splenectomy. Furthermore, no increase in mortality due to venous thrombo-embolism was observed in a study of veterans of the Second World War who had undergone splenectomy following trauma [83]. However, this latter study did reveal an excess mortality from ischaemic heart disease, principally myocardial infarction, which raises the possibility that the well recognised thrombocytosis and increased blood viscosity [85] that occur after splenectomy might predispose to coronary artery thrombosis.

Management

The conventional surgical dogma that an injured spleen should be removed has been challenged [86]. Alternatives include conservative management, splenorrhaphy, partial splenectomy and splenic auto-transplantation [4]. Moore *et al.* [87] found that some form of splenic salvage was possible in 56 per cent of 200 patients with splenic injury. On the basis of experiments in animals, it seems that procedures which conserve the normal blood supply and more than 25 per cent of normal splenic mass are most likely to preserve normal splenic function [88,89]. The value of auto-transplantation is controversial [90] and there are reports of fatal, overwhelming sepsis occurring in patients with 'functional' auto-transplants, as judged by their ability to accumulate radio-colloid [91,92].

Despite evidence that the antibody response following vaccination is blunted after splenectomy [71,93], and reports of vaccine-type pneumococcal infection occurring in vaccinated hyposplenic patients [94,95], use of pneumococcal vaccine is recommended [96], and, whenever elective splenectomy is considered, the vaccine should be given at least two weeks beforehand. From a study of the distribution of serotypes of pneumococci isolated from patients previously given pneumococcal vaccine compared with the distribution of serotypes isolated from unvaccinated persons, the efficacy of vaccination has been calculated to be 85 per cent (albeit with wide confidence limits) in adults with hyposplenism [97]. Vaccination of children under the age of two is less effective [98,99] and penicillin-prophylaxis should be employed in these patients. In older patients, poor compliance with long-term prophylaxis is a problem, but administration of oral penicillin is recommended for at least two years after splenectomy [100].

Finally, the patient and his family should be made aware of the risks of infection and be advised to seek prompt medical attention, and the physician should be willing to administer antibiotics freely for any symptoms of infection.

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