EDITORIAL REVIEW

Consequences of impaired splenic function

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Introduction
Interest in the effects of splenectomy began about a hundred years ago. By 1900, there were several reports of successful splenectomies and in 1913 Eppinger suggested the term 'hyposplenism' to describe the condition which develops after removal of the spleen. Subsequently the term was also applied to impairment of splenic function in congenital hypoplasia or acquired splenic atrophy. However, because absence of the spleen was not clearly associated with illness, it was thought that hyposplenism was of little importance to the clinician.

Over the last three decades it has become increasingly evident that, in some circumstances, hyposplenism may be a vital factor in the development of serious or fatal illness, and this knowledge has stimulated much interest in the role of the spleen and the consequences of impaired splenic function.

The purpose of this review is to consider (1) aspects of splenic function which are altered in hyposplenism and are of clinical relevance, (2) the risk of development of complicating illness in hyposplenism and (3) ways of lessening the risks associated with hyposplenism.

Aspects of splenic function which are altered in hyposplenism

Erythrocyte morphology
The spleen removes fragmented, damaged or old erythrocytes from the blood circulating through it ('culling') and remolds the surface of maturing erythrocytes, thereby preserving their normal surface area to volume ratio. Erythrocyte inclusions (Howell–Jolly bodies, siderotic granules and Heinz bodies) are selectively removed ('pitting') (Crosby, 1963; Nathan, 1969; Crosby, 1977). When these three functions are not performed the appearance of acanthocytes, target cells and Howell–Jolly bodies in the peripheral blood film provides evidence of hyposplenism (Lipson, Bayrd & Watkins, 1959; Crosby, 1963). Although in patients with little or no splenic function changes in the blood film, especially the presence of Howell–Jolly bodies, may be obvious, with lesser degrees of impairment the changes are subtle, and Howell–Jolly bodies may be absent (Pettit, 1977). However, the detection of blood-film changes provides a useful screening test for hyposplenism, which may have been unsuspected by the clinician and may lead to the diagnosis of underlying disease (Ferguson, Hutton, Maxwell & Murray, 1970; Bullen, Hall, Gowland & Losowsky, 1978). Hyposplenism due to splenic atrophy is associated with several diseases including coeliac disease (Marsh & Stewart, 1970), dermatitis herpetiformis (Pettit, Hoffbrand, Seah & Fry, 1972), ulcerative colitis (Ryan, Smart, Holdsworth & Preston, 1978), autoimmune disease (War drop, Dagg, Lee, Singh, Dyet & Moffat, 1975), previous thorotrast administration (Horta, 1967) and thrombo cythaemia (Marsh, Lewis & Szur, 1966). Impaired splenic function without diminution in size of the spleen is found particularly in sickle-cell disease (Pearson, Spencer & Cornelius, 1969; Spencer, Dhawan, Suresh, Antar, Sziklas & Wasserman, 1978).

Conventional blood-film examination is not a sensitive or quantitative way of documenting splenic functional impairment, but counting of erythrocyte membrane abnormalities, consisting of surface indentations or 'pits' detected by interference phase microscopy, provides a more accurate method of assessment (Kent, Minick, Volini & Orfei, 1966; Holroyde, Oski & Gardner, 1969; Pearson, Johnston, Smith & Touloukian, 1978).
Platelet counts

Thrombocytosis is a well-recognized hazard in the early post-splenectomy period (Wintrobe, 1967; Coltheart & Little, 1976) and in some patients the thrombocytosis may persist for years (Lipson et al., 1959), particularly if there is continuing anaemia (Hirsh & Dacie, 1966; Nagasue, Inokuchi, Kobayashi & Saku, 1977). Thrombocytosis also occurs in association with splenic atrophy. In some patients with ulcerative colitis (Ryan et al., 1978) or coeliac disease (Nelson, Ertan, Brooks & Cerda, 1976; Bullen, Hall, Brown & Losowsky, 1977) both activity of the inflammatory lesion and hyposplenism contribute to thrombocytosis. Splenic atrophy secondary to thrombocytosis may further increase the platelet count (Hardisty & Wolff, 1955; Marsh et al., 1966).

The mechanism of production of thrombocytosis in hyposplenism is not well understood. Possible roles for the spleen include removal of platelets from the circulation, a reservoir function, and secretion of a humoral factor which suppresses platelet production (Bessler, Mandel & Djaldetti, 1978).

There are several reports of thromboembolism and bleeding occurring in association with thrombocytosis in post-splenectomy patients, mostly soon after operation but sometimes months or years later (Hayes, Spurr, Hutaff & Sheets, 1963; Balz & Minton, 1975; Nagasue et al., 1977). A recent survey of mortality in 1939–1945 war veterans splenectomized because of trauma showed an excess of deaths from ischaemic heart disease, which the authors speculated might be due to persistent thrombocytosis (Robinette & Fraumeni, 1977).

Clearance of particulate matter

The clearance from the blood of radio-labelled damaged erythrocytes trapped in the splenic microcirculation may be used to quantify splenic function (Pettit, 1977). Splenic reticuloendothelial cells take up smaller particles by phagocytosis, and use is made of this in visualization of the spleen by scanning after injection of radioactive colloids (Spencer & Pearson, 1975). The reduction of particle clearance in splenic hypofunction may partly explain the occurrence of attacks of malaria or babesiosis in splenectomized individuals (Pryor, 1967; Fitzpatrick, Kennedy, McGeown, Orpopoulos, Robertson & Soyannwo, 1969; Bruce-Chwatt, 1972), since some infected erythrocytes are phagocytosed in the spleen (Schnitzer, Sodeman, Mean & Contacos, 1973), which may also 'pit' parasites from the cells (Schnitzer, Sodeman, Mead & Contacos, 1972).

In the non-immune host the spleen assumes greater importance in the clearance of blood-borne bacteria (Leung, Szal & Drachman, 1972), and it has a higher capacity for uptake per unit weight than the liver, irrespective of immune status (Schulkind, Ellis & Smith, 1967). Specific antibody promotes efficient phagocytosis in the liver (Ellis & Smith, 1966; Schulkind et al., 1967) and immunization before splenectomy will give some degree of protection from intravenously administered organisms (Leung et al., 1972).

Immune responses

In protection from blood-borne infective organisms the spleen is uniquely equipped as an anatomical and phagocytic filter in association with lymphoid tissue, which can produce opsonizing antibody. Hyposplenism causes defective antibody responses to intravenously administered particulate antigens (Rowley, 1950; Schwartz & Pearson, 1972). The primary antibody response is decreased and the secondary response is also abnormal, with impairment of the normal switching from IgM to IgG (Lozzio & Wargon, 1974; Baker, Verrier Jones, Peacock & Read, 1975; Sullivan, Ochs, Schiffman, Hammerschlag, Miser, Vichinsky & Wedgwood, 1978). The response to subcutaneously administered antigen is normal (Ammann, Adiegeo, Wara, Lubin, Smith & Mentzer, 1977; Sullivan et al., 1978). Splenectomy in children may result in depressed serum IgM concentrations (Schumacher, 1970; Claret, Morales & Montaner, 1975; Andersen, Cohn & Sorensen, 1976; Constantoulakis, Trichopoulos, Avgoustaki & Economou, 1978), which are also found in splenic atrophy due to sickle-cell disease (Gavrili, Rothenberg & Guy, 1974).

In addition to specific antibody, the spleen also produces non-specific stimulators of the immune response, which may be of great importance in combating the early stages of infection. Splenectomized dogs have impairment of the activity of leukokinin, a γ-globulin which coats blood leucocytes and is necessary for their phagocytic activity (Najjar, Fidalgo & Stitt, 1968). Normal leukokinin activity is maintained by a tetrapeptide which originates from the spleen, is incorporated in the leukokinin molecule and is enzymatically
cleaved from leucokinin after attachment to the leucocyte (Najjar & Constantopoulos, 1972). The activity of the phagocytosis-promoting tetrapeptide (tuftsin) has been shown to be decreased in splenectomized subjects (Spirer, Zakuth, Diamant, Mondorf, Stefanescu, Stabinsky & Fridkin, 1977) and in hyposplenism due to sickle-cell disease (Constantopoulos, Najjar, Wish, Necheles & Stolbach, 1973). Familial tuftsin deficiency has been reported in a few patients, some of whom had recurrent severe infections alleviated by γ-globulin injections (Constantopoulos, Najjar, Wish, Necheles & Stolbach, 1973). Familial tuftsin deficiency has been described in patients with splenic atrophy (Winkelstein, Shin & Wood, 1972; Winkelstein, 1973; Winkelstein, Bocchini & Schiffman, 1976).

In sickle-cell disease diminished alternative pathway activity (Johnston, Newman & Struth, 1973) and impaired opsonization of pneumococci (Winkelstein & Drachman, 1968) have been demonstrated and it has been suggested that these two features might be related to splenic hypofunction.

Although diminished alternative pathway activity has been described in splenectomized individuals (Polhill & Johnston, 1975), it cannot be concluded that the impaired opsonization in sickle-cell disease is related to splenic function since studies have shown no difference in opsonizing activity after splenectomy even in patients who have had severe sepsis (Winkelstein & Lambert, 1975; Kitchens, 1977).

Cell-mediated immunity is probably normal in hyposplenism. Lymphocyte-transformation studies with common antigens and mitogens are normal after splenectomy (Andersen et al., 1976) and delayed hypersensitivity skin tests or rejection of skin allografts are not affected by hyposplenism (Battisto, Borek & Busci, 1971; Lozzio & Wargon, 1974; Bullen, Hall, Cooke & Losowsky, 1977b). Sparing of cell-mediated immunity may be the reason for the finding that there is no increased risk of malignancy after splenectomy (Robinette & Fraumeni, 1977).

**Peripheral blood lymphocyte counts**

Although splenectomy involves removal of about one-quarter of the body’s lymphoid tissue, there is often persistent lymphocytosis in the peripheral blood (Lipson et al., 1959). Animal experiments suggest that there is a loss of splenic inhibition of lymphocyte production (Ernstrom & Sandberg, 1970) and the release of increased numbers of newly formed lymphocytes from the bone marrow, perhaps in compensation for depressed thymic activity (Hougen, Hansen, Kehn Jensen & Ropke, 1977). The relative proportions of lymphocytes in the peripheral blood are altered by splenectomy, with an increase in the percentage and absolute numbers of Null cells, but normal T cell numbers (Andersen et al., 1976; Bullen & Losowsky, 1978).

**Formation of auto-antibodies**

A high frequency of auto-antibody formation has been described in patients with splenic atrophy (Wardrop et al., 1975; Bullen et al., 1978), but whether this is due to the hyposplenism is not clear, since, in some of the disorders studied, autoantibody formation might be due to concomitant T cell depletion secondary to the underlying illness (Allison, Denman & Barnes, 1971; Bullen & Losowsky, 1978). However, a direct role for the spleen is suggested by a study in the mouse (Sy, Miller, Kowach & Claman, 1977) showing that the generation of suppressor T cells is dependent on the presence of the spleen. Whether suppressor T cell precursors are activated in the spleen, or whether the spleen provides a humoral or cellular factor is not clear, but the spleen has been shown to be the major source of suppressor cells (Pierce & Kapp, 1976; Romball & Weigle, 1977) and these are thought to be an important mechanism for immunoregulation (Gershon, Lance & Kondo, 1974) and the regulation of autoimmunity (Allison, 1974a, b; Talal, 1976).

In man, it seems that the clinician might expect auto-antibody formation in patients with splenic atrophy, but whether this applies to other forms of splenic hypofunction is not known. The relationship of the well-recognized decrease in splenic size with ageing to the increased development of autoantibodies has not been studied in man, although animal studies suggest that suppressor T cell mechanisms of immunoregulation are impaired in aged individuals (Naor, Bonavida & Walford, 1976).

**Risk of complicating illness in hyposplenism**

**Thrombosis or bleeding**

The risks of thrombosis or bleeding and the association with thrombocytosis in the early post-
thromboembolism in 10.7% of 150 consecutive splenectomies, and a relationship to thrombocytosis in patients not receiving heparin. Whereas cytosis in patients not receiving heparin, Coon, Penner, Clagett & Eos (1978) detected deep leg-vein thrombosis in 6% of 86 patients undergoing elective splenectomy, with no relationship to thrombocytosis. Robinette & Fraumeni (1977) found no excess late mortality from thromboembolism after splenectomy for trauma, but there was a significantly increased mortality from ischaemic heart disease, a previously unreported complication. The number of infections is not related to the anatomical size of the spleen (Robinson & Watson, 1966; Kabins & Lerner, 1970), which is not surprising since Pearson et al. (1969) have shown that early functional asplenia can occur in sickle-cell disease, even though the spleen may be enlarged.

However, the disease for which splenectomy was undertaken must also be considered. The risk of thrombocytosis and thrombosis is probably increased in patients with haemolytic anaemia, cirrhosis and myeloproliferative disorders (Miller & Hagedorn, 1951; Hayes et al., 1963; Balz & Minton, 1975; Gordon, Schaffner, Bennett & Schwartz, 1978); persistent thrombocytosis and its complications may be increased by anaemia (Hirsh & Dacie, 1966; Hayes et al., 1963; Nagasue et al., 1977).

Severe infection

Interest in the complex role of the spleen in immune defence has been stimulated by increasing awareness of the risk of serious infection in hypoplastic states. Without the spleen, prompt action against bacteremia is diminished and organisms may rapidly proliferate (Torres & Bisno, 1973). Since 1952, when King & Shumacker drew attention to the risk of major sepsis after splenectomy in childhood, many severe infections have been reported. A recent survey has shown increased late mortality from pneumonia in adult subjects splenectomized for trauma (Robinette & Fraumeni, 1977), a group in whom the risks are thought to be least. However, the most characteristic type of post-splenectomy infection is fulminating septicaemia, which is difficult to diagnose early and has a high mortality. The pneumococcus is the most commonly involved organism and some such cases also show evidence of disseminated intravascular coagulation. About a quarter of the cases are due to the meningococcus, Escherichia coli or Haemophilus influenzae (Singer, 1973). The syndrome of overwhelming post-splenectomy infection may occur in adults splenectomized for trauma, who have no serious underlying disease (Gopal & Bisno, 1977) and has been described in congenital asplenia (Myerson & Koelle, 1956; Gopal & Bisno, 1977; Waldman, Rosenthal, Smith, Shurin & Nadas, 1977), hereditary splenic hypoplasia (Kevy, Tefft, Vawter & Rosen, 1968) and splenic atrophy due to previous infection (Grant, Horowitz, Lorian & Brodman, 1970), throrotrast-induced fibrosis (Bensinger, Keller, Merrell & O’Leary, 1971), ulcerative colitis (Ryan et al., 1978) or undetermined causes (Parr, Shipton & Holland, 1953; Whitaker, 1969; Bisno & Freeman, 1970). In some of these cases the hypoplasemia was not suspected until after the onset of severe infection. A correlation between infection and splenic hypofunction in sickle-cell disease has been described (Falter, Robinson, Kim, Go & Taubkin, 1973). The number of infections is not related to the anatomical size of the spleen (Robinson & Watson, 1966; Kabins & Lerner, 1970), which is not surprising since Pearson et al. (1969) have shown that early functional asplenia can occur in sickle-cell disease, even though the spleen may be enlarged.

The risk of severe infection after splenectomy is influenced by several factors. Singer (1973), having examined 23 series from the literature and added his own series, concluded that the overall incidence was 4-25%, with an overall mortality of 2-52%, but the incidence varied widely with the disease for which splenectomy was performed, being lowest in splenectomy for trauma (1.45%) and highest in thalassaemia (24.8%). The risk is particularly high if splenectomy is associated with pre-existing abnormalities of immunity (Eraklis & Filler, 1972; Eraklis, Kevy, Diamond & Gross, 1967; Singer, 1973) and/or combined with immunosuppressive therapy, for example in Hodgkin’s disease (Chilcote et al., 1976; Hancock, Bruce, Ward & Richmond, 1976) or after renal transplantation (McEnery & Flanagan, 1977; Schroter, West & Weil, 1977).

Another factor influencing the risk of sepsis is the age at which splenectomy is performed (Horan & Colebatch, 1962; Walker, 1976). Owing to immaturity of the immunological system (Norden, Melish, Overall & Baum, 1972) or the lack of previous exposure to antigens (Greenfield, Peter, Howie, Ploussard & Smith, 1972), young children may not have developed specific opsonizing antibody to a variety of organisms (Ellis & Smith, 1966). Furthermore, the risk is greatest within the first 2 or 3 years after operation (Singer, 1973; Walker, 1976). However, although underlying disease, age at operation and time since operation
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influence the incidence of infection, cases have been reported in which patients with no serious underlying disease, operated on as adults, have developed infection several years later (Grinblat & Gilboa, 1975; Gopal & Bisno, 1977).

Patients with hyposplenism due to splenic atrophy or agenesis are also at risk of infection. Thus sepsis occurred in 27% of 59 children with congenital asplenia (Waldman et al., 1977). In splenic atrophy, presumably developing in adult life, the incidence appears to be much lower, although several reports show that the risk is present in this heterogeneous group of patients (Whitaker, 1969; Bisno & Freeman, 1970; Grant et al., 1970; Bensinger et al., 1971; Ryan et al., 1978). Patients with sickle-cell disease have a 5% risk of meningitis and an additional 4% risk of septicaemia (Powars, 1975); in addition to the hyposplenism, the risk may be increased by the decrease in serum opsonizing activity for pneumococci (Winkelstein & Drachman, 1968; Johnston et al., 1973).

Risk of infection after splenectomy for trauma

Although splenectomy after traumatic rupture carries an increased risk of subsequent infection (Gopal & Bisno, 1977; Robinette & Fraumeni, 1977), the risk is lowest in this group of patients (Singer, 1973) and some authors have concluded that it is negligible (Pedersen & Videbaek, 1966). Recent evidence suggests that the explanation for these findings is that splenic function may return because of heterotopic autotransplantation of splenic tissue within the peritoneal cavity. Serum tuftsin concentrations (Spier et al., 1977) and the numbers of 'pitted' erythrocytes (Pearson et al., 1978) are normal in some patients splenectomized for trauma, and in a few patients 'spleen' scanning has confirmed the presence of multiple nodules of reticuloendothelial tissue (Pearson et al., 1978).

Lessening the risks of hyposplenism

Careful consideration of the indications for splenectomy

The risks associated with hyposplenism should be taken into account whenever splenectomy is considered.

About 20% of splenectomies are incidental to another surgical procedure, either to increase exposure or because of operative injury (Danforth & Thorbjarnarson, 1976). A recent article describes the anatomical basis of operative injury to the spleen and, if it should occur, a way of achieving topical haemostasis (Morgenstern, 1977). Although some incidental splenectomies are unavoidable, the number might be decreased. Conservative surgery after traumatic rupture might also be feasible in some cases (Grosfeld & Ranochak, 1976; Sherman & Asch, 1978).

The advantages and risks of elective splenectomy should be carefully weighed. There is considerable debate as to the advantages of splenectomy in Hodgkin's disease (Desser & Ultmann, 1972; British National Lymphoma Investigation, 1975; Chilcote et al., 1976; Hancock et al., 1976; Spier et al., 1977; Dearth, Gilchrist, Telander, O'Connell & Weiland, 1978). In congenital haemolytic anaemia and idiopathic thrombocytopenia splenectomy can usually be deferred until the child is over 3 years of age (Walker, 1976).

Possibility of autotransplantation

By analogy with the accidental autotransplantation of splenic tissue, which occurs after traumatic rupture, deliberate autotransplantation in suitable cases might be considered. In animal models, splenic tissue implants can restore some immunological activities (Likhite, 1975) and in man inadvertently autotransplanted tissue may function (Mazur, Field, Cahow, Schiffman, Duffy & Forget, 1978) and be responsible for the low incidence of infection after trauma. However, autotransplanted splenic tissue does not protect from pneumococcal challenge in rats (Schwartz, Goldthorn, Winkelstein & Swift, 1978).

Management of thrombocytosis

The treatment of post-splenectomy thrombocytosis remains controversial (Balz & Minton, 1975; Coon et al., 1978) but in high-risk patients, particularly those with myeloproliferative disorders, the use of a variety of antiplatelet agents has been recommended (Bensinger, Logue & Rundles, 1970; Zucker & Mielke, 1972; Gordon et al., 1978). Persistent anaemia should be avoided if possible (Hirsh & Dacie, 1966; Nagasue et al., 1977). The finding of excess mortality from ischaemic heart disease after splenectomy (Robinette & Fraumeni, 1977) raises the question of whether antiplatelet therapy should be given long term (Weiss, 1978).
Infection in hyposplenism

There are several suggestions for the prevention of infection in hyposplenism.

Malarial zones should be avoided if possible, otherwise suppressive therapy should be assiduously taken (Shute, 1975).

Several authors recommend penicillin prophylaxis against pneumococcal infection (Chilcote et al., 1976; Walker, 1976; Gopal & Bisno, 1977; Waldman et al., 1977; Winkelstein, 1977), in children especially, but perhaps also in the first 2 years after splenectomy in adults. However, overwhelming infection by penicillin-insensitive organisms may occur (Ertel, Boles & Newton, 1977).

Polyvalent pneumococcal polysaccharide vaccine is immunogenic in hyposplenic patients and may protect against systemic infection (Ammann et al., 1977; Sullivan et al., 1978): it has been recommended that all such patients be vaccinated, although this may not be useful in Hodgkin’s disease (Siber, Weitzman, Aisenberg, Weinstein & Schiffman, 1978; Sullivan et al., 1978). Development of vaccines against other organisms may increase the effectiveness of prophylaxis.

In familial tuftsin deficiency, γ-globulin administration decreased the incidence of infection and, by analogy, γ-globulin has been recommended for prophylaxis after splenectomy (Reeves, 1977). It has also been suggested that tuftsin, which can be synthesized, may be useful (Najjar & CONSTANTOPOULOS, 1972; Mikulski, Von Hoff, Rozencweig & Muggia, 1977; Spirer et al., 1977).

The hazards of overwhelming sepsis might be reduced if doctors and patients were aware of the risks and the need for early and intensive therapy of any infection in any patient with splenectomy or a condition associated with hyposplenism.

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