

## Leading article

# Hyposplenism in gastrointestinal disease

The hazards of living without a spleen were recognised by paediatricians in the early 1960s when they focused attention on the syndrome of fulminant sepsis occurring within the first two years of splenectomy.<sup>1</sup> We now recognise that the danger of post splenectomy sepsis extends into adult life and splenectomised patients remain at risk beyond 30 years after surgery.<sup>2</sup> It has been suggested that up to 2% of splenectomised patients are at risk of post splenectomy sepsis,<sup>3</sup> and while rare, the splenectomised patient has a relative risk of fulminant infection greater than 500 times that of subjects with an intact spleen.<sup>4</sup> Infection is often caused by the pneumococcus but any organism may be responsible, including meningococcus<sup>5</sup> and *Haemophilus influenzae*.<sup>6</sup> Furthermore, patients are unusually vulnerable to protozoal infections including malaria<sup>7</sup> and babesiosis.<sup>8</sup>

Problems after splenectomy may just be the tip of the iceberg. It is now clear that many other diseases are associated with impaired splenic function in the presence of intact spleens (Table<sup>9 10</sup>) and these patients with functional hyposplenism are also vulnerable to similar syndromes of fulminant sepsis. For patients with sickle cell disease and thrombocythaemia, in whom there is infarction of splenic tissue, the cause of the hyposplenism is obvious and it is also easy to understand the mechanisms involved in the infiltrative diseases. In gastrointestinal disorders, including inflammatory bowel disease and coeliac disease, however, the reasons for the hyposplenism are obscure. There is now good evidence that impaired splenic function also occurs in alcoholic liver disease<sup>11</sup> and in patients receiving long term parenteral nutrition for intestinal failure.<sup>12</sup>

### Assessment of splenic function

Early studies to define those patients with hyposplenism in gastrointestinal disease relied on the identification in a peripheral blood film of Howell-Jolly bodies, acanthocytes,

and target cells. It soon became apparent that this method was not sufficiently sensitive to pick up lesser degrees of hyposplenism. To overcome this problem Marsh *et al* measured the clearance of isotopically labelled heat damaged erythrocytes.<sup>13</sup> This test relies on the fact that red cells damaged by heat become mildly spherocytic and are cleared preferentially by the spleen when re-injected. In this way they behave in a similar way to erythrocytes in hereditary spherocytosis. Impaired clearance of these labelled cells has been shown to be a reliable index of hyposplenism.

While the clearance of heated red cells proved a useful experimental tool, it was time consuming and needed careful calibration. A simpler method was provided by Corazza *et al*, who were able to exploit some earlier observations on erythrocytes from splenectomised patients.<sup>14 15</sup> If these erythrocytes are viewed by differential interference contrast microscopy (which gives a three dimensional view), pits or craters are seen. The number of pits or craters can be counted in a simple and reproducible way.<sup>15</sup> In health, less than 2% of erythrocytes contain pits, whereas after splenectomy up to 50% of cells show pits.<sup>16</sup> This therefore gives a method of assessing splenic function which correlates with the more complex methods.<sup>15</sup> Electron microscopy suggests that these pits are really vacuoles containing intracellular debris of ferritin, haemoglobin, and cell membranes.<sup>17</sup> This method, supplemented with ultrasonic measurements of spleen size,<sup>18 19</sup> therefore provides a relatively easy way of assessing splenic size and function.

### Coeliac disease

Several groups using the clearance of isotopically labelled erythrocytes or pitted red cell counts have shown that between 25 and 75% of patients with coeliac disease have hyposplenism.<sup>20 21</sup> The severity of the hyposplenism increases with age at diagnosis and with the duration of exposure to gluten. Although in most patients hyposplenism improves with gluten withdrawal, some investigators have identified patients in which it progresses in spite of apparently strict dietary control.<sup>22</sup> This reflects two components of the impaired splenic function in coeliac disease, reversible hyposplenism and irreversible splenic atrophy.<sup>22 23</sup> The severe complication of gut lymphoma does not seem to be influenced by whether or not hyposplenism is present.<sup>24</sup>

No single mechanism has been put forward to explain the hyposplenism of coeliac disease. In some patients the hyposplenism is associated with generalised lymph node atrophy and it has been suggested that this is all part of a more widespread atrophy of the lympho-reticular system. This hypothesis was not supported by Palmer *et al*,<sup>25</sup> who demonstrated that Kupffer cell function in patients with hyposplenism, determined by a technique of clearance of micro-aggregated albumin, was similar to that of control

Diseases associated with impaired splenic function in patients with intact spleens

Haematological	Sickle cell disease Thrombocythaemia
Auto-immune	Systemic lupus erythematosus Thyroid disease Rheumatoid arthritis
Gastrointestinal	Coeliac disease Ulcerative colitis Crohn's disease Whipple's disease Idiopathic ulcerative enteritis Tropical sprue Intestinal lymphangiectasia Alcoholic liver disease
Miscellaneous	Sarcoid Amyloidosis Old age Long term parenteral nutrition

splenectomised subjects. Increased levels of circulating immune complexes have been found in untreated coeliac disease<sup>26</sup> and this might lead to functional blockade of the splenic reticulo-endothelial system. Very high levels of immune complexes in childhood, however, are insufficient to induce splenic hypofunction in childhood coeliac disease.<sup>27</sup> Patients with dermatitis herpetiformis, a disease linked closely with coeliac disease, may also show evidence of impaired splenic function.

### Chronic inflammatory bowel disease

Severe hyposplenism in inflammatory bowel disease has been shown by both the method of heated red cell clearance<sup>28-30</sup> and pitted erythrocyte counts.<sup>18</sup> The relationship with disease activity seems much clearer with ulcerative colitis: here both medical and surgical treatment may improve the hyposplenism, which is dependent on the extent of the disease.<sup>29,30</sup> Some patients, however, as with their coeliac counterparts, have irreversible splenic atrophy<sup>29</sup> and remain at risk of infection even when their colitis is in remission.<sup>18,31</sup> Pereria *et al.*,<sup>32</sup> using the simple measure of spleen length at laparotomy, noted that patients with ulcerative colitis and Crohn's disease shown to have small spleens had more severe disease and more complications such as perforation, fistulas, abscesses, bleeding, and toxic megacolon. Disseminated intravascular coagulation has also been shown in hyposplenic patients with inflammatory bowel disease,<sup>30</sup> a complication noted previously in asplenic subjects.<sup>33</sup> The association between Crohn's disease and hyposplenism is less well defined,<sup>18,30,34</sup> and there are suggestions that the link is strongest with colonic Crohn's disease. The mechanisms, as with coeliac disease, are poorly understood but the profound enteric loss of lymphocytes<sup>35</sup> and raised levels of circulating immune complexes<sup>26</sup> in inflammatory bowel disease might contribute to the splenic hypofunction.

### Chronic liver disease

The spleen in liver disease sometimes plays a dual role in that it may contribute to haematological hypersplenism concurrently with functional hyposplenism.<sup>11</sup> Earlier suggestions of functional hyposplenism in immune chronic active hepatitis and primary biliary cirrhosis<sup>36</sup> have not been confirmed<sup>37</sup> but there are now clear indications that hyposplenism frequently complicates alcoholic liver disease.<sup>11</sup> The alcohol itself, rather than the presence of chronic liver disease, seems to be more important since in most patients abstinence reverts the hyposplenic changes.<sup>38</sup>

### Miscellaneous gastroenterological conditions

Hyposplenism has been described in several other gastrointestinal diseases though they have been less extensively investigated. Low spleen weights (between 5 and 75 g) have been noted at necropsy in subjects with tropical sprue though no formal studies of splenic function have ever been undertaken.<sup>39</sup> Splenic atrophy or Howell-Jolly bodies, or both, are often features of chronic idiopathic ulcerative enteritis though of course these findings may be primarily related to the pre-existing gluten enteropathy. Increased pitted cell counts with other confirmatory evidence of hyposplenism have been noted in Whipple's disease<sup>40</sup> and intestinal lymphangiectasia.<sup>41</sup>

A recent report<sup>12</sup> has highlighted impaired splenic function in patients with intestinal failure who are receiv-

ing parenteral nutrition. The degree of hyposplenism, measured by pitted erythrocyte counts, seemed to increase with the duration of intravenous feeding but was unrelated to the administration of lipid.

### Is hyposplenism important in gastrointestinal disease?

Some authors have argued that the risks of post splenectomy sepsis have been overstressed.<sup>42,43</sup> Holdsworth *et al.*<sup>43</sup> found that splenectomy performed for trauma in otherwise normal adults did not seem to be associated with an increased risk of infection. The increased risk resulted from coexisting disease, particularly liver disease. Nevertheless most paediatricians, haematologists, and physicians regard post splenectomy sepsis as a very real and much feared entity. A series of reports from Sheffield<sup>28-30</sup> have disclosed high rates of postoperative infections after surgery for ulcerative colitis in patients with defective splenic function and Pereira *et al.*<sup>32</sup> have shown that patients with the smallest spleens at laparotomy have the most complications. Overwhelming pneumococcal septicaemia has been recorded in both ulcerative colitis and coeliac disease.<sup>31,44</sup> It has also been reported in patients with alcoholic liver disease and hyposplenism, which seems to be an additional factor in the susceptibility of alcoholics to infections.<sup>45</sup> Patients receiving long term parenteral nutrition for intestinal failure have also been shown to be at risk of infection that is unrelated to the central line, particularly with the pneumococcus and *Haemophilus influenzae* in the presence of hyposplenism.<sup>12</sup>

### Management of hyposplenism in patients with gastrointestinal disease

The improvement in the medical and surgical management of patients with inflammatory bowel disease over the past decade or so may explain the lower incidence of hyposplenism noted in a recent study<sup>18</sup> compared with previous reports.<sup>30</sup> None the less, patients with ulcerative colitis complicated by hyposplenism remain susceptible to serious infections, particularly in the immediate post colectomy period, and which may be associated with disseminated intravascular coagulation. Treatment with heparin in these cases, has met with some success.<sup>29,30</sup> The hyposplenism associated with alcoholic liver disease may be reversible with abstinence from alcohol.<sup>38</sup> This is another reason why we should continue to advise these patients strongly to stop drinking.

### Should we attempt to protect potentially hyposplenic patients?

While it is now standard practice to protect splenectomised patients from fulminant sepsis with pneumococcal vaccines and prophylactic antibiotics using penicillin, there are few recommendations about hyposplenic subjects.

In patients with sickle cell disease no pneumococcal infections were observed in a two year follow up after immunisation with the octavalent vaccine.<sup>46</sup> Unfortunately, the antibody responses to pneumococcal antigen are blunted in splenectomised subjects<sup>47</sup> and in patients with immunodeficiency states.<sup>48</sup> There are no reports of the antibody responses to pneumococcal vaccination in hyposplenic gastrointestinal disease. Nevertheless, it would seem prudent to vaccinate frail, ill patients with chronic inflammatory bowel disease or coeliac disease in an attempt to boost their resistance to pneumococcal infections. The possibility of fulminant pneumococcal or meningococcal infections must be borne in mind when these patients become febrile,

and prompt and appropriate antibiotic therapy must be administered.

Functional hyposplenism is a recognised complication of many gastroenterological diseases and is associated with the small but identifiable risk of fulminant sepsis. Differential interference contrast microscopy is a quick and accurate method of assessing patients thought to be susceptible.

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