

Historical Review

THE SPLEEN

'In Englysche it is named a man's Splene. A spongius substance lienge under the ribbes on the left side, and it doth make a man to bee mery and to laughe, although melancholy resteth in the splene if there be impedimentes in it. If any man be splenitike let him use mery company, be joconde, and not to study upon any supernatural thynges.' (Andrew Boorde; *The Breviarie of Helthe*, 1547).

The spleen has been considered a mysterious organ since classical times. For many years after its existence became known, it appeared to have no function. Now we know this to be far from the truth, yet many individuals survive perfectly well in the absence of a functioning spleen, following surgery or as a result of diseases causing hyposplenism. We still cannot say that we understand the spleen's functions and diseases completely. Over centuries, this puzzling organ has attracted the interest of thinkers and researchers, from Galen to Gaucher and beyond, as I shall try to show in this article.

CLASSICAL CONCEPTS OF SPLENIC FUNCTION

Long before the anatomy and physiology of the spleen began to be unravelled, the organ had an important place in classical medicine that has left its mark on our language. To describe a person as being splenic is to consider them to be hot-tempered or hasty in judgement. In venting one's spleen, one is releasing a burst of pent-up anger. These terms reflect early ideas of the spleen as the site of removal from the body of black choler (Gray, 1854; Burton, 1989), one of the four humours believed by Hippocrates (c. 460–380 BC; Fig 1) to regulate bodily functions. Black choler, or black bile, also gives its name to melancholy, a state of unhappiness and inactivity due to an excess of this humour, attributed to failure of the spleen to absorb and remove it from the body – possibly the earliest concept of hyposplenism.

Hippocratic ideas regarding the humoral regulation of bodily functions were developed further and formalized by Galen (129–201 AD), gaining unchallenged respectability for many centuries after his death (for further description see McClusky *et al*, 1999a). While blood (hot, sweet and red) and phlegm (cold and moist) were considered 'profitable' humours, black choler (cold, dry and thick) was one of the body's two 'excrementitious' humours, the other being yellow bile (hot, dry and bitter). Yellow bile was known to be excreted via the gallbladder into the small intestine. The route of excretion of black choler was unknown; it was

believed to counteract the effects of the two hot humours and to nourish the bones. Hippocrates thought that the spleen drew watery elements from food in the stomach as the gallbladder draws yellow bile from the liver.

It is interesting that, although the physical existence of blood, phlegm and yellow bile is readily apparent, there is no equivalent evidence for the existence of black bile as a normal bodily fluid. It has been speculated that haematemesis, melaena, haematuria or haemoglobinuria due to haemolytic anaemia and metabolic disorders causing black urine may have provided the basis of belief in this humour (Voswinckel, 1991). Others have suggested that black bile existed as a concept purely because of a philosophical desire for symmetry in explanations of the natural world. There were four natural elements (air, water, fire and earth) and these were linked conceptually with four humours regulating bodily function.

Hippocrates noted the soft and fibrous nature of the spleen and Aristotle (384–322 BC) later described its anatomical position. Erasistratus (310–250 BC), a Greek anatomist and physician, was impressed by observations that internal organs appeared to be organized symmetrically to either side of the midline. Both Aristotle and Erasistratus thought that the spleen represented a left-sided equivalent of the liver. This may seem surprising today, as the normal sizes of the two organs are so disparate. However, malaria was endemic in the Middle East in the time of Erasistratus and a 'normal' sized spleen then would probably be regarded as marked splenomegaly today. Ultimately, Erasistratus concluded that the spleen had no function of its own, a view that prevailed for several centuries.

Ancient Babylonian, Egyptian, Greek and Roman writings implicated the spleen in impairing the athletic capacity of men and horses, with suggestions that a variety of potions (ingested or placed over the left flank) could reduce spleen size and improve running ability. Caution of the left flank to achieve the same effect was also described. Today, these approaches seem unscientific and, in the case of cautery for splenic extirpation, barbaric. It should again be remembered, however, that many individuals in those times and places would have had splenomegaly, as a result of malaria infection, and that this would be likely to impair athletic abilities (Oren *et al*, 1998). Moreover, the effect of asplenia on athletic performance has been proved scientifically in the modern era. In 1922, groups of splenectomized and non-splenectomized laboratory rats were raced against one another and the splenectomized animals won! (cited in McClusky *et al*, 1999a). Perhaps our ancient forebears were nearer to the truth than we might care to give them credit for.

The spleen has also been regarded as 'the seat of mirth and pleasure, of lascivious dreams, of imagination and the

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Fig 1. Hippocrates examining the upper abdomen (possibly palpating the spleen?) of a patient. Photograph courtesy of Dr Barbara Bain, St Mary's Hospital, London.

golden age of life' (Stukeley, 1722; Fig 2). The prevailing view for many centuries was, however, one of gloomy and irritable influences emanating from the spleen. This is evident in the following verse, which is the opening stanza of a lengthy composition published privately in 1709. The author was a lady with poetic aspirations and, presumably, time on her hands. Nowadays she would probably be writing scientific papers and worrying about the next Research Assessment Exercise!

The Spleen – a Pindarique Ode by the late, right honourable Countess of Winchilsea (First Section)

*What art thou, Spleen, which everything dost ape?
 Thou Proteus to abuse Mankind,
 Who never yet thy hidden Cause cou'd find,
 Or fix thee to remain in one continu'd Shape;
 Still varying thy perplexing Form,
 Now a dead Sea thou represent,
 A Calm of stupid Discontent,
 Then dashing on the Rocks wilt rage into a Storm:
 Trembling sometimes thou dost appear,
 Dissolved into a panic fear,
 On Sleep intruding do'st thy Shadows spread,
 Thy gloomy Terrors round the silent Bed,
 And crowd with boding Dreams the melancholy Head.*

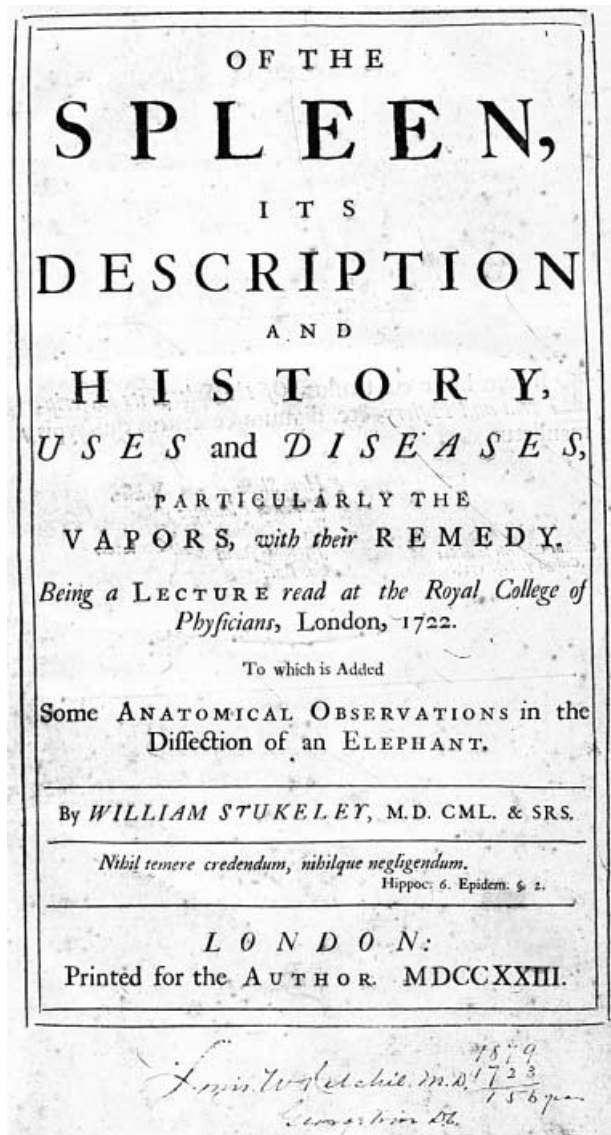


Fig 2. Title page from the lecture by Stukeley, delivered to the Royal College of Physicians in 1722. Reproduced with permission from the Wellcome Library, London.

DISCOVERY OF THE STRUCTURE OF THE SPLEEN

The lack of any obvious excretory duct or external opening connected to the spleen puzzled early anatomists. Then Galen described communicating structures between the spleen and the stomach. In addition to performing animal dissections, he had plenty of opportunity to make direct anatomical observations of the human spleen in his capacity as staff surgeon to the Roman gladiators. He believed his findings provided the missing link between the spleen and digestion. He considered that thick and muddy juices from the liver provided nourishment for the spleen and those which could not be 'transformed' in the spleen during this process were delivered to the stomach to be excreted. At about this time, ideas were current that the spleen and liver warmed the stomach to aid digestion.

These concepts remained prevalent until approximately 1725, when Vesalius described the true nature of the vasa brevia of the stomach and challenged the existence of Galen's gastro-splenic communications. Any idea of the spleen as a supplementary liver was also overturned by Vesalius, who showed that the vascular anatomy of these two organs had significant differences. Nonetheless, Vesalius adhered to the Hippocratic concept of humoral regulation of health, with the spleen acting as a filter of black bile from blood.

Glisson was the first to describe the distribution of 'nerves' supplying the spleen in 1654. He was actually describing the connective tissue trabeculae that permeate the substance of the organ. Marcello Malpighi (1628–1694) correctly interpreted the connective tissue nature of these trabeculae, although his best-known contribution to understanding splenic microanatomy is his description of what are now known to be lymphoid follicles forming the white pulp of the spleen. He thought these 'corpuscles', which were subsequently given his name, were filled with liquid and functioned like the excretory glands. In the absence of an excretory duct, he postulated that they released their contents into trabeculae and thence into veins to be carried elsewhere in the body by the bloodstream. The functions of these secretions (perhaps more appropriately regarded as hormones in modern terminology) remained obscure; Malpighi postulated that they assisted with secretion of bile by the liver.

Stukeley thought that Malpighian bodies were the tendons of trabecular muscles, glands to lubricate these tendons or, possibly, nerve plexuses. He subscribed to a 'safety valve' theory in which the spleen acted as a reservoir to even out fluctuations in circulatory volume. Observation of fluctuations in splenic size in some animals led to this concept of the spleen as a reservoir, an idea that persisted for some time. It was suggested that, during episodes of rage, splenic engorgement would reduce blood volume and prevent apoplexy. In fact, it is now known that in animal species having splenic reservoir function, the spleen does the exact opposite – it enlarges at rest and contracts with exercise or excitement. Another interesting idea espoused by Stukeley was that vomiting in pregnancy could be attributed to retention of menstrual blood, normally delivered from the spleen to the uterus in a regulated fashion.

Ruysch, in 1701, injected spleens with wax to define their microanatomy and emphasized that the bulk of the spleen is a vascular meshwork. In our own times, corrosion casting after injection of latex has been an important technique for defining the nature of splenic microvasculature in great detail (Redmond *et al*, 1994). It is remarkable that early studies along these lines should have been undertaken nearly three centuries ago. Debate concerning the nature of blood circulation through the splenic red pulp has remained the subject of controversy until recent years. For many decades, protagonists of 'open' and 'closed' circulatory pathways defended vigorously the existence and primacy of their favoured route. The debate is now happily resolved; both occur and each is significant in quantitative terms. Blood circulates from arterioles, via

sinusoidal lumina, into collecting venules (closed circulation) and also percolates through the interstitium of splenic cords (open circulation).

In the 1820s, erythrophagocytosis for removal of senescent red cells from the circulation was first described and the true nature of splenic red pulp began to be appreciated. The occurrence of red cell destruction in the spleen was contested by no less a person than Virchow. He felt that cell death was always a sign of disease and could not be a normal process. In addition, at about this time, the microanatomical structure of splenic red pulp cords was elucidated by Theodor Billroth. Billroth, a surgeon better known today because of the gastrectomy techniques that bear his name, adhered to the notion of haemopoiesis being a major function of the splenic red pulp. However, the cords that he described provided an anatomical basis for the concepts of filtration and removal of senescent red blood cells that were being proposed by his contemporaries.

Wide variation in the sophistication of thoughts on the subject of splenic anatomy and function during the mid-19th century is striking. In keeping with the amazing zeal of Victorian naturalists, Edwards Crisp in 1855 recorded in detail the sizes and appearances of 334 spleens from mammals, birds, fishes and reptiles, including those from an English vulture, a rock kangaroo, an opossum and a puff adder. His painstaking illustrations are a testament to the assiduity with which he pursued his task but are otherwise disappointingly uninformative. The contrast is dramatic between his treatise and a superbly detailed monograph produced by Henry Gray 1 year earlier (Gray, 1854). In the latter, Gray summarizes the long history of concepts and discoveries relevant to structure and function of the spleen. Included in his monograph are microscopic drawings clearly showing Malpighian corpuscles in their correct spatial relationships with trabecular blood vessels (Fig 3). Gray describes studies of Malpighian corpuscles reported by Heusinger in 1817. According to Heusinger, the corpuscles were 'whitish bodies, occasionally small, occasionally dilated, disappearing on inflation of the splenic vein but reappearing on incising the part'. In retrospect, these observations were probably due to variations in red pulp congestion rather than true changes in white pulp volume. Gray considered that the function of Malpighian corpuscles was to add albumen to the blood; not a bad thought so many years before the discovery of the true nature of antibodies in blood plasma.

At around this time, there was a revival of the view, originally proposed by Hewson in the 1780s, that the spleen had a role in haemopoiesis. The spleen was considered to be important in red blood cell production, 'colourless corpuscles' being transformed into red ones. However, the prominence of splenomegaly in seriously ill patients with increased white cells in their blood (probably suffering various forms of leukaemia) led to the view that the spleen was also responsible for white blood cell production. Observations of splenic extramedullary haemopoiesis in laboratory animals supported a mistaken notion that such activity was also physiological in humans for nearly two more centuries.

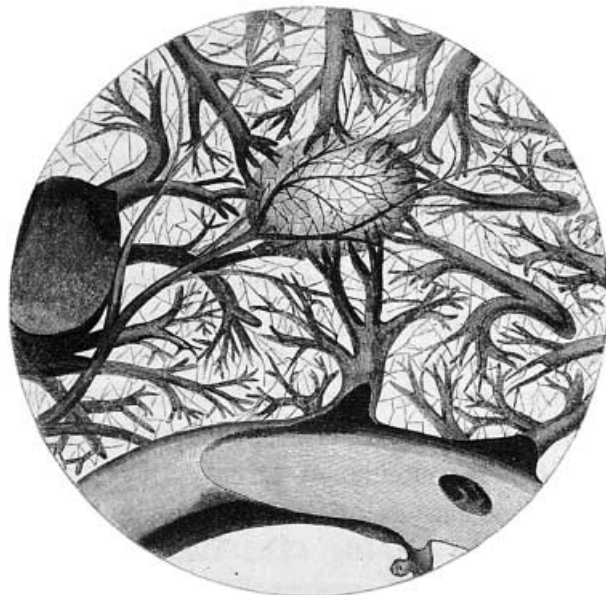


Fig 3. Splenic white pulp structure, as illustrated in Henry Gray's monograph *On the Structure and Use of the Spleen*, published in 1854. Reproduced with permission from the Wellcome Library, London.

HISTORICAL DESCRIPTION OF DISEASES INVOLVING THE SPLEEN

In 1855, Philippe Charles Ernest Gaucher described the post-mortem examination of a 32-year-old woman with massive splenomegaly that had developed progressively over many years before her death. The spleen weighed more than 4.5 kg, was almost normal in shape and colour but was said to be hard in consistency. Gaucher recorded the microscopic features as being total substitution of normal splenic components by huge epithelial cells, accompanied by interstitial haemorrhages and complete absence of Malpighian corpuscles. He interpreted these appearances as representing a primary splenic neoplasm, although he commented specifically that nothing about the clinical behaviour of the lesion suggested malignancy. He did not speculate about possible consequences for the patient that might have arisen as functional effects of her hugely enlarged spleen. He stated specifically that she had no fever, ascites or leukaemia, but he did note that she experienced episodes of nosebleed, purpura and haemorrhagic gingivitis during her years of worsening splenomegaly. She may therefore have been thrombocytopenic and, if so, this could have been due to a combination of bone marrow infiltration and platelet destruction in the spleen. However, patients with massive splenomegaly due to Gaucher's disease are more likely to become hyposplenic, due to loss of normal cordal macrophage function, than to develop hypersplenism secondary to enlargement of the organ. Hypo- and hypersplenism, of course, can co-exist. Her bleeding tendency might alternatively have

been due to hepatic dysfunction and associated coagulopathy, although absence of ascites argues against severe liver failure.

We now know that Gaucher's cells are not epithelial at all, or neoplastic, but are cordal macrophages congested with glycolipid that cannot be metabolized (see Desnick, 1982 for additional historical review of aspects of this disease). Patients have an inherited deficiency of the enzyme glucocerebrosidase. Gaucher himself conducted no further investigations into the condition he had described, or into any other aspect of splenic disease. His description was written as part of a thesis submitted for his doctorate in medicine. He went on to become an expert in genito-urinary medicine and, later, a professor of dermatology.

Early in the 20th century, another disorder of the spleen was described by Banti, a pathologist from Florence. Banti's disease is a chronic anaemia arising in patients with splenomegaly and hepatic cirrhosis. The spleen, rather than the liver, was thought to be the primary seat of pathology in this condition, possibly because splenic enlargement sometimes appeared to precede development of cirrhosis. Banti considered an unknown infection or toxin to be the cause. The term 'chronic splenic anaemia' (Rolleston, 1914) was later coined to describe those cases without liver fibrosis. It consisted of idiopathic splenomegaly, absence of lymph node enlargement, 'chlorotic' (presumably hypochromic) anaemia, absence of leucocytosis, liability to gastro-intestinal haemorrhage and a prolonged course. Spontaneous resolution did not occur but splenectomy was often curative. Cases of Gaucher's disease were specifically excluded, having a distinctive (albeit at that time poorly understood) pathogenesis. Most examples of congenital anaemias, such as hereditary spherocytosis, had been identifiable since Chauffard introduced measurement of red cell osmotic fragility in 1907 and could therefore also be excluded. Now, we recognize both chronic splenic anaemia and Banti's disease as effects of portal hypertension. Only long after the clinical features were described was it realized that progressive hepatic fibrosis was the cause, rather than an effect, of splenomegaly and hypersplenism in portal hypertension.

Hyper- and hyposplenism, as we understand these terms today, were first described in the 1920s. Analogies were drawn with excessive or deficient function of endocrine organs such as the thyroid gland. It was suggested that splenectomy should be used for hypersplenism and that, to treat hyposplenism, some activator of the spleen and reticulo-endothelial system should be sought. Discovery of such an agent would still be welcome today!

Felty's syndrome, the association of rheumatoid arthritis with splenomegaly and hypersplenism, was first described in 1924. Concepts of primary and secondary hypersplenism gradually emerged over the next two decades. In primary hypersplenism, an essentially normal (sometimes moderately enlarged) spleen destroys structurally abnormal or antibody-coated blood cells, as in hereditary spherocytosis, auto-immune haemolytic anaemia or idiopathic (auto-immune) thrombocytopenic purpura. Secondary hypersplenism describes the destruction of normal blood cells by an

abnormal, usually significantly enlarged, spleen. In fact, there is no fundamental difference in the mechanism of blood cell destruction occurring in each of these forms of hypersplenism. Sequestration and phagocytosis of blood cells by red pulp macrophages underlie both and distinctions between primary and secondary forms are sometimes quite arbitrary. As terminology is clearly unhelpful and potentially misleading in this area, the terms primary and secondary hypersplenism are probably better avoided. Historical 'advance' based, as in this case, on incomplete understanding of splenic physiology should not bind us in perpetuity to use ambiguous terminology.

In the 1940s, hypersplenism was attributed correctly, by most thinkers on the subject, to over-activity of the spleen causing excessive sequestration and destruction of blood cells. Another explanation was considered possible, however; namely, that the effects were due to inhibition of bone marrow haemopoiesis resulting from production of a hormone-like substance in the enlarged spleen. Lack of direct evidence for such a humoral factor and growing understanding of the reticulo-endothelial functions of the spleen led to the gradual demise of this alternative view. Damashek and Estren, in 1947, noted post-splenectomy changes in red blood cells and concluded that the spleen must normally have made red cell capsules thicker, controlled their de-nucleation, modified their lifespans and contributed to haemoglobin breakdown. Incidentally, they believed that the spleen was involved in haemopoiesis in childhood, with this activity gradually being lost in adolescence. Only in recent years has the occurrence of significant splenic extramedullary haemopoiesis during early life in humans been challenged. It is now clear that fetal liver is the major source of haemopoiesis, after yolk sac activity diminishes and prior to bone marrow haemopoiesis developing. The normal fetal spleen probably only has a role in filtering immature erythroid precursors from the circulation, permitting their terminal differentiation in contact with red pulp macrophages and endothelium (Wilkins *et al.* 1994).

DEVELOPMENTS IN SPLENIC SURGERY

Several accounts of splenectomy performed in animals appeared during the 1600s. Malpighi himself performed a splenectomy on a dog and reported that it lived afterwards with no ill effects other than increased appetite and weight gain.

The first reported human splenectomy in the Western world was performed in Naples by Adriano Zaccarelli in 1549. Details of the surgery and its outcome were recorded by a colleague of Zaccarelli's, Leonardo Fioravanti, who acted as surgical assistant during the operation. The patient survived but the precise nature of this operation has since been questioned. It has been suggested that an ovarian cyst, rather than the spleen, was removed. The first documented splenectomy for trauma was performed in 1590 and, during the next two centuries, many splenectomies were undertaken, usually following traumatic injury to the organ (Sherman, 1980).

The first American splenectomy was performed in 1816 following a dramatic incident. A 39-year-old man was in the process of raping a prostitute when he was stabbed by his victim, using his own clasp-knife, and sustained a severe laceration. On removal of the knife, the man's spleen protruded through the wound; the presenting part was ligated successfully and the patient made a full recovery, despite suffering haematuria as a result of kidney injury sustained from the same wound.

Sporadic reports of removal of enlarged spleens began to appear in the mid-19th century. Spencer Wells is credited with performing the first deliberate splenectomy for splenomegaly in England in 1866. The spleen was possibly involved by leukaemia (see below) and the patient died 1 week later, from infection. Such operations during this period were almost universally unsuccessful, with deaths occurring immediately after surgery or in the first few postoperative days. However, splenectomy following traumatic injury had become an accepted and successful part of the surgical repertoire. By the end of the 19th century, more than 270 splenectomies had been performed on human subjects and 170 patients had recovered (Coon, 1991).

A surgeon named Thomas Bryant performed the first recorded splenectomy for leukaemia in 1866. He was among those who believed that the observed blood leucocytosis originated from white cell production occurring predominantly in the spleen. He therefore considered that splenectomy might be curative. Unfortunately, the patient died within 1 h of the surgery being completed. He and others continued to attempt splenectomy for leukaemia for another 20 years, but only six patients survived out of approximately 50 cases reported during this time, giving a mortality rate of 88%. Meanwhile, the haemopoietic functions of bone marrow were being elucidated and the idea that splenectomy could remove the source of leukaemic cells was challenged. Splenectomy for leukaemia declined rapidly, and then effectively ceased, as radiotherapy became the treatment of choice for control of splenic symptoms in leukaemic patients. For a brief period in the 1970s there was a revival of use of splenectomy for chronic granulocytic leukaemia, but a controlled trial demonstrated no benefit and the practice has been largely abandoned.

Happily, a more accurate line of physiological reasoning underpinned the emergence of splenectomy as a means to treat auto-immune thrombocytopenic purpura and haemolytic anaemia in the first 20 years of the 20th century. Careful observations had by this time led to the conclusion that red cells and platelets ended their natural lifespans by destruction within the spleen. It seemed logical to propose that increased destruction in disease states could be ameliorated by splenectomy. In 1911, Micheli cured a patient in Italy of severe haemolytic anaemia using splenectomy and, in 1916, Kaznelson reported prompt recovery from severe thrombocytopenia following splenectomy. Peripheral cytopenias gradually became a prime indication for splenectomy. Digby Chamberlain, speaking in 1962, reported that congenital haemolytic anaemias (hereditary spherocytosis and similar conditions) were the most

common indications for splenectomy at that time (Chamberlain, 1962). Only in recent years has use of splenectomy declined somewhat for treatment of hereditary and auto-immune cytopenias, as a result of increasing concerns about risks of significant infection in asplenic patients (Ketley *et al.*, 1992; Marble *et al.*, 1993).

Splenectomy from the 1920s onwards has continued to be practised for diagnosis and symptomatic relief of splenomegaly, for control of auto-immune cytopenias, following abdominal trauma and to gain access to difficult intra-abdominal surgical sites during a variety of other procedures (Crosby, 1983; McClusky *et al.*, 1999b). For some years, splenectomy was also performed as part of the laparotomy conducted for staging in patients with Hodgkin's disease. Post-splenectomy sepsis has been responsible for significant morbidity and mortality in these patients. Fortunately, computerized tomography (CT) and other non-invasive imaging techniques have now completely replaced laparotomy for staging purposes. Today, the most common indication for splenectomy is trauma, followed by splenomegaly due to involvement of lymphoma or chronic myeloproliferative disorders.

Alternative surgical techniques

Edwin Beer (1928), reviewing progress in splenic surgery, voiced his opinion that nothing less than total removal of the spleen was acceptable in cases warranting splenectomy, whatever the underlying cause. However, in recent years there has been increasing concern to preserve splenic function whenever possible and this has driven developments of surgical techniques for partial splenectomy, splenorrhaphy to repair traumatized spleens and splenic re-implantation. Improved understanding of the segmental nature of the splenic vasculature has assisted here, as relatively avascular planes for dividing the organ can be defined and used to minimize intra- and postoperative haemorrhage (Redmond *et al.*, 1994). Concurrent trends towards minimally invasive surgery have led to development of laparoscopic methods for splenectomy and partial splenectomy. To date, the additional time and operative complexity involved in performing laparoscopic and partial splenectomies, compared with open, total splenectomy, have restricted their uptake in general surgery. However, it is likely that this situation will change rapidly as surgical expertise and confidence in performance of these techniques increases. The benefits for patients and health service professionals in terms of reduced operative morbidity, preserved splenic function and reduced hospital bed occupancy should encourage progress in this direction. Currently, partial splenectomy is most often performed for idiopathic thrombocytopenic purpura and appears highly successful.

Alternative diagnostic techniques

Traditionally, it has been considered that a high risk of haemorrhage accompanies any procedure other than total splenectomy for the removal of splenic tissue from the body. This has meant that total splenectomy has been performed for diagnostic purposes even when a small biopsy sample

would provide sufficient material. Needle biopsy, with ultrasound or CT guidance, is used occasionally to sample identifiable solid masses within the spleen, but this technique is still considered by many to be hazardous and has not found widespread application.

Moeschlin (1947) described the technique of splenic puncture, which he believed had been practised since the end of the 19th century for diagnosis of typhoid fever. Later it was also used to diagnose leishmaniasis, tuberculosis and Hodgkin's disease. By 1924, the technique had been optimized by using a specifically designed spleen puncture needle, not unlike a modern bone marrow aspiration needle, and performing puncture at maximal inspiration. Moeschlin espoused the technique with enthusiasm and his monograph on the subject is replete with beautiful hand-drawn and photographic records of cytological films ('splenograms') prepared from diagnostic puncture samples. He performed detailed differential cell counts and correlated these with individual disorders. It seems astonishing that this method has vanished almost completely from diagnostic practise in the developed world today, at a time when minimally invasive fine needle aspiration biopsy methods are being used increasingly to achieve diagnoses from other tissues. Splenic puncture is still used very effectively for diagnosis of leishmaniasis in parts of India; perhaps a revival of the technique is due elsewhere.

UNDERSTANDING THE SPLEEN'S ROLE IN IMMUNITY⁹

Hewson, in 1777, classified the spleen together with the lymphatic system and, by the mid-1800s, association of the spleen with the lymphatic system was growing. Julian Evans made a presentation to the Royal Society in London in 1844 in which he concluded that Malpighian corpuscles were lymphatic glands and that the spleen had two disparate sets of functions. Firstly, it was a multiloculated ('cellated') reservoir and, secondly, it separated fluid from blood to be processed in the Malpighian corpuscles and discharged into efferent lymphatics. As discussed earlier, Henry Gray believed that Malpighian corpuscles contributed to regulation of the amount of albumen in the blood. He noted that they became atrophied in starved animals and were enlarged under conditions of ideal nourishment. Other authors at about this time were also emphasizing structural similarities between Malpighian corpuscles and the lymphoid nodules forming Peyer's patches in the intestines. Germinal centres and mantle zones in lymphoid tissues were also described in the mid-19th century, but I have not been able to discover when the first description of marginal zones was made. These peripheral zones, composed of cytologically distinctive lymphoid cells, are present in Peyer's patches and splenic white pulp nodules, but are generally absent or inconspicuous in normal lymphoid tissues at other sites.

In recent years, routes of entry of lymphoid cells into the splenic white pulp, and cellular interactions occurring there to generate immune responses, have been studied

extensively in rodent spleens. The marginal zone is of prime importance in these processes and, although it is somewhat different anatomically, the human marginal zone probably serves similar functions. A detailed description of the development of concepts in this area of research is beyond the scope of this article and the reader is referred elsewhere for further information (Liu *et al.* 1991).

As the nature of infectious microorganisms and the diseases caused by them became clear, evidence began to accumulate that absence of a spleen was associated with increased susceptibility to infections. Experiments performed using splenectomized rodents and dogs established this increased risk. Excess mortality from infectious diseases was also found in splenectomized animals when compared with animals that were similarly infected but retained normal splenic function. When plasma antibody levels became measurable, it could be shown that levels of antibacterial antibodies following injection with sublethal doses of bacteria were higher in animals with spleens than in those without.

Recognition that susceptibility to infection in asplenic individuals is particularly associated with infection by encapsulated bacteria has contributed significantly to our understanding of the spleen's role in immunity to such organisms (Hazlewood & Kumararatne, 1992). It appears that the splenic marginal zone represents a major site for generation of T cell-independent antibody responses that are the immune system's major defence against carbohydrate antigens of bacterial capsules. This understanding has, in turn, influenced vaccination strategies to prevent post-splenectomy infection with organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type B and *Neisseria meningitidis* types A and C. It was initially considered essential that vaccination should be performed prior to elective splenectomy, in order to ensure development of adequate antivaccine responses before removal of the organ. However, it is now clear, from studies of trauma patients and others undergoing emergency splenectomy without prior vaccination, that post-splenectomy vaccination can also be successful. It remains unknown whether intestinal Peyer's patches substitute for splenic marginal zone function in these circumstances or if other lymphoid tissues are able to respond.

THE RECOGNITION OF POST-SPLENECTOMY INFECTION

Looking back into historical accounts of patients and experimental animals surviving splenectomy (Sherman, 1980) reveals documented evidence of systemic sepsis as far back as the early 18th century, although the significance of these findings was not understood until much later. Only in the first years of the 20th century was a link formally demonstrated between splenectomy and susceptibility to infection using experimental infection of laboratory animals. The first report of lethal post-splenectomy sepsis in a human subject was made in 1929. The patient was a child who had been splenectomized years earlier for haemolytic

anaemia. The child's father, tragically, had also died from septicaemia following splenectomy for the same condition. Further reports of life-threatening post-splenectomy sepsis in infants followed (e.g. King & Shumacker, 1952) but only with the seminal review by Singer (1973) was the full extent of the problem made clear.

In recent years, overwhelming post-splenectomy infection (OPSI), usually caused by encapsulated bacteria, has been a major focus of concern. The occurrence of OPSI has provided the impetus for development of vaccines to protect asplenic patients against infection by encapsulated organisms, particularly *Streptococcus pneumoniae*, *Haemophilus influenzae* type B and *Neisseria meningitidis* (types A and C). It has also significantly influenced trends in the practice of splenectomy in recent years. There has been an overall reduction in the number of splenectomies performed and an increase in use of conservative techniques such as partial splenectomy. Splenectomy is currently avoided in childhood wherever possible.

Studies over many decades have established that not all splenectomized individuals are at equal risk of OPSI. Infants and children have the highest risk, presumably because they have not built up levels of immunity equivalent to those in adults. However, splenectomies performed for trauma in otherwise healthy adults, or for technical reasons during abdominal surgery, are associated with only a low risk compared with splenectomy for haematological disease or lymphoma. Patients with Hodgkin's disease who had their spleens removed during staging laparotomies represent one of the highest risk groups. As many such patients are still alive today, despite the procedure now being obsolete, it is important that their risk is not forgotten. Most cases of OPSI occur during the first 2 years after splenectomy, but infection has been reported decades later and the risk must therefore be recognized as being lifelong. The particular risk in Hodgkin's disease patients is almost certainly not related to splenic involvement by their disease, as most spleens removed did not show evidence of tumour infiltration. Instead, the combined effects of asplenia and immunosuppressive therapy, especially radiotherapy, is the probable basis of their susceptibility to OPSI. There may also be a contribution from immunodeficiency directly related to the underlying Hodgkin's disease.

It has also become appreciated that hyposplenism due to diseases that destroy or overwhelm the normal functions of the spleen can lead to OPSI without splenectomy. Thus, patients with conditions such as coeliac disease, sickle cell disease, auto-immune cytopenias or extensive splenic involvement by lymphoma require consideration of their risk for OPSI even while they retain their spleens. In addition, rare cases of familial asplenia, with consequent hyposplenism, have been described in otherwise apparently normal individuals (Feder & Pearson, 1999), so that unexplained OPSI occurring in the absence of splenectomy or an obvious cause for hyposplenism should prompt screening of other family members.

Severe sepsis, of course, is not the only serious illness that has been documented as a pathological consequence of

splenectomy. Thrombotic complications may occur as a result of post-splenectomy thrombocytosis. Less readily explained phenomena have also been documented. An increased mortality from pneumonia and ischaemic heart disease was recorded in World War II soldiers splenectomized for abdominal trauma (Robinette & Fraumeni, 1977). No entirely satisfactory explanation has been found for this but some of the cardiovascular disease may have represented thrombo-embolic events associated with thrombocytosis.

EVOLUTION OF CONCEPTS RELATING TO SPLENIC LYMPHOMAS

It has long been recognized that the spleen may be enlarged owing to involvement by leukaemia or lymphoma. In 1913, several cases of 'chronic lymphocytic hyperplasia' were recorded at the Mayo Clinic, which probably represented splenic lymphomas (Coon, 1991). Controversy over the nature of lymphomas involving the spleen has been as lively as debate over the functions of normal splenic lymphoid cells. Curiously, despite the spleen's prominent involvement in most patients with hairy cell leukaemia, increasing knowledge of that disease during 42 years since its first description has not cast much light on lymphoid cell functions within the normal spleen (Bouroncle *et al.*, 1958; Troussard *et al.*, 1998). In recent years, however, concepts about the functions and behaviour of lymphocytes found in the splenic marginal zone have developed directly as a result of observations of lymphomas that preferentially occupy this compartment of splenic tissue (Schmid *et al.*, 1992; Mollejo *et al.*, 1995; Pawade *et al.*, 1995). Currently, haematopathologists use the term splenic marginal zone B-cell lymphoma (SMZBL) to describe this entity and most consider it to be essentially the same as the disease better known to haematologists as splenic lymphoma with villous lymphocytes (SLVL) (Isaacson *et al.*, 1994). If not a single disease entity, SMZBL and SLVL at least exhibit considerable overlap of features in many patients.

Emerging conceptual models of the roles and circulatory pathways of marginal zone cells in humans predict fairly accurately the behaviour of mucosa-associated lymphoid tissue (MALT) and its neoplastic counterparts, which are also believed to be of marginal zone derivation. Extranodal lymphomas of MALT-type tend to be indolent, spread only to local lymph nodes or to other MALT sites via marginal zone cell recirculation pathways and rarely become disseminated. However, evidence suggests that involvement of splenic marginal zones by recirculating MALT-type lymphoma cells is minimal in most cases (Harris *et al.*, 1996; Du *et al.*, 1997). Moreover, the behaviour of SMZBL is quite different from that of MALT-type extranodal marginal zone B-cell lymphomas. Splenic marginal zone B-cell lymphoma is often widely disseminated at diagnosis, with circulating cells in the bloodstream (villous or otherwise). Curiously, despite these features, long-term remission or possibly even cure may be achieved in SMZBL by splenectomy.

Perhaps there are differences yet to be discovered between Peyer's patch marginal zone cells and those of the spleen, which will account for these differences in lymphoma behaviour. Meanwhile, despite increased recognition that SMZBL is biologically distinct from MALT-type marginal zone B-cell lymphomas and their node-based counterparts ('nodal marginal zone B-cell lymphomas', with or without monocytoid B cells, in the World Health Organization classification), the similar terminology used for their classification is confusing.

It has also become apparent, as experience of SMZBL has increased, that many other lymphomas can show marginal zone differentiation if they spread to involve the spleen (Piris *et al.*, 1998). Presumably this phenotypic modulation occurs in response to local microenvironmental signals. This challenges the entire notion of lymphoma classification based on defining the histological appearance and immunophenotype of tumour cells in relation to a putative normal cell of origin. No unique, defining marker of a lymphocyte intrinsically programmed to home to the marginal zone has been found to date, despite extensive searching. What, then, is a marginal zone cell (normal or neoplastic) other than a lymphocyte that has come under the influence of the marginal zone microenvironment? The last decade has been an interesting time for emergence of ideas about the splenic marginal zone and splenic lymphomas but the next few years should be even more fascinating!

WHOSE SPLEEN IS IT, ANYWAY?

The question 'the spleen-who needs it?' has been raised since classical times and, I hope, no longer causes significant controversy. A more modern debate, paraphrased in the heading above, arose in the mid-1980s and remains a source of ethical dilemma today. (Annas, 1990; Curran, 1991; Bergman, 1992; Hartman, 1993).

In 1984, the Regents of the University of California were sued for a share of the profits arising from a cell line that had been developed in their laboratories. A physician employed by the university had diagnosed hairy cell leukaemia in one of his patients; splenectomy was performed in 1976 and tissue was retained for research. Subsequently, a cell line, Mo, was derived from this splenic tissue. The Mo cell line proved to be of commercial interest and the University of California obtained a patent governing its use.

The patient sued the University of California, arguing that his physician should have informed him of the potential financial interest in his tissue. A lengthy legal case resulted. Finally, in 1990, the California Supreme Court ruled against the patient. It argued that the nature of the cell line could not have been predicted at the outset and that the patient's cells were not themselves of intrinsic commercial value.

This was a landmark ruling for biomedical research. Although legally binding only in California, a precedent had been established, making it unlikely that medical researchers would be sued for development of cell lines from tissues discarded after therapeutic or diagnostic procedures. Had the outcome been otherwise, the cost of commercial

development of products using human cell lines could rapidly have become prohibitive.

However, the California Supreme Court was also anxious to protect patients' rights to privacy and autonomy with respect to their tissues. Their ruling included a statement that any physician wishing to obtain cells or tissues for research or commercial use must first obtain the patient's informed consent. This aspect of the case brings the debate right up to date, as public sensitivities about retention and subsequent use of human tissues are currently very high, albeit focused predominantly on post-mortem organ retention. Adequacy of informed consent for educational or research use of tissues removed during surgical procedures has yet to be addressed by many hospitals in the United Kingdom.

This is obviously an issue with much broader implications than simply the appropriate use of tissue from splenectomy specimens. The legal position in England and Wales with regard to patients' property rights in their tissues is currently unclear, as no case law equivalent to *Moore versus the Regents of California University* exists. However, tissue and cells retrieved from human splenectomy specimens have provided a valued resource to medical scientists for many years. Without the use of such material, much of what I have described in this article could not have been discovered. It would be a tragedy if lack of sensitivity in anticipating patients' concerns about the fate of surgically removed body organs were to deprive us of future scientific benefits accruing from the use of such cells.

CONCLUSIONS

Over many centuries, since the first descriptions of the spleen and early attempts to explain its function, much has been learned about this complex organ. The spleen is certainly not a useless or vestigial tissue and, unless it has become significantly involved by disease, it is generally better to have a spleen than to be without it. Red pulp functions are generally well understood and the therapeutic challenge of controlling these, in order to prevent hyper- and hyposplenism without surgical intervention, awaits attention. Much remains to be learned about the homing of normal and neoplastic lymphoid cells to specific areas within the spleen, the precise immunological functions of white pulp and how to influence these for clinical benefit. The spleen remains an important friend to medical scientists investigating the biology of these processes and seeking to alleviate the effects of diseases involving this organ. In 2002 AD, the human spleen is still as fascinating as it was in 400 BC, the time of Hippocrates.

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