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IM - REVIEW

From sadness to stiffness: the spleen's progress

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Abstract
The spleen is a lymphoid organ that has been poorly studied compared to other solid organs, probably because it has been considered a useless and unnecessary part of the body. For many centuries it has been considered a mysterious organ with uncertain functions. The first descriptions of the spleen date back to ancient ages. The spleen has been considered as a reservoir of liquids, strictly linked to stomach digestion, and in different cultures, it has been linked to melancholy and sadness due to the accumulation of black bile (humoral doctrine). A detailed anatomic description was first made by Vesalius during the Renaissance, and further implemented with the description of its microscopic structure by Marcello Malpighi in the seventeenth century. The first case reports regarding spleen functions and pathology regarded common causes of splenomegaly, such as malaria infection, and traumatic rupture. At the beginning of the last century, the pivotal concepts of hypo- and hypersplenism were introduced, along with the cumulating evidence of the relation between spleen removal and increased susceptibility to infections and thromboembolism. The study of hyposplenic states, which occur much more commonly than originally thought in many immune-mediated disorders, has rapidly increased after the validation of a simple method for assessing spleen function, namely pitted red cell count. In recent years, spleen morphology, in particular spleen stiffness, has been proposed as a marker of portal hypertension. In this paper, we retrace the fundamental steps of the discovery of the functions of the spleen.

Keywords Hyposplenism · History · Infections · Spleen · Splenectomy

The spleen in ancient times

Unlike other organs, the spleen has not been extensively studied through history. Its reduced size could not be the only reason of the lack of description of this organ, as in the case of the appendix. Whatever the reason, the spleen has been considered a mysterious organ for centuries.

The etymology of the spleen might provide some information about the significance attributed to this organ in ancient times [1–3]. The English term *spleen* derived from the Greek word σπλήν, which was also related to the word σπλάγχνα (viscera). The *Etymologicum Magnum* (Ἐτυμολογικὸν Μέγα), one of the main lexicographic sources of antiquity (twelfth century AD), linked the term σπλήν to the verb ἐπισπᾶσθαι, stating "σπλήν· παρά τό ἐπισπᾶσθαι είς ἑαυτόν τά φαυλισθέντα τῶν ὑγρῶν" ("spleen; from the one which breaks through to itself the remedies of the liquid") [4, 5]. The Latin word for spleen, "lien", was probably cognate with the Greek term, after losing the root -sp. The German "milz" and the Italian "milza" may derive from old-German "meltan" that literally means "to melt", probably because the role of the spleen was related to digestion [6]. Actually, these terms may also derive from German "milch" (milk), due to the white color of the spleen follicles (white pulp) [6]. Similarly, the Spanish term "bazo" seems to derive from the Latin "badius" ("reddish brown"), referring to its purple color. Finally, the French term for spleen, "rate", could be related to the ovular form of this organ, similar to a rat [7]. This brief etymological analysis indicates that the words used to indicate the spleen in different languages were mainly related to its anatomy (shape and color) rather than to its function, since this latter was still unknown.

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One of the oldest descriptions of the spleen can be found in the *Ebers Papyrus* written around 1500 BC: "there are four vessels to the intestines and to the spleen which likewise convey moisture and air" [5]. In the *Talmud*, the central text of Rabbinic Judaism, the spleen was associated with happiness; it was believed to produce laughter [8]. Instead, according to Traditional Chinese Medicine, the spleen was one of the zang-fu organs. More in detail, Chinese medicine recognized five "yin" organs (heart, liver, spleen, lung, and kidney) and six "yang" organs (gall bladder, stomach, small intestine, large intestine, bladder, and the so-called "triple burner"), also known as "zang" and "fu" organs, respectively. In this context, spleen was linked to digestion, storage of "food essence", and production of *qi*, the essential life lymph transported by the blood [9]. Finally, in ayurvedic medicine, the spleen was described as "the root of the ducts which transport the blood" [10].

In classical antiquity, the spleen was related to melancholy and sadness. Hippocrates (ca. 460–377 BC) and his followers developed the theory of four humors: blood produced by the liver, yellow bile produced by the gallbladder, phlegm produced by brain, and, finally, black bile produced by the spleen. According to the Greek physician, an excess of black bile (μέλαινα χολή, *melaina cholè*) could cause melancholy [11, 12]. Hippocrates provided a first anatomical description of the spleen, hypothesizing a role in absorbing the excess of liquids in the abdomen. The Greek philosopher Plato (427–347 BC), in his dialogue *Timaeus*, provided an accurate description of the spleen and drew its connection with the liver, stating that this organ was created in order "to maintain the liver bright and pure" [13]. Aristotle (384–322 BC) also described the spleen and its functions in his text *On the parts of animal*, suggesting that the spleen might be considered as a "bastard liver", assisting the liver in the transformation of food into blood [5]. In the fourth century BC, Erasistratus contrasted these theories, stating that the spleen had no functions at all [5].

In the Roman Empire, Galen (ca 129–201 AD) collected all the theories by previous authors, developing a single unifying theory, universally accepted in the following centuries. In his works *On the Usefulness of the Parts of the Body* and *On Anatomical Procedures*, he assumed a role for the spleen in clearing the black bile and melancholy through the digestive system [14]. According to this theory, the liver assimilated the digested food by the stomach and then directed the residues to the spleen, as black bile, via *vena lienalis* [14].

In the Middle Ages Galen's doctrine influenced Christian and Arab authors, who accepted his theory about the role of spleen, without adding further insights [5, 15]. For example, Meletios, a monk who lived in northwest of Phrygia and who introduced himself explicitly as a physician experienced in phlebotomy and cauterization, supported Galen's theory of the spleen as a cleansing organ [5]. One of the first medical authors to provide new insights into spleen function was the Persian physician Ibn Sina (980–1037), also known as Avicenna. In his masterpiece, *The Canon of Medicine*, he stated that spleen functions were not limited to Galen's doctrine. A whole chapter of the *Canon* was dedicated to "spleen functions, diseases and anatomy", examining the consequences of splenectomy and other abnormal conditions [16]. If absent or impaired, the spleen could not be able to store the black bile, which would then accumulate, resulting in "sclerosis" or, in case of deposition in the arteries, in "atherosclerosis" [16].

The modern age: the rediscovery of the spleen

During the Renaissance, physicians still supported Galen's theory. Several anatomists tried to combine old and new approaches, considering the spleen as an organ that, at the same time, attracted the melancholic *humor* and produced blood. For example, in *Isagogae breves*, the Italian anatomist Berengario da Carpi (ca. 1460–1530) stated that the spleen contained black bile, but "from time to time it makes blood, stirs the appetite, and aids the digestion of the stomach" [17].

Renaissance scholars showed a new interest towards the spleen. The Venetian anatomist Niccolò Massa (1485–1569), in his *Liber introductorius anatomiae* (1536), offered a detailed description of the spleen, reporting its site, substance, color, form and vascular connection, but did not mention its function [18]. Andreas Vesalius (1514–1564) represented a turning point for anatomical and medical studies. His masterpiece *De humani corporis fabrica* contains a whole chapter dedicated to the spleen, in which he partially rejected the theory of the role of the spleen in blood production, providing no alternative hypotheses about its functions [19]. Examining the spleen, Vesalius found it to be very different from the other organs, with a lack of blood vessels that linked it to the rest of the body. Hence, according to his opinion, it could not have a role in blood production. He also contested the idea that the residue of the "melancholic humor" was then discharged into the stomach, precisely because he could not find any vascular connection between the two organs. These vessels, now known as *vasa breve*, actually existed and were discovered a few years later [14].

A monograph entirely dedicated to the spleen, *De liene libellous* (1578), written by François Umeau of Poitier (ca. 1530–1594) testifies the interest of Renaissance anatomists towards this mysterious organ. While accepting the theory of the role of the spleen in blood production, Umeau did not consider the spleen as similar to the liver, but believed instead that it was part of the arterial system [20]. He stated that blood was pre-concocted by the spleen and then

sent to the left ventricle of the heart, infused with the heat and then released to the body [14].

The seventeenth century saw the birth of the scientific method, an empirical method of knowledge acquisition that soon spread to every scientific and research field. Several scientists claimed the need for a more accurate examination and description of the anatomy and morphology of the human body, including the spleen. Scientists of that time "believed in the perfection of human frame" [21] created by a perfect God, hence it was hard to accept the existence of the spleen, an organ with unclear functions. In that period, the introduction of microscopy in medicine allowed to study the microanatomy of all human organs, including the spleen [22]. The first to describe its microstructure was the British anatomist Francis Glisson (1597–1677). In his book *Anatomia Hepatis* (1654), Glisson reported what he believed to be a network of spleen "nerves" [23], but they actually were the trabeculae of the connective tissue. Their nature was correctly interpreted in the work "De liene" (1666) by the Italian physician Marcello Malpighi (1628–1694), who also described the "corpuscles" that constitute the white pulp of the spleen [24]. He erroneously thought that these corpuscles, filled with liquid, functioned like excretory glands and released their contents into the trabeculae and, consequently, the veins and the bloodstream. Malpighi's theory was contested by William Stukeley (1687–1765), who disagreed about the nature of the "corpuscles", hypothesizing them to be tendons of trabecular muscles, glands or nerve plexus [21]. William Hewson (1739–1774) was the first to associate the spleen with the lymphatic system and thus with an immune function. Hewson strongly rejected the traditional humoral doctrine and carefully examined the spleen structure through numerous animal experiments. He did not only describe the external appearance, but also the internal structure, stating that "The spleen is composed of arteries, veins, nerves, and lymphatic vessels, which are distributed to every point of it, so that it seems a mere congeries of vessels" [25]. After performing a ligature on the splenic vessel, the veins were still turgid with a red liquid which was revealed to be composed for the most part of red particles. The successful repetition of the experiment brought him to state that "the spleen is the organ ordained by nature for the more perfectly forming of these red particles" [26]. Hewson also performed a series of experiments that were part of a broader research on the lymphatic system and, thanks to the observation of splenomegaly in patients suffering from leukemia and immunodeficiencies, he hypothesized a role of the spleen in the production of white cells. As reported in his *Experimental Inquiries: part the third*, published posthumously, Hewson had the chance to observe a "thickish, white, milky fluid" inside the lymphatic vessels that he identified as white cells [27].

Literature and fine arts may provide important information about the advances of medicine [28, 29], as in the case of the spleen. In the Modern Age literature, the spleen was constantly associated with emotions. For example, William Shakespeare (1564–1616) and Alexander Pope (1688–1744) often used the term "spleen" in their plays to indicate both positive and negative emotions [30]. In this context, it should be mentioned "The anatomy of melancholy" (1621) by the English scholar Robert Burton (1577–1640), in which the author analyzed all the causes of melancholy, including the weakness of the spleen ("Their spleen is weak") [31]. The association between spleen and emotions continued during the nineteenth century, particularly in the famous poem *The Flower of Evil* (1857) by the French writer Charles Baudelaire (1821–1867) [32].

The contemporary era

At the beginning of the nineteenth century, Benjamin Rush (1746–1813) summarized the main characteristics and functions of the spleen, its relation with physical exercise, and the quality of blood filtered by the organ [33]. In the subsequent years, most of the published papers focused on spleen rupture, especially post-traumatic rupture that was the most commonly reported cause. However, the attention also shifted towards atraumatic spleen rupture as an increasingly incident condition [34]. Infectious diseases were increasingly recognized as a cause of spleen enlargement, and researchers hypothesized a protective role of the spleen, especially against malaria, even if the scientific community had no univocal consensus in this regard [35].

The twentieth century marked a turning point into the knowledge of the physiological functions of the spleen. Sir William Osler (1849–1919) commented on a few cases of "chronic cyanotic polycythemia with enlarged spleen", concluding that "Cyanosis and polycythemia are met with then in primary tuberculosis of the spleen, but it does not seem at all likely that the cases of chronic cyanotic polycythemia are due to this cause" [36]. This consideration paved the way to subsequent studies regarding the relationship between hypoxia, polycythemia, and bone marrow. In the first half of the century, apart from splenic rupture due to abdominal trauma, the other indications of splenectomy were "exceedingly rare primary malignant neoplasms and some of the primary (or "predominant") tuberculous and other chronic infectious (parasitic)" [37]. Other conditions affecting the spleen were increasingly recognized, including malaria, syphilis, hydatid cysts, kala-azar, schistosomiasis, mycoses, and rarer cases of splenomegaly, such as the diseases described by Guido Banti (1852–1925) and Philippe Gaucher (1854–1918), now known by their eponyms. In 1913, the term hyposplenism appears for the first time to describe the post-splenectomy state [38], but it was not

considered as a threatening condition. In 1929, Frederick Parkes Weber (1863–1962) further expanded the concepts of hypersplenism and hyposplenism "by analogy with the terms "hyperthyroidism" and "hypothyroidism"" [37]. The main treatment for "harmful" hypersplenism was indeed splenectomy, but no treatment for splenic hypofunction was available. Only after the second half of the twentieth century has the attention shifted towards defective spleen function. In 1955, the American hematologist William Dameshek (1900–1969) described a patient suffering from non-tropical sprue in whom blood smear alterations were found, including the presence of Howell–Jolly bodies and target cells [39]. A post mortem diagnosis of spleen atrophy was made, and Dameshek concluded that the examination of a blood smear was needed for corroborating the clinical diagnosis of hyposplenism. The alterations found in the blood smear were linked to the impaired ability of the reticuloendothelial system of the spleen to remove damaged and older blood cells. A few years later, the so called "pitted red cells" were described as the most relevant and characteristic blood smear finding in splenectomized patients [40, 41]. "Pits" are a crater-like, morphological alteration of the erythrocytes that can be seen with an interference contrast microscope equipped with Nomarsky optic. Hence, a rather inexpensive and reproducible test for the diagnosis of defective spleen function became available.

The relation between spleen hypofunction, thrombocythemia, and infections became clearer [42], in particular the susceptibility to life-threatening infections triggered by encapsulated bacteria, namely *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*. The first reports of severe, overwhelming infections occurring after splenectomy regarded pediatric patients [43]. Over time, different degrees of hyposplenism have been described in many other conditions, especially immune-mediated disorders of the gastrointestinal tract, but also infectious, autoimmune, and hepatic disorders [44]. Interestingly, splenectomized wild-type mice have a reduction of the B-1a B cell pool, with reduction of IgA plasma cells and absence of soluble IgA. This evidence shades new possible insights into the pathogenesis of immune-mediated disorders of the gastrointestinal tract and results in humans are eagerly awaited [45].

Celiac disease has probably been the most studied condition in relation to hyposplenism. Counting of pitted red cells, with a normal cutoff of $<4\%$, was validated in patients with celiac disease [46]. The prevalence of hyposplenism is even higher in patients with other concomitant autoimmune disorders and in refractory celiac disease [47]. There is evidence of a high susceptibility to infections in hyposplenic celiac patients, and a loss of IgM memory B-cells occurring in the spleen is thought to contribute and to be linked to this predisposition [48]. Similarly, IgM B-memory cells were found to also be decreased in patients suffering from inflammatory bowel disease and defective spleen function [48]. This has a relevant significance, given that many effective vaccines are now available, even if the correct timing and best type of vaccination (conjugated *vs* polysaccharidic) are yet to be determined for these patients [49].

Finally, in recent years, the evolution of morphological studies of the spleen has provided novel clinical applications. The spleen plays a central role in determining portal hypertension by increasing splanchnic blood flow. However, splenomegaly, which was initially thought to reflect spleen hyperfunction, does not univocally correlate with portal hypertension. Spleen stiffness, which is evident in patients with advanced liver disease, is a relatively novel feature that can be measured by FibroScan. Particularly, spleen stiffness has been shown to predict the presence of esophageal varices in liver cirrhosis and can be used as a more precise marker of portal hypertension [50].

To conclude, future studies will have to focus on many open issues and unexplored areas of research, including the fine mechanisms that hamper immune functions in hyposplenic patients, the prevention of spleen hypofunction and its complications, and the relation between immunological and morphological aspects. From this point of view, the spleen is still a mysterious and fascinating organ that needs to be discovered.

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