Received: 19 October 2021 | Revised: 22 February 2022 | Accepted: 24 March 2022

DOI: 10.1002/ca.23867

REVIEW

CLINICAL ANATOMY WILEY

The lymphatic system throughout history: From hieroglyphic translations to state of the art radiological techniques

Caroline J. van Schaik[1] | Lucas L. Boer[2] | Jos M. T. Draaisma[3] | Carine J. M. van der Vleuten[4] | Jan Jaap Janssen[1] | Jurgen J. Fütterer[1] | Leo J. Schultze Kool[1] | Willemijn M. Klein[1]

[1]Department of Medical Imaging, Radboud University Medical Center, Nijmegen, The Netherlands

[2]Department of Medical Imaging, Radboud University Medical Centre, Nijmegen, The Netherlands

[3]Department of General Pediatrics, Radboud University Medical Centre, Nijmegen, The Netherlands

[4]Department of Dermatology, Radboud University Medical Centre, Nijmegen, The Netherlands

Correspondence
Caroline Johanna van Schaik, Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, The Netherlands.
Email: caroline.vanschaik@radboudumc.nl

Abstract

A comprehensive lymphatic system is indispensable for a well-functioning body; it is integral to the immune system and is also interrelated with the digestive system and fluid homeostasis. The main difficulty in examining the lymphatic system is its fine-meshed structure. This remains a challenge, leaving patients with uninterpreted symptoms and a dearth of potential therapies. We review the history of the lymphatic system up to the present with the aim of improving current knowledge. Several findings described throughout history have made fundamental contributions to elucidating the lymphatic system. The first contributions were made by the ancient Egyptians and the ancient Greeks. Vesalius obtained new insights by dissecting corpses. Thereafter, Ruysch (1638–1731) gained an understanding of lymphatic flow. In 1784, Mascagni published his illustration of the whole lymphatic network. The introduction of radiological lymphography revolutionized knowledge of the lymphatic system. Pedal lymphangiography was first described by Monteiro (1931) and Kinmonth (1952). Lymphoscintigraphy (nuclear medicine), magnetic resonance imaging, and near-infrared fluorescence lymphography further improved visualization of the lymphatic system. The innovative dynamic contrast-enhanced magnetic resonance lymphangiography (DCMRL) transformed understanding of the central lymphatic system, enabling central lymphatic flow disorders in patients to be diagnosed and even allowing for therapeutic planning. From the perspective of the history of lymph visualization, DCMRL has ample potential for identifying specific causes of debilitating symptoms in patients with central lymphatic system abnormalities and even allows for therapeutic planning.

KEYWORDS

dynamic MR lymphangiography, lymphatic system, lymphography, therapeutic embolization

Abbreviations: CE, common era; BCE, before common era; DCMRL, dynamic contrast-enhanced magnetic resonance lymphangiography; ICG, indocyanine green; MR, magnetic resonance; MIP, maximal intensity projection; NIRF, near infrared fluorescence imaging; SPECT, single photon emission computed tomography.

1 | INTRODUCTION

A comprehensive lymphatic system is indispensable for a well-functioning body. It is integral to the immune system and is also closely intertwined with the digestive system and fluid homeostasis (Chavhan et al., 2017). The phrase "lymphatic system" denotes lymphatic vessels, lymph nodes and accessory organs, collectively part of the cardiovascular system. "Lymph", originally derived from the Greek *νύμφη* (Nymph: a being or creature associated with clear streams) and the Latin *Lympha* (an ancient Roman deity of fresh water) (Andrews & Gardiner, 2014; Shields, 1994), contains lymphocytes crucial for infection control; intestinal lymph (also called chyle) contains peptides and lipids essential for nutrition, growth and energy (Chavhan et al., 2017).

Lymph flows into and through lymphatic vessels, which arise in the interstitial space and debouche into the thoracic duct, a 38–45 cm long structure with an average diameter of 5 mm, typically carrying 1.5–2.5 L of lymph per day. This duct eventually drains into the junction of the left subclavian and left internal jugular veins. Disrupted or dysfunctional lymph and/or chyle flow can result in lymph edema and leakage of lymph and/or chyle with severely debilitating and even lethal outcomes (Chavhan et al., 2017).

The main difficulty in imaging and examining the lymphatic system is its fine-meshed structure. In addition, lymph fluid is mostly colorless (though chyle is milky). Therefore, lymph vessels are barely visible to the naked eye, which was the standard study method during autopsies and anatomical dissections during previous centuries. Even today, when high resolution radiological imaging is readily available, the lymphatic system is hard to identify and barely visible. Moreover, these fine structures are easily overlooked as 'radiological attention' is mainly on the larger blood circulation and macroscopically visible organs. These difficulties leave patients with uninterpreted symptoms and consequently a dearth of potential therapies.

However, there have been times during past millennia when scientists conducted extensive studies on the lymphatic system, an extensive circulatory network with important functions in all vertebrates (Hedrick et al., 2013). In this article, we offer a historical overview of the lymphatic system and emphasize its importance. If this system is better understood, further improvements in both diagnostic and treatment options can be expected. Therefore, we review the lengthy history of knowledge about it, discussing the most important discoveries and the way understanding has grown from approximately 1600 BC to the present day. We conclude with an overview of current state of the art imaging techniques for visualizing this intriguing circulatory structure, which extends throughout the body.

1.1 | Ancient Egypt (3100 BC–30 BC)

Lymph nodes were apparently first mentioned in the hieroglyphs describing case 39 in the Edwin Smith Papyrus, inscribed around 1600 BC. This papyrus is acknowledged as the earliest known medical scientific paper (Breasted, 1930). It is a copy dating from the 17th century BCE, the original manuscript having been created at least a 1000 years earlier. The author is not named anywhere in the text and therefore remains unknown. The Norwegian physician Bendix Ebbell (1865–1941) suggested that "lymphatic glands swelling" rather than "swelling" in case 39 is probably the correct translation of the hieroglyph (Ebbell, 1937; Veiga, 2009). This probably makes it the first known denotation of the lymphatic system.

1.2 | Classical antiquity (8th century BCE–6th century CE)

After that first description of lymph nodes in hieroglyphs, the Greek physician Hippocrates in the 5th century BCE wrote in the Hippocratic Corpus: "all men have glands, smaller or larger, in the armpit and many other parts of the body" (Ambrose, 2006). The different Ionic dialects in the Hippocratic Corpus, and the occasional contradictory content, suggest that Hippocrates was not the only author. Therefore, this work is attributed to 'the Hippocratic author' (Suami et al., 2009). The Hippocratic author described lymph nodes specifically in the axilla, around the ears, near the jugular vessels, the groin, the mesentery and near the kidneys (Suami et al., 2009), and later presented three significant and original descriptions concerning the physiology of the lymphatic system. First, the lymphatic system is described as comprising lymphatic vessels and lymph nodes. Secondly, its drainage function is described by observing that lymph nodes receive fluid from numerous afferent vessels. Thirdly, lymph nodes and lymphatic vessels are described as part of the inflammatory system. The latter statement was supplemented by the observations of enlarged lymph nodes during (local) infections (Crivellato et al., 2007).

Following these pioneering accounts of the lymphatic system, one of the first reports of (assumed) lymphatic vessels found during an animal dissection was in *Historia Animalium* (Book III, chapter VI) by Aristotle (384–322 BC): "fibers, which take position between blood vessels and nerves and which contain colorless liquid." Aristotle investigated and dissected multiple types of animals to compile this report; he did almost certainly not use human corpses. He used the word '*ινες*' (ines), which is usually translated as 'fibers', though its exact meaning is not clear, so what he was describing remains uncertain (Crivellato et al., 2007; Kanter, 1987).

The Alexandrian School also contributed substantially to describing the lymphatic system, as indicated in *Anatomicae administrationes* (Book VII, chapter XVI) by Galen (2nd and 3rd centuries CE). Galen reported that Erasistratos (310–250 BCE) had demonstrated that the abdominal arteries in a young goat filled with milk when incised (Ambrose, 2006; Ambrose, 2007). This is possibly the first description of mesenteric lymphatic vessels. Galen repeated Erasistratos's work in full-grown animals and dismissed his finding. However, he did describe mesenteric lymph nodes. He named the transport of chyle to the liver and its further transportation into blood '*αναδοσις*', which is chylification. Galen also addressed the description by Erophilus, a Greek physician of 335–280 BCE, of particular venous vessels associated with feeding the gut. In these descriptions, Galen perhaps recognized the difference between milky and clear lymphatic fluid (Ambrose, 2006; Ambrose, 2007).

In contrast to the substantial progress made during Classical Antiquity, interest in the human body declined in the Middle Ages, also referred to as the Dark Ages owing to a supposed lack of cultural and scientific advancement. There were few scientific publications during this time. Further important contributions to knowledge of the lymphatic system had to await the Renaissance.

1.3 | Renaissance: Vesalius (16th century CE)

Andreas Vesalius (1514–1564) is considered the father of modern anatomy (Natale et al., 2017). He published *De Humani corporis fabrica* in 1543, identifying many mistakes in Galen's work through the use of human rather than animal dissections. Vesalius described the 'glandulous body' in the mesentery. He maintained the Galenic belief that the entire venous system originated from the liver, labeled '*iecurvenarum principium*' (liver source of the veins). Later, after multiple observations, the word 'circulation' was first used for the cardiovascular system, recognizing the heart as the central organ instead of the liver. This opened the door to greater understanding of the lymphatic system, since the 'innumerable and extremely small veins with valves at the end' received renewed interest and attention. Thus, understanding of the lymphatic system was enhanced by the conversion from hepatocentrism to cardiocentrism in the cardiovascular system (Tonetti, 2017; Vesalius et al., 2007). Vesalius's mentor, Niccolò Massa (1485–1569), described the renal lymphatic lymph vessels (Ambrose, 2006).

Galen's hypothesis regarding arteries filling with milk was recognized by Ambroise Paré (1510–1590): "The chyme resulting from digestion in the stomach, which is indeed often a thin creamy porridge, forms a liquid known as almond milk, which, after passing through the wall of the intestine, conducts the fluid via 'mesaraic' (mesenteric) veins to the portal vein" (Schuchhardt et al., 2003).

Vesalius' student, Gabriele Falloppio (1523–1562), performed vivisections on criminals sentenced to death. He described vessels "coursing over the intestines full of yellow matter, going to the liver and lungs", clearly the mesenteric lymphatic vessels (Ambrose, 2006). Falloppio's observation was not disseminated in the scarce literature until it was rediscovered during the 17th century.

The thoracic duct, including valves, was first described by Bartolomeo Eustachi (1520–1574) in horses. The name *vena alba thoracis* was given to this structure, but Eustachi did not succeed in determining its role: "Several times I believed to this structure of the nature: a certain vein in horses, which is very particular and uncommon. It does not act to feed the thorax. However, since it is pleasant and useful, it deserves to be described. In those animals, a great formation arises from this left trunk of the throat, from the posterior part of the root of the internal jugular vein. Other than to have a semicircular hole at its beginning, it is also white and contains aqueous humor; not so far from its beginning, it divides into two parts that early reunite in a unique structure along the left side of the vertebral column, without branches, that crosses the diaphragm to reach the lumbar region, where it becomes larger and envelopes an artery. I did not understand its unknown end" (Natale et al., 2017).

1.4 | Seventeenth century

Several discoveries aided progress in the investigation of the lymphatic system throughout the 17th century, though there was not complete agreement among scientists. In 1622, Gaspare Aselli (1581–1625) described "several thin and beautiful white cords" in vivisected dogs. At first, these were interpreted as part of the nervous system. Subsequently, after numerous dissections, Aselli was convinced he had discovered another circulatory system. The *'white cords'* were named 'venae albae aut lacteae' (lacteals): white vessels carrying milky fluid (Loukas, Bellary, et al., 2011). Fabrice de Peiresc (1580–1637) repeated this investigation in humans and subsequently identified lacteals (Ambrose, 2006).

Remarkably, William Harvey (1578–1657) rejected some of this progress in understanding the lymphatic circulation. He denied the presence of chyle in lacteals and its trajectory from the thoracic duct into the subclavian vein. He concluded that the lymphatic network was too vast to contribute to the movement of nutrients from the gut to the cardiovascular system (Loukas, Bellary, et al., 2011).

Another important contribution was made by Jean Pecquet (1624–1674). He described the reservoir of the chyle (cisterna chyli) and the thoracic duct. Of even greater importance, Pecquet established that lacteals debouch into the thoracic duct rather than the liver. However, Francis Glisson (1597–1677), an English anatomist, claimed to have been the first to show that lacteals do not enter the liver, together with his pupil George Joyliffe (1621–1658) (Ambrose, 2006; Ambrose, 2007). Glisson claimed that Joyliffe had been "busy with another practice" and failed to publish his discoveries, claiming credit for the new knowledge about the flow of the lacteals on behalf of his pupil (Fulton, 1938).

1.5 | Enlightenment (17th and 18th centuries)

Olaus Rudbeck (1630–1702) was a Swedish scientist affiliated to Uppsala University. He began dissecting animals as a young student and discovered the lymphatic connection between the intestines and the blood circulation, specifically the course of absorbed nutrients through the thoracic duct to the veins. Rudbeck reported these findings in 1652 (Ambrose, 2006). In 1653, he made another exciting contribution to knowledge of the lymphatic system, describing subepicardial lymphatics in the heart of a dog (Loukas, Abel, et al., 2011). Only recently was he acknowledged, by Patek, as the first scientist to describe the cardiac lymphatic system (Loukas, Abel, et al., 2011). However, the Danish anatomist Thomas Bartholin had reported roughly the same discoveries a little earlier, resulting in a great precedence dispute (Ambrose, 2006).

One of the most remarkable scientists of the Enlightenment was the Dutch physician Frederik Ruysch (1638–1731). In 1666, Ruysch started as *Praelector Anatomiae* (Lecturer in Anatomy) of the Amsterdam Guild of Surgeons. He practiced this profession for more than 65 years. He dissected executed criminals at the anatomical theater to educate people in anatomy (Ijpma & van Gulik, 2013). He was encouraged to investigate the lymphatic system by his tutor Van Horne (1621–1670). Ruysch noticed that the lymphatic valves had not been visualized by other scientists and that knowledge of the lymphatic system was limited. He devised methods to preserve human anatomical structures including lymph vessels, injecting glycerol and mercury sulfide into even the smallest vessels. Partly because of this method he was able to study well-preserved cadavers with life-like appearances. He dissected the lymphatic vessels and inflated them with air by inserting a small tube and blowing through it. This led him to observe multiple semilunar valves, a groundbreaking discovery and a milestone in understanding the direction of lymph flow. In 1670, Ruysch was shown performing a dissection on inguinal lymph nodes, surrounded by members of the Guild of Surgeons, in a painting by Adriaen Backer called 'Anatomy Lesson of Dr. Frederik Ruysch' (Figure 1). It is thought not to be a coincidence that Ruysch was portrayed dissecting lymph nodes, in view of his groundbreaking research on the lymphatic system (Ijpma & van Gulik, 2013).

The discovery of the microscope by Antoni van Leeuwenhoek was a milestone in the history of science. The Italian scientist Marcello Malpighi (1628–1689), regarded by some as the founder of microscopic anatomy, contributed greatly to its development by introducing Van Leeuwenhoek's pioneering instrument. From that point, the microscope proved to be of great value in revealing the smallest details in anatomy, histology and pathology (Natale et al., 2017). Malpighi was convinced that most organs contained glandular structures, the characteristics of which regulated each organ-specific function. He applied the same reasoning to his study of spleen anatomy. He distinguished two anatomical parts, which he called "red and white pulp." He observed that the sizes of human glands changed under specific disease conditions and inferred that the splenic glands were components of an extensive glandular system corresponding (according to current knowledge) to the lymphatic system. He published his work in *De Viscerum Structura* in 1666 (Pizzi et al., 2018).

The French anatomist Raymond Vieussens (1641–1715), pioneer in cardiac anatomy and the anatomy of the nervous system, achieved further insights into the lymphatic system. In 1706, he published his pioneering work in *Nouvelles Découvertes sur le Coeur* (1706), depicting the cardiac lymphatic system in detail (Loukas et al., 2007). Following Malpighi and Vieussens, William Hunter (1718–1783) described the function of the lymphatic system more extensively (Loukas, Bellary, et al., 2011; Natale et al., 2017). In 1743, he started researching this system (he preferred the term 'absorbent system'), and in 1746 was teaching students that lymphatics are "the same as lacteals and that these together constitute one great and general system dispersed throughout the whole body for absorption."

Another major contributor to knowledge of the lymphatic system was the Italian anatomist Paolo Mascagni (1755–1815). He injected mercury into lymphatic vessels through his self-designed glass instrument while dissecting over 300 corpses. In 1784, he published his illustrated masterpiece in French, depicting the entire lymphatic network in great detail (Figure 2) (Vannozzi, 2015). In 1787, this work was published in Latin as *Vasorum lymphaticorum corporis humani historia et ichnographia*. This earned him fame throughout Europe and the honorable title 'prince of anatomists' was conferred on him (Natale et al., 2017).

1.6 | Recent times (19th century–present)

The French anatomist Marie Sappey (1810–1896) significantly advanced knowledge of lymphatic system anatomy, particularly the cutaneous lymphatic system and the lymphatic system of the breast.

FIGURE 1 Adriaen backer, anatomy lesson of Dr. Frederik Ruysch, 1670. Ruysch, demonstrating the inguinal lymph nodes, is surrounded by members of the Guild of Surgeons (Leendert Fruijt, Aert van Swieten, Gillis Hondekoeter, Rogier de Coen, Joris van Loon Tilanus, and Jacob Brandt). Courtesy of the Amsterdam Museum

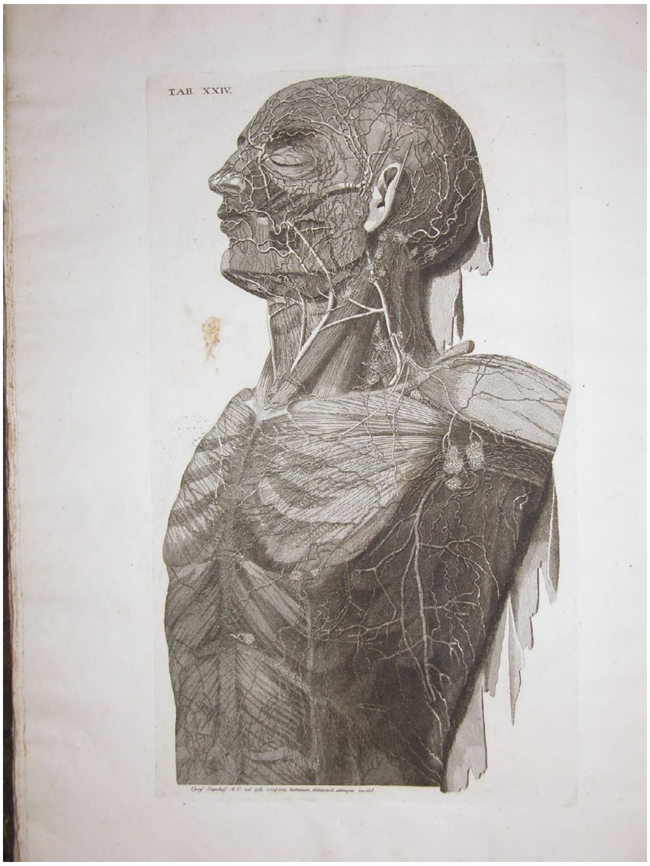

FIGURE 2 Paolo Mascagni, Table XXIV (from *Vasorum Lymphaticorum Corporis Humani Historia et Ichnographia*, 1787. Courtesy of the health sciences library, University of Washington)

Sappey published his work in *Anatomie, Physiologie, Pathologie des vaisseaux lymphatiques* (Suami et al., 2009). He was able to count the valves in lymphatic vessels (Natale et al., 2017).

The Polish pathologist Alfred Biesiadecki (1839–1889) made great contributions to the knowledge of the lymphatic system in the skin. Through his research, he refuted the prevailing hypothesis that blood capillaries in the skin are located inside lymphatic vessels. For the first time in history, he described an adjacent connection between lymphatic vessels and blood vessels (Gonkowski & Grzybowski, 2020).

Following these impressive discoveries, further knowledge was obtained by the German physician Carl Ludwig (1816–1895) in 1858. He conjectured that lymph starts as a blood filtrate originating from the capillary wall, caused by intracapillary pressure. However, the German physiologist Rudolph Heidenhain (1834–1897) thought differently. In 1891, he hypothesized that lymph is actively secreted through the lymphatic endothelium. Eventually, the British physiologist, Ernest Starling (1866–1927) demonstrated that lymph results from movement of fluid across the capillary wall caused by a balance between hydrodynamic and osmotic forces (Natale et al., 2017).

Thereafter, the British physician William Handley made a substantial contribution to the development of surgery for lymphatic disorders. In 1908, he presented his technique of "lymphangioplasty", introducing silk threads subcutaneously in effort to create a conduit for lymphatic drainage. This technique was eventually abandoned owing to postoperative infections and spontaneous ejection of the foreign material (Handley, 1908).

In 1939, Paul Patek published his impressive work regarding the cardiac lymphatic system. He showed that the mammalian cardiac lymphatic system perfused all three layers of the heart, subepicardium, myocardium and subendocardium, and demonstrated that cardiac lymph fluid emerges from the subendocardium, courses through the myocardium and drains into local lymph nodes via the subepicardium (Loukas et al., 2007; Patek, 1939).

Professor Miltiadès Papamiltiadès (1910–1987), a renowned Greek anatomist, is known for his research on multiple components of the lymphatic system. He was the first to describe parts of the respiratory lymphatic system: lymphatics of the pulmonary artery, pulmonary bronchi and pulmonary segments. He also presented the anatomy of the lymphatics in the female genital organs in great detail. Additionally, he achieved major milestones in knowledge of the lymphatic system elsewhere in the body (Androutsos et al., 1994).

Leonetto Comparini (1924–1999), former director of the Institute of Human Anatomy in Siena, investigated the walls of lymphatic vessels in humans. He demonstrated that lymphatic vessels could be subdivided into three types on the basis of morphology and molecular characteristics: lymphatic capillaries, pre-collecting lymphatic vessels, and collecting lymphatic vessels. Lymphatic pre-collectors drain into pre-nodal collectors after deriving from the absorbing lymphatic network (Comparin & Bastianini, 1965). He showed that lymphatic valves are distributed irregularly throughout the lymphatic vessels. Subsequently, Comparini described the muscular elements of the lymphatic wall that are arranged helically. In 1958, he provided very detailed illustrative reconstructions of the lymphatic vessels of the liver. The three-dimensional graphic visualizations were and remain highly original because they drew specifically on graphic reconstructions based on histological preparations. These reconstructions demonstrated the relationship of the lymphatic system to the surrounding arterial and venous vessels and biliary ducts (Comparini & Bastianini, 1965).

Following these exciting developments, new discoveries were made about the central nervous system. In 2012, a waste clearance system in the central nervous system was first suggested in mice, referred to as the glymphatic system (Yang et al., 2013). In 2017, pioneering researchers documented a glymphatic system in the human brain (Ringstad et al., 2017). It is considered a waste clearance pathway in the brain that uses perivascular tunnels formed by astroglial cells to drain soluble waste proteins and metabolites. It thereby facilitates the distribution of indispensable molecules such as glucose, lipids, growth factors and neuromodulators. Interestingly, researchers have recently discovered that the glymphatic activity is significantly more active during sleep than wakefulness (Jessen et al., 2015).

Another major discovery was made in 2015 concerning the meningeal lymphatic network. Two groups independently showed that mouse brain meninges contain a lymphatic network. This research validated a forgotten anatomical finding by Mascagni in 1787 regarding the lymphatic network of the brain and observations of a lymphatic

FIGURE 3 Pedal lymphography

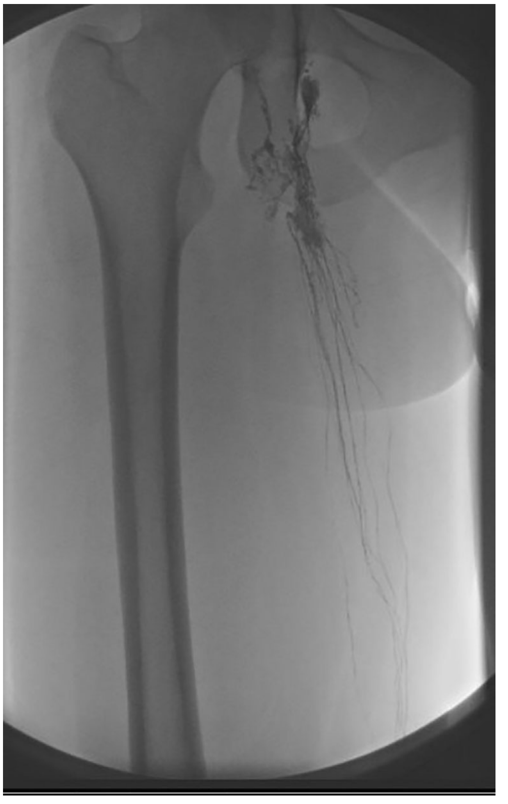

FIGURE 4 Pedal lymphography

network in the dura of rat brains (Ulvmar & Mäkinen, 2016). In 2017, a group demonstrated meningeal lymphatic vessels in humans using magnetic resonance imaging (Absinta et al., 2017). In summary: the fascinating and recently discovered glymphatic system and meningeal lymphatic network function as essential fluid transport systems for, respectively, the central nervous system and the meninges.

Visualization and therefore knowledge of the lymphatic system was significantly improved by the introduction of lymphography. In 1931, Hernani Monteiro first described pedal lymphangiography by injecting ethiodized oil in the subcutaneous space between the toes and then following this contrast material through the lymphatic vessels by radiography (Kinmonth, 1952; Kinmonth, 1954). John Bernard Kinmonth made an important contribution to this imaging technique in 1952. He used subcutaneously injected patent blue dye to locate the lymphatics, after which he injected a radiopaque contrast medium directly into the identified lymphatic vessel. This development significantly promoted studies of the lymphatic system (Kinmonth, 1952; Kinmonth, 1954). Two examples of the technique first described by Kinmonth are shown in Figure 3 and Figure 4. It has been used in clinical practice to demonstrate oncological lymphadenopathy (Strijk, 1987).

The introduction of cross-sectional imaging techniques such as computed tomography (CT) shifted attention away from the lymphatic system mainly because of its small size and difficult labor-intensive radiological visualization. For decades, radiological imaging of lymph vessels lacked attention and fell behind in both knowledge and skills. Only recently has imaging of lymph gained interest again, leading to the invention of intranodal contrast injection (Chavhan et al., 2017). Dynamic intranodal contrast-enhanced MR lymphangiography (DCMRL) uses contrast injected into the superficial inguinal lymph nodes and follows its spread through the retroperitoneal space into the thoracic duct. This new technique provided many new insights into the anatomy and flow physiology of the central (thoraco-abdominal) lymphatic lymph vessels, which had not previously been visualized in high resolution and three dimensions (Chavhan et al., 2017). DCMRL has contributed significantly to knowledge of lymphatic system pathologies such as leakage from the thoracic duct with subsequent chylothorax. In addition, this modality can allow therapeutic planning such as embolization of the leakage to be made.

Two examples of DCMRL are shown in Figure 5 and Figure 6.

2 | IMAGING TECHNIQUES

In current practice, the lymphatic system can be visualized using various imaging techniques, each with its own strengths and weaknesses. We present the most relevant diagnostic imaging techniques and therapeutic interventions below, including their main indications.

2.1 | Lymphoscintigraphy

Lymphoscintigraphy provides imaging of the peripheral lymphatics (Figure 7). Radioactive material is injected subcutaneously into the hands or feet. This technique delivers dynamic imaging with images every

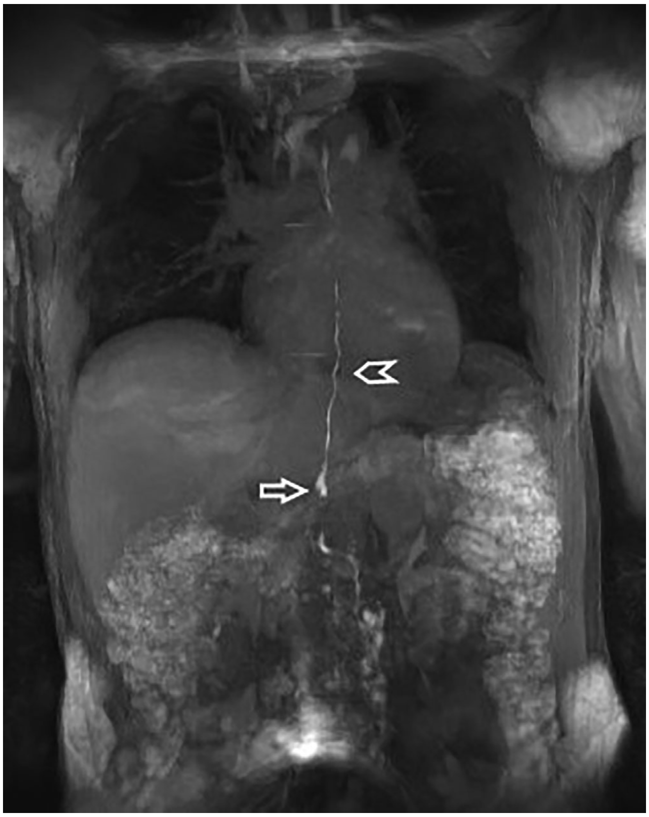

FIGURE 5 Dynamic contrast-enhanced magnetic resonance lymphangiography demonstrating a normal central lymphatic system. Coronal maximum intensity projection (MIP) of T1-weighted sequences post intranodal contrast shows the thoracic duct (arrow point) and cisterna chyli (arrow)

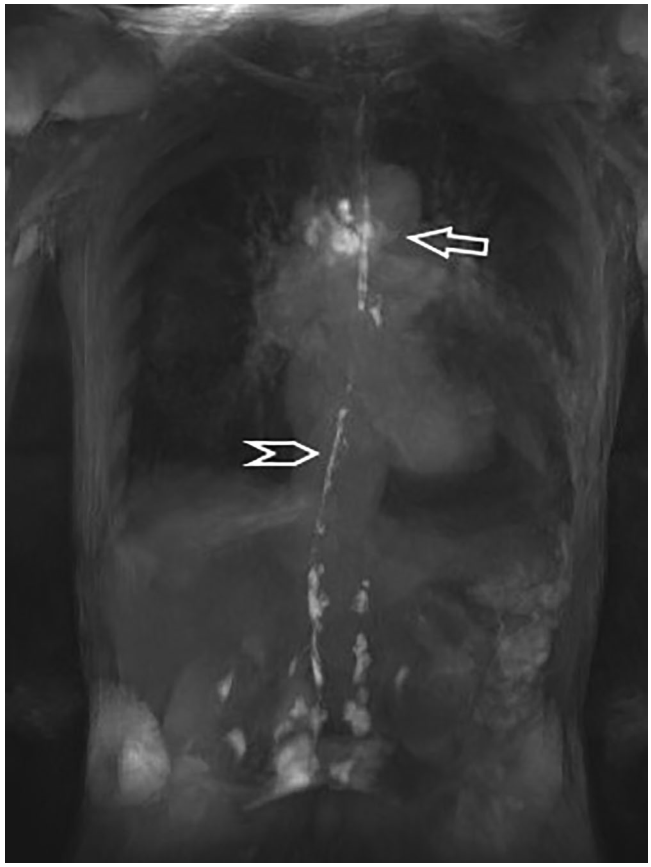

FIGURE 6 Dynamic contrast-enhanced magnetic resonance lymphangiography demonstrating a central lymphatic flow disorder. Coronal maximum intensity projection (MIP) of T1-weighted sequences post intranodal contrast shows leakage into pericardial fluid (arrow) from the thoracic duct (arrow point)

30 minutes in general. However, spatial resolution is limited so detailed images are hard to acquire. Single photon emission computed tomography (SPECT) can be performed for more specific three-dimensional localization of the lymph if this is valuable (Chavhan et al., 2017).

2.2 | Near-infrared fluorescence with indocyanine green

Near-infrared fluorescence (NIRF) with indocyanine green (ICG) is used to visualize superficial lymphatics (Figure 8). ICG is injected into the region of interest. Thereafter, dynamic continuous imaging is performed using near-infrared radiation on the skin and detecting emission by ICG. Unfortunately, this technique is only available for subcutaneous lymphatics (up to 15 mm depth) owing to the absorption of near infrared light (Mihara et al., 2012). It is used to locate lymphatic vessels for potential venolymphatic anastomoses to alleviate lymphedema.

2.3 | MR lymphangiography

Static MR lymphangiography uses high T2-weighted MR images without contrast to provide adequate imaging of the lymphatic system and possibly also to demonstrate pathological lymphatic structures. This technique lacks dynamic data, so information about lymphatic flow disorders is limited. It is used to obtain anatomical information about the lymphatic system. Dynamic intranodal MR lymphangiography overcomes these limitations by injecting a gadolinium-based contrast agent bilaterally into an inguinal lymph node and following it through the retroperitoneal space into the subclavian vein (Figures 5 and 6) (Chavhan et al., 2017). DCMRL is indicated if lymph flow disorders such as thoracic duct leakage are suspected.

3 | INTERVENTIONAL TECHNIQUES

3.1 | Diagnostic intranodal intervention

Intranodal intervention includes injecting ethiodized oil into an inguinal lymph node and following it radiographically to the thoracic duct. Owing to its high density and its accumulation at the point of leakage, ethiodized oil could have a collateral therapeutic effect: sealing the leak (Itkin & Nadolski, 2018).

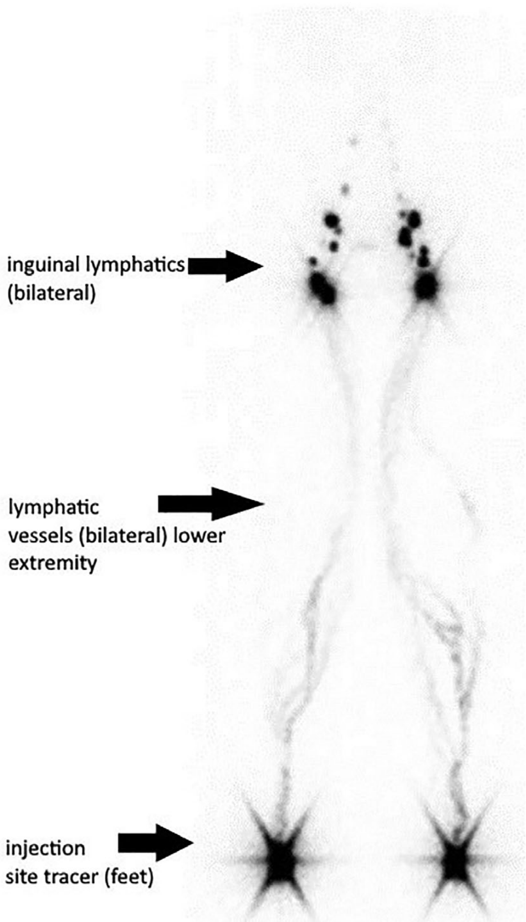

FIGURE 7 Normal lymphoscintigraphy of the lower limbs

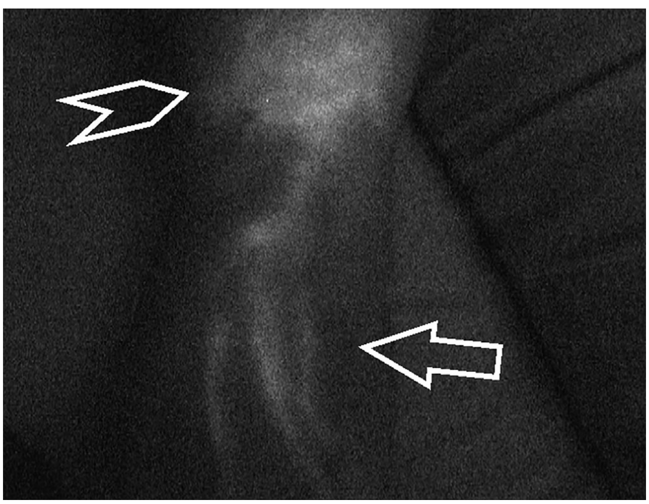

FIGURE 8 Near-infrared fluorescence with indocyanine green (ICG) of the distal upper limb demonstrating functional lymph vessels on the dorsal side of the hand (arrow) and diffuse dermal backflow proximal to the wrist (arrow point)

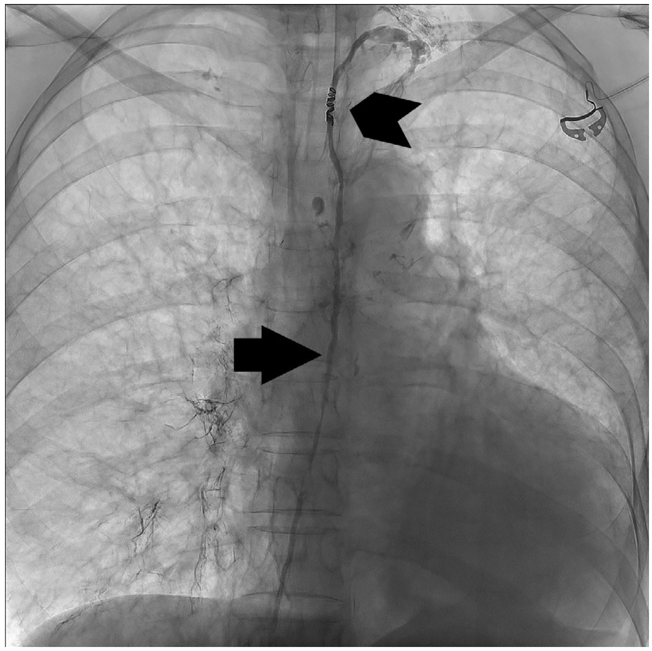

FIGURE 9 Lymphography, showing the thoracic duct (arrow), after occluding leakage points with Lipiodol® (ethyl esters of iodinated fatty acids of poppy seed oil; manufacturer: Guerbet, Villepinte, France) and through coils (arrow point)

3.2 | Therapeutic percutaneous intervention

Thoracic duct embolization can succeed intranodal intervention and visualization of the cisterna chyli and thoracic duct. Percutaneous access to the cisterna chyli is obtained with a needle, after which the cisterna chyli and thoracic duct are cannulated with a microcatheter. The thoracic duct can then be embolized (or a leaking side branch on indication) (Itkin & Nadolski, 2018), as shown in Figure 9.

Altogether, these evolving imaging techniques have markedly enhanced anatomical and pathophysiological knowledge of the lymphatic system (Figure 10). Therefore, patients with abnormalities in the lymphatic system (chylothorax, chylous ascites, lymphedema) are potentially provided with a specific cause of their debilitating or even lethal symptoms. These imaging techniques, mainly DCRML, can even allow for therapeutic planning. Given the impairing and sometimes lethal nature of the clinical symptoms of central lymph flow abnormalities, discovering an anatomical cause and potentially providing treatment is of the utmost importance for patients whose pathology has seemed poorly understood for ages.

4 | SUMMARY

Several findings described throughout history have contributed fundamentally to current knowledge of the lymphatic system. The first contributions were presumably made by the ancient Egyptians, who mentioned lymph nodes in hieroglyphs around 1600 BC. Thereafter,

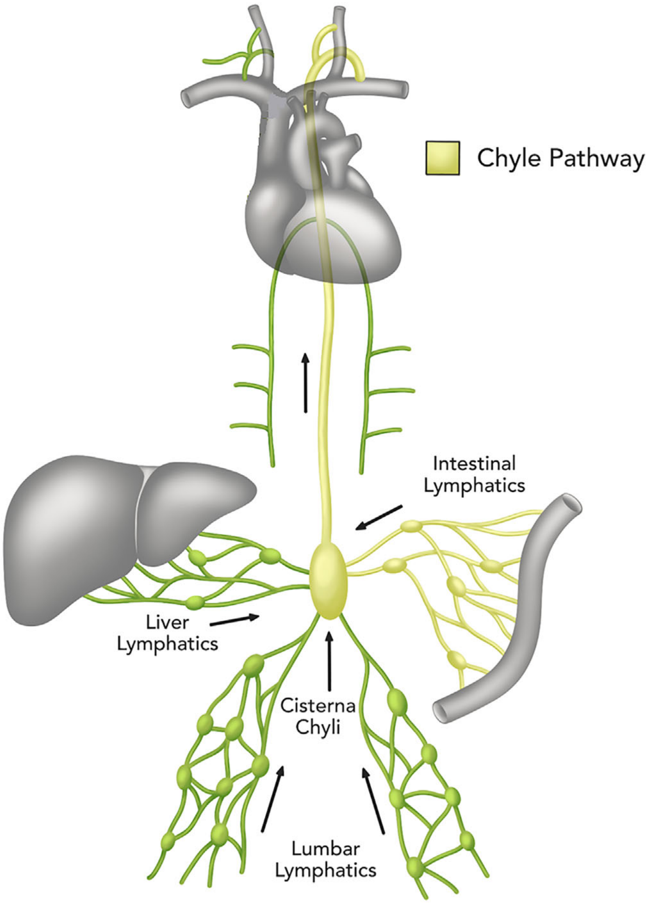

FIGURE 10 Graphic display of the central lymphatic anatomy. Illustration rights owned by the Department of Medical Imaging, Radboudumc Nijmegen

The Hippocratic School and The Alexandrian School described lymph nodes and the functions of the lymphatic system. Following these discoveries, many other scientists contributed substantially to knowledge of the lymphatic system. These include Andreas Vesalius, who brought new insights by dissecting human corpses and publishing his anatomical findings in his masterpiece '*De Humani corporis fabrica*' (1543). Following these groundbreaking findings, Gaspare Aselli described "several thin and beautiful white cords" in dogs in 1622. During the Enlightenment, Frederik Ruysch (1638–1731) dissected executed criminals and observed valves in the lymphatic vessels and thereby established the direction of lymphatic flow. Subsequently, the Swedish scientist Olaus Rudbeck reported the cardiac lymphatic system in 1653. Only recently was his work acknowledged by Paul Patek as the first scientist to describe the cardiac lymphatic system. In 1666, the Italian scientist Marcello Malpighi described two anatomical sections in the spleen: "red and white pulp." In 1784, Paolo Mascagni published his illustration of the whole lymphatic network.

Following these remarkable contributions, a waste clearance system of the central nervous system was indicated in mice in 2012, referred to as the glymphatic system. In 2017, the glymphatic system was first described in the human brain, simultaneously with the first documentation of the meningeal lymphatic network.

The introduction of radiological lymphography transformed knowledge of the lymphatic system. Pedal lymphangiography was first described by Monteiro (1931) and Kinmonth (1952). Thereafter, magnetic resonance imaging (MRI), lymphoscintigraphy (nuclear medicine) and near-infrared fluorescence (NIRF) lymphography further improved the visualization of the system.

The innovative dynamic contrast-enhanced MR lymphangiography (DCMRL) revolutionized understanding of the anatomy and pathophysiology of the central lymphatic system, precisely locating the impairing and sometimes lethal symptoms in patients with central lymphatic flow disorders and even allowing for therapeutic planning.

Further research is necessary for a complete understanding of the fetal development of the lymphatic system and its physiology throughout human life, which will lead to a better understanding of lymphatic flow disorders and improved treatment.

ORCID

Caroline J. van Schaik https://orcid.org/0000-0002-2540-5181
Lucas L. Boer https://orcid.org/0000-0003-1564-0847

REFERENCES

Absinta, M., Ha, S. K., Nair, G., Sati, P., Luciano, N. J., Palisoc, M., Louveau, A., Zaghloul, K. A., Pittaluga, S., Kipnis, J., & Reich, D. S. (2017). Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI. *eLife*, *6*, e29738.

Ambrose, C. T. (2006). Immunology's first priority dispute—An account of the 17th-century Rudbeck-Bartholin feud. *Cellular Immunology*, *242*(1), 1–8.

Ambrose, C. T. (2007). Rudbeck's complaint: A 17th-century Latin letter relating to basic immunology. *Scandinavian Journal of Immunology*, *66*, 486–493.

Andrews, R. K., & Gardiner, E. E. (2014). Lymphomania. *Blood*, *123*(20), 3057–3058.

Androutsos, G., Marketos, S., & Marketos, S. (1994). In memoriam Miltiades Papamiltiades (1910–1987): Eminent Greek anatomist and ambassador of Franco-Hellenic friendship. *Surgical and Radiologic Anatomy*, *16*(4), 445–448.

Breasted, J. H. (1930). *The Edwin smith surgical papyrus*. University of Chicago Press.

Chavhan, G. B., Amaral, J. G., Temple, M., & Itkin, M. (2017). MR lymphangiography in children: Technique and potential applications. *Radiographics*, *37*(6), 1775–1790.

Comparini, L., & Bastianini, A. (1965). Graphic reconstructions in the morphological study of the hepatic lymph vessels. *Angiologica*, *2*(2), 81–95.

Crivellato, E., Travan, L., & Ribatti, D. (2007). The Hippocratic treatise 'on glands': The first document on lymphoid tissue and lymph nodes. *Leukemia*, *21*(4), 591–592.

Ebbell, B. (1937). In H. Milford (Ed.), *The papyrus Ebers: the greatest Egyptian medical document*. Levin and Munksgaard.

Fulton, J. F. (1938). The early history of the lymphatics: With particular reference to Bartholin, Rudbeck and Joyliffe. *Bulletin of the Hennepin County Medical Society*, *9*, 5–10.

Gonkowski, S., & Grzybowski, A. (2020). Alfred Biesiadecki (1839–1889) and his place in the history of dermatology. *Clinics in Dermatology*, *38*(5), 591–597.

Handley, W. S. (1908). Lymphangioplasty: An new method for the relief of the brawny arm of breast-cancer and for similar conditions of lymphatic oedema. *The Lancet*, *171*(4411), 783–785.

Hedrick, M. S., Hillman, S. S., Drewes, R. C., & Withers, P. C. (2013). Lymphatic regulation in nonmammalian vertebrates. *Journal of Applied Physiology (Bethesda, MD: 1985)*, *115*(3), 297–308.

Ijpma, F. F. A., & van Gulik, T. M. (2013). "Anatomy lesson of Frederik Ruysch" of 1670: A tribute to Ruysch's contributions to lymphatic anatomy. *World Journal of Surgery*, *37*, 1996–2001.

Itkin, M., & Nadolski, G. J. (2018). Modern techniques of lymphangiography and interventions: Current status and future development. *Cardiovascular and Interventional Radiology*, *41*(3), 366–376.

Jessen, N. A., Munk, A. S., Lundgaard, I., & Nedergaard, M. (2015). The glymphatic system: A beginner's guide. *Neurochemical Research*, *40*(12), 2583–2599.

Kanter, M. A. (1987). The lymphatic system: An historical perspective. *Plastic Andreconstructivesurgery*, *79*(1), 131–139.

Kinmonth, J. B. (1952). Lymphangiography in man: A method of outlining lymphatic trunks at operation. *Clinical Science (London)*, *11*, 13–20.

Kinmonth, J. B. (1954). Lymphangiography in clinical surgery and particularly in the treatment of lymphoedema. *Annals of the Royal College of Surgeons of England*, *15*, 300–315.

Loukas, M., Abel, N., Tubbs, R. S., Grabska, J., Birungi, J., & Anderson, R. H. (2011). The cardiac lymphatic system. *Clinical Anatomy (New York, N.Y.)*, *24*(6), 684–691.

Loukas, M., Bellary, S. S., Kuklinski, M., Ferrauiola, J., Yadav, A., Shoja, M. M., Shaffer, K., & Tubbs, R. S. (2011). *The lymphatic system: a historical perspective*. Clinical Anatomy (New York, N. Y.), 24(7), 807–816.

Loukas, M., Clarke, P., Tubbs, R. S., & Kapos, T. (2007). Raymond de Vieussens. *Anatomical Science International*, *82*(4), 233–236.

Mihara, M., Hara, H., Araki, J., Kikuchi, K., Narushima, M., Yamamoto, T., Iida, T., Yoshimatsu, H., Murai, N., Mitsui, K., Okitsu, T., & Koshima, I. (2012). Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. *PLoS One*, *7*(6), e38182.

Natale, G., Bocci, G., & Ribatti, D. (2017). Scholars and scientists in the history of the lymphatic system. *Journal of Anatomy*, *231*, 417–429.

Patek, P. R. (1939). *The morphology of the lymphatics of the mammalian heart* (Vol. 64, pp. 204–239). The American Journal of anatomy.

Pizzi, M., Chaviano, F., Rugge, M., & Orazi, A. (2018). A lucky mistake: The splenic glands of Marcello Malpighi. *Human Pathology*, *72*, 191–195.

Ringstad, G., Vatnehol, S., & Eide, P. K. (2017). Glymphatic MRI in idiopathic normal pressure hydrocephalus. *Brain: A Journal of Neurology*, *140*(10), 2691–2705.

Schuchhardt, C., Wittlinger, H., & Rabe, H. (2003). *Eine Kleine Geschichte der Lymphologie*. Viavital-Verlag.

Shields, J. W. (1994). Lymph, lymphomania, lymphotrophy, and HIV lymphocytopathy: An historical perspective. *Lymphology*, *27*, 21–40.

Strijk, S. P. (1987). Lymphography and abdominal computed tomography in the staging of non-Hodgkin lymphoma: With an analysis of discrepancies. *Acta Radiologica (Stockholm, Sweden: 1987)*, *28*(3), 263–269.

Suami, H., Pan, W. R., & Taylor, G. I. (2009). Historical review of breast lymphatic studies. *Clinical Anatomy (New York, N.Y.)*, *22*(5), 531–536.

Tonetti, L. (2017). The discovery of lymphatic system as a turning point in medical knowledge: Aselli, Pecquet and the end of hepatocentrism. *Journal of Theoretical and Applied Vascular Research*, *2*(2), 67–76.

Ulvmar, M. H., & Mäkinen, T. (2016). Heterogeneity in the lymphatic vascular system and its origin. *Cardiovascular Research*, *111*(4), 310–321.

Vannozzi, F. (Ed.). (2015). *L'eredit a intellettuale di Paolo Mascagni*. Accademia deiFisiocritici.

Veiga, P. (2009). *Oncology and infectious diseases in ancient Egypt*. VDM Verlag.

Vesalius, A., Richardson, W. F., & Carman, J. B. (2007). *On the fabric of the human body: a translation of De humani corporis fabrica libri septem*. Norman Publications.

Yang, L., Kress, B. T., & Weber, H. J. (2013). Evaluating glymphatic pathway function utilizing clinically relevant intrathecal infusion of CSF tracer. *Journal of Translational Medicine*, *11*, 107.

How to cite this article: van Schaik, C. J., Boer, L. L., Draaisma, J. M. T., van der Vleuten, C. J. M., Janssen, J. J., Fütterer, J. J., Schultze Kool, L. J., & Klein, W. M. (2022). The lymphatic system throughout history: From hieroglyphic translations to state of the art radiological techniques. *Clinical Anatomy*, *35*(6), 701–710. https://doi.org/10.1002/ca.23867