Annals of Anatomy 223 (2019) 49–69

Contents lists available at ScienceDirect

Annals of Anatomy

journal homepage: www.elsevier.com/locate/aanat

The history of anatomical research of lymphatics — From the ancient times to the end of the European Renaissance

Regina Irschick, Claudia Siemon, Erich Brenner*

Division of Clinical and Functional Anatomy, Medical University of Innsbruck, Austria

ARTICLE INFO

Article history:
Received 9 November 2018
Received in revised form 23 January 2019
Accepted 24 January 2019

Keywords:
Lymphatics
Lymphatic vessels
History

ABSTRACT

Very often, descriptions of the scientific discovery of the lymphatic system start with Gaspare Aselli, probably because of his so captivating account. Nevertheless, there was prior and even very old evidence of the lymphatic vessels, which was of course known to Aselli himself, as he cited most of these antique references.

In fact, the first insights were contributed by the Hippocratic School. The Alexandrian School added quite a lot but unfortunately most of that knowledge is not extant and can only be appreciated by translations or citations by other authors such as Galen.

The 'dark' middle ages did not add to the anatomical knowledge of the lymphatics, and only the rise of the Renaissance brought new insights. Even at that time, Aselli was not the first to identify at least some components of the lymphatic system, but he was actually the first to present a proper account in a book dedicated to the "lacteal veins". Afterwards the interest rose enormously and cumulated in one of the first priority – or plagiarism – disputes, the Rudbeck–Bartholin feud. Surprisingly, William Harvey, the discoverer of the systemic blood circulation, ignored, at least in part, the progress of the discoveries in lymphatic circulation.

This narrative review tries to summarize the major contributions to the anatomical knowledge of the lymphatic system from the ancient times up to the end of the European Renaissance.

Contents

This paper belongs to the special issue Human lymph vessels.

* Corresponding author at: Division of Clinical and Functional Anatomy, Medical University of Innsbruck, Müllerstrasse 59, 6020, Innsbruck, Austria.
E-mail address: erich.brenner@i-med.ac.at (E. Brenner).

https://doi.org/10.1016/j.aanat.2019.01.010
0940-9602/

1. Introduction

It is well known and has often been described that the initial descriptions of at least parts of the lymphatic system date back to the 5th century BC, when the *Hippocratic Corpus* mentioned 'lymph glands'. Most short descriptions continue with Galen and then jump to Gaspare Aselli as the "discoverer" of the lymphatics. This narrative review aims to summarize the (anatomical) research on the lymphatic (vascular) system including also the often unmentioned researchers between Hippocrates and Galen and those thereafter until the end of the European Renaissance (Table 1).

When talking of the lymphatic vascular system, we abbreviate this by the term 'lymphatics'. At their peripheral beginning these consist of a network of initial lymphatics, previously often named 'lymphatic capillaries'. As there are important differences between these 'lymphatic capillaries' and 'blood capillaries' we use the term 'initial lymphatics', coined by Casley-Smith (1972).

The main problems in investigating lymphatics is the fact that their content, the lymph fluid, is colorless, and so are the lymphatics themselves, with the exception of the milky chyle in the mesenterial lymphatics, often called lacteals, shortly after a solid meal. Furthermore, the lymphatics form a delicate and intricate network (Natale et al., 2017).

2. The ancient era

2.1. The Hippocratic School

The first parts of the lymphatic system to be investigated were the lymphatic nodes, as they form visible and palpable lumps beneath the skin; they were first mentioned in the *Hippocratic Corpus* named *On Joints* in the 5th century BC: "*all men have glands, smaller or larger, in the armpit and many other parts of the body*" (Ambrose, 2006). The *Hippocratic Corpus* is a collection of medical writings compiled during a period of about three centuries by various authors, mostly from the fifth to the third century BC. This collection of inestimable value represents the central nucleus of ancient Greek medical literature (Crivellato et al., 2007).

In the treatise *On Glands* (Περιάδενων; 'periadenôn'), of the late 5th or early 4th century BC (Marmelzat, 1991), the Hippocratic Author coins the term 'glands' (αδένες; 'adenes') for lymph nodes (Chapter 1). The Hippocratic Author proceeds with rigorous methods: from an almost histological definition of these 'lymph glands', via a short account of their functional significance in health and disease, to a well-ordered topographic classification. 'Lymph glands', i.e. the lymph nodes, are described as whitish and phlegmy structures, which present a woolly consistence to the touch and, if you forcefully squeeze them with your fingers, they discharge an oily moistness (Chapter 1) (Craik, 2009). The Hippocratic Author provides an absolutely modern interpretation of their pathophysiological significance. Lymph nodes are described to 'attract and receive' fluids (Chapter 3). They receive the moisture flowing to them from different regions of the body via a large number of afferent vessels (Chapter 2) (Craik, 2009). If the amount of moisture is moderate, there is no fluid accumulation in any part of the body since lymph nodes drain off such liquid (Alexander et al., 2010). By contrast, when these lymph nodes are overfilled by humors, they become swollen and inflamed and can transmit their disease to the rest of the body. Three fundamental concepts concerning the pathophysiology of lymph nodes and lymphatic vessels are mentioned for the first time in medical literature. First, the lymphatic system is made up of lymphatic vessels and the lymph nodes through which they pass. Second, the drainage function of lymph nodes is firmly established. Third, their involvement in inflammatory processes and systemic diseases is also foreshadowed because it is asserted that lymph nodes are subject to inflammatory responses and enlargement as a consequence of either local or general affections (Crivellato et al., 2007).

Then, the Hippocratic Author proceeds by enumerating the principal gland stations. For the most part, lymph nodes are situated near the great flexures of the body (Chapter 3). It is claimed that these organs are particularly numerous where there is much internal fluid to be drained and in regions rich with blood vessels, whereas they are lacking in regions where the body is dry. This is indeed a skillful observation insofar as lymphatics can be recognized in nearly all tissues and organs which contain blood vessels. These non-vascular structures, such as cartilage, nails, hair and cornea, have no lymphatics. In the head – the Hippocratic Author maintains – lymph nodes are scattered around the ears and near the jugular vessels of the neck. These are indeed the posterior and pre-auricular lymph nodes, and the superficial and deep cervical lymph nodes, respectively. Lymph nodes are numerous in the axillary and inguinal flexures, the axillary and inguinal lymph nodes of modern nomenclature (Crivellato et al., 2007).

Remarkably, the intestinal glands are also mentioned (Chapter 5). Here, the Hippocratic Author provides a fascinating explanation

Table 1
History of the discovery of the lymphatic system.

Name	Discovery	Term according to the current International Anatomical Terminology
Hippocratic School (5th–4th century BC)	Description of lymphatic "*glands*" (αδένες)	Lymph nodes
Aristotle (384–322 BC)	"*Fibers* (ινές), which take position between blood vessels and nerves and which contain colorless liquid"	Lymph vessels (?)
Herophilus of Chalcedon (335–280 BC)	Observation of lymphatic vessels "*veins*" inside the mesentery	Lymph vessels
Erasistratos of Ceos (ca. 304–ca. 250 BC)	Observation of chyliferous vessels	Mesenteric lymph vessels
Rufus of Ephesos (1st–2nd century)	Description of axillar, inguinal and mesenteric lymph nodes	Axillar, inguinal and mesenteric lymph nodes
Galenus (129–200)	Description of chyliferous vessels and mesenteric lymph nodes "transport of chyle from the gut to the liver runs via small side branches of the portal vein"	Mesenteric lymph vessels and nodes
Paul of Aegina (ca. 625–ca. 690)	Description of surgical interventions in case of lymph node tumors	Lymph nodes
Avicenna (Ibn Sīnā) (980–1037)	Description of elephantiasis	Lymphedema
Cofone (il vecchio) 11th century	Description of the "vena chilis"	Mesenteric lymph vessels
Massa (1485–1569)	Description of lymph vessels in the fat surrounding the kidneys	Renal lymph vessels
Èstienne (1504–1564)	Description of "arteries called *lactes*" transporting the chyle	Mesenteric lymph vessels
Vesalius (1514–154) Paré (1510-1590)	Description of the "*glandulous body*" (pancreas & kallikreas) in the mesentery "*mesaraic veins*"	
Falloppio (1523–1562)	Observation of "*vessels coursing over the intestines full of yellow matter*"	Mesenteric lymph vessels
Eustachi (1520–1574)	Description of the "*vena alba thoracis*" in horses	Thoracic duct
De Costa (1528–1603)	Coined the term "*venae lacteae*"	
Aselli (1581-1626)	Description of lacteals in the intestine of the dog	Mesenteric lymph vessels
Peiresc (1580–1637) Gassendi (1592-1655)	Observation of lacteals in the intestine in man	Mesenteric lymph vessels
Mentel (1599–1671)	Observation of mesenteric lymphatics terminating in the thoracic duct	
Vesling (1598–1649)	Observation of lacteals and the thoracic duct in humans and the lymphatic vessels of the liver	
Read (1580–1641)	Description of "*lacteal veins*"	Mesenteric lymph vessels
Pecquet (1622–1674)	Description of the "*receptacle of the chyle*", main lymphatic vessels and the thoracic duct	Cisterna chyli
Van Horne (1621-1670)	Description of a "*novus ductus chyliferous*" and a "*saccum lacteum*" collecting the lacteal vessels and thoracic duct	Cisterna chyli
Bartholin Th. (1616–1680)	Observation of "*venae lacteae*" Coining of the term "*vasae lymphaticae*" for lymph vessels from the liver to the thoracic duct	Mesenteric lymph vessels, hepatic lymph vessels
Stensen (1638-1686)	Description of cervical lymph nodes and vessels Description of the terminal confluence of lymphatic trunks at the confluence of the subclavian and jugular veins including the valves.	
Rudbeck (1630–1702)	Description of the "vesicula chyli", "ducti hepatici aquosi", and "vasa glandularum serosa" Description of a general lymphatic drainage system throughout the body	Cisterna chyli, hepatic lymph vessels, lymph vessels
Joyliffe (1621–16858)	Observation of a general lymphatic system	
Ruysch (1638–1731)	Description of valves within lymph vessels	

as to the drainage mechanism of intestinal lymph nodes: the fluid produced by the bowel is first absorbed by the omentum and then passes into mesenteric lymph nodes. This, of course, implies the existence of small, hollow channels running through the mesenteric folds – the lymphatic, lacteal or chyliferous vessels – and the transport of the intestinal lymph to the lymph nodes scattered in the mesentery (Crivellato et al., 2007).

There are also lymph nodes near the kidneys (Chapter 6). These nodes are larger than the others. Here, the Hippocratic Author probably speaks of the paraaortic lymph nodes, which are very large indeed. At last, the Hippocratic Author describes the 'glands' of the throat, calling them 'paristhmia' (παρίσθμια; Chapter 7). These are located at the isthmus of the fauces on both sides and must be interpreted as the palatine tonsils (Crivellato et al., 2007).

Aselli, too, cited the Hippocratic Author's books, for instance *On Flesh* (περι σαρκων), extensively (Aselli, 1640), as did several other authors (Pecquet, 1651; Bartholin, 1652, 1653).

The Hippocratic Author was obviously a practicing doctor, well aware of the limitations of even the best medical knowledge and skills to treat the serious conditions he described. He seems to have been accustomed to dissection, or rather to cutting up bodies. Despite its many inaccuracies when viewed on modern terms, this short treatise is often correct, or nearly so. His work is clearly based on – at least some – anatomical knowledge and much clinical observation (Craik, 2009).

2.2. Aristotle

Aristotle (384–322 BC) is principally known as a theoretical philosopher and logician but he was also an eminent natural scientist. Actually, his father was court physician to King Amyntas II of Macedonia, and his mother also came from a family of physicians. Aristotle was often called the first anatomist in the modern sense of the term. He largely wrote about human anatomy but it seems certain that he did not perform dissections of adult human cadavers. He did, however, perform dissections of numerous animals. More than 500 kinds of mammals, birds, fish, reptiles, amphibians, cephalopods, insects, and other invertebrates were referred to in his biological treatises, and many of them were also investigated by dissection (Crivellato and Ribatti, 2007). Concerning the lymphatic system, only a short note has been passed down in his *Historia Animalium* (book III, chapter VI): "*fibers, which take position between blood vessels and nerves and which contain colorless liquid*". Aristotle used the term 'ινές' (inés), which is commonly translated as 'fibers'. As the precise meaning of the word is questionable, it is uncertain what Aristotle really described (Kanter, 1987).

2.3. The Alexandrian School: Herophilos of Chalcedon & Erasistratos of Ceos

Herophilos (335–280 BC) was deemed to have been one of the first anatomists after Aristotle. He was born in Chalcedon (now

Kadiköy, Istanbul, Turkey) on the Asiatic side of the Bosporus, opposite Byzantium. During his adolescence he was sent to the island of Cos where Hippocrates' school was located. Hippocrates had been dead for approximately 65 years when the young Herophilus arrived at Cos. However, the Hippocratic school was very highly regarded, and Herophilus was thoroughly introduced to the Hippocratic teaching by Praxagoras, a famous physician and anatomist who lived on the island during the 4th century BC (Wiltse and Pait, 1998). Herophilus left Cos about 300 BC and went to Alexandria, Egypt, where he spent the remainder of his life (Reveron, 2014). He was the first scientist known to have systematically performed scientific dissections of human cadavers; he recorded his findings in more than nine treatises, which are now all lost but were extensively 'quoted' by Galen in the second century AD (Wikipedia contributors, 2016). The first description of lymphatic vessels is attributed to Herophilos. When he described the hepatic portal system, he concluded – incorrectly – that the hepatic portal vein received "*all absorptive veins in the intestines*", probably referring to the lymphatics there. Nevertheless, according to Galenus, Herophilus asserted that there existed 'veins'[1] inside the mesentery which "*ended in certain glandular bodies, whereas all the others ascended to the porta hepatis*" (Sheldon, 1784; May, 1968); thus one may conclude that Herophilus already distinguished lymphatic vessels and the portal venous system (Trapnell, 1965). Herophilus observed these structures while performing at least 600 dissections on humans (Ambrose, 2006; Wikipedia contributors, 2016). Sources from antiquity, such as the renowned Roman medical encyclopedist Celsus, or Tertullian, claim that Herophilus and Erasistratos also practiced vivisection. The Egyptian pharao[2] apparently sent convicted criminals to them, and they were free to perform any experiments on them (Strkalj and Chorn, 2008).

Erasistratos (ca. 304–ca. 250 BC) was probably born in Ioulis on the island of Ceos (now Kea, Greece). His father and brother were physicians, and his mother the sister of a physician. He began his studies of medicine in Athens, under Metrodorus and Theophrastus, who was a preferred disciple of Aristotle (Reveron, 2014).

Having spent some years at the court of Seleucos I Nicator in Antioch he seems to have moved to Alexandria to join the elder Herophilos; nevertheless there are some doubts thereon (Fraser, 1969). He and his colleague practiced anatomy with great success. By dissection of new-born goats Erasistratos found that the mesenteric lymphatics pass the whole length of the mesentery (Sheldon, 1784). Galen mentions the following experiment from the works of Erasistratos: "*For on dividing the epigastrium, and along with it the peritoneum, we may clearly see arteries, on the mesentery of sucking kids, full of milk*." (Cruikshank, 1786). Erasistratos concluded that food stuffs were digested and fragmented into numerous droplets termed "chyle" and thought that the chyliferous vessels alternately transported air and milk (Chikly, 1997). Erasistratos appears to have died in Asia Minor (Wikipedia contributors, 2017a).

Unfortunately, none of their original books have survived, and our knowledge of this era is entirely due to the works of Galen of Pergamon. Descriptions of the lymphatics are vague, and lymph channels appear to have been equated to small blood vessels (Kanter, 1987).

2.4. Rufus of Ephesos

Little is known about Rufus's life. Rufus (or: Ruphus) of Ephesos practiced medicine in the 1st and 2nd century AD. He probably studied at Alexandria, for he made personal comments about the citizens' general health and specific diseases. He then established himself at Ephesus, which was a center of the medical profession (Wikipedia contributors, 2017d). Rufus wrote about forty medical treatises; only a dozen survived in Greek, together with a few in Latin or Arabic translation, and fragments in Greek and Arabic (Langslow, 2012). He described axillar, inguinal and mesenteric lymph nodes (May, 1968; Ambrose, 2006). Most of the works have been preserved by Galen, the Suda[3], and especially by Arab physicians, who appear to have translated almost all of them into Arabic (Wikipedia contributors, 2017d).

2.5. Claudius Galenus

Aelius Galenus or Claudius Galenus (Κλαύδιος Γαληνός; September 129 AD–ca. 200; other historians mention the year 216 AD), often anglicized as Galen and better known as Galen of Pergamon, was a prominent Greek physician, surgeon and philosopher in the Roman Empire. As a son of Aelius Nicon, a wealthy architect with scholarly interests, Galen received a comprehensive education that prepared him for a successful career as a physician and philosopher. Born in Pergamon (present-day Bergama, Turkey), Galen traveled extensively, acquainting himself with a wide variety of medical theories and discoveries before settling in Rome, where he served prominent members of the Roman society and eventually was given the position of personal physician to several emperors. Galen's understanding of anatomy and medicine was principally influenced by the then-current theory of humorism (also known as the four humors — black bile, yellow bile, blood, and phlegm), as advanced by ancient Greek physicians such as Hippocrates. His theories dominated and influenced Western medical science for more than 1300 years. His anatomical reports, based mainly on the dissection of monkeys, especially the Barbary macaque, and pigs, remained uncontested until 1543, when printed descriptions and illustrations of human dissections were published in the seminal work *De humani corporis fabrica* by Andreas Vesalius (Wikipedia contributors, 2017b). There is no handed-down manuscript of Galen's work but all of his manuscripts were copied by Byzantine scholars. In the Abbasid period (after 750 AD) Arab Muslims began to be interested in Greek scientific and medical texts for the first time and had some of Galen's texts translated into Arabic, often by Nestorian Christian scholars, for instance Hunayn ibn Ishaq al-Ibadi (809–873). As a result, some of Galen's texts exist only in Arabic translation. Later on, the Arab and Byzantine texts were translated into Latin.

In his copious treatises, Galen of Pergamon readopted the works of Herophilos and Erasistratos and added some results of his own dissections of apes and pigs describing vessels in the mesentery, which appeared bloodless but turbid. Galen wrote that these vessels pass from the intestine to the "spongy flesh bodies", do not go to the liver, and nourish other parts beside the intestines, thereby referring to the mesenteric lymph nodes containing chyle (Sheldon, 1784; Ambrose, 2006; Loukas et al., 2011).

Galen's ideas on the lymphatic system are reported mainly in De usu partium (book IV, chapter XIX) and Anatomicis administrationibus (books VI and XIII). According to Galen's peculiar physiological descriptions, the transport of chyle from the gut to the liver runs via small side branches of the portal vein, where the further transformation of the chyle into blood takes place (Natale et al., 2017). Nevertheless, Galen described "*that the intestines and mesentery receive veins that do not end in the liver*", a statement that confused Vesalius (2007).

[1] Most probably, lymphatic vessels were meant but Herophilus wrote about "veins".

[2] Ptolemaios I. Soter and/or Ptolemaios II. Philadelphos

[3] The Suda or Souda (Medieval Greek: Σοῦδα; Latin: Suidae Lexicon) is a large 10th-century Byzantine encyclopedia of the ancient Mediterranean world.

2.6. Paul of Aegina

Paul of Aegina or Paulus Aegineta (Greek: Παῦλος Αἰγινήτης; Aegina, ca. 625–ca. 690 AD) was a Byzantine Greek physician who is best known for writing the medical encyclopedia *Medical Compendium in Seven Books*. In the Byzantine Empire this work contained the sum of all Western medical knowledge for many years and was unrivaled in its accuracy and completeness. In his compendium he described a tonsillectomy (book VI, chapter 30) and also the surgical intervention in the case of tumors of the lymphatic nodes (infected nodes) at the neck (book VI, chapter 35) (Loukas et al., 2011; Natale et al., 2017).

2.7. Islamic Medicine

In Europe, the progress of medicine and knowledge after the Golden Greco-Roman era was interrupted by the fall of the Western and Eastern Roman empires. While the new ideas of Western medicine were extinguished to enter the long night of the Middle Ages, the achievements in research were primarily gained in more Easterly countries. The books of Hippocrates, Aristotle and Galen were translated by the Arabs in the 9th century. Arab medicine thus adopted the ideas of Hippocrates and Galen. The theory of the humors was introduced into the Eastern civilization (Ferrandez, 2006).

The medical scholars seem to have been very eager to translate as much as possible of the ancient medical knowledge into the Arabic language and thus preserved quite a lot of it. At this time, the texts of medical as well as philosophical works were written in Arabic. The authors were not Muslims but Arabs, Jews and Christians who wrote in Arabic, in the same way that European texts would later be written in Latin. In the 10th century, the Greek works, for instance, were preserved and extended by the University of Cordoba. The fact that the Arabs extended their domain from Syria to Spain allowed them to advance a practical medicine and to open hospitals associated with teaching according to the principles of the then current clinical knowledge. From this point of view, the Arab-Muslim civilization was not only seen as the civilization that allowed translating the ancient medical texts but also as the one that obtained true findings in medical matters. Arab writers also collected the synthesis of more distant medicines, such as those from India and China (Ferrandez, 2006).

As their own contribution, Islamic doctors, especially Avicenna (Ibn Sīnā, 980–1037), gave interesting descriptions of lymphedema (elephantiasis), due to the frequent parasitic infections that are more common in oriental than in European regions (Golzari et al., 2012; Natale et al., 2017). Ibn Sina learned to read very early and greedily devoured the treatises of Hippocrates and Galen. At the age of sixteen he became interested in medicine and at seventeen already taught his own courses. Therefore he was granted access to the library of the Bukhara sovereign. Avicenna authored a five-volume medical encyclopedia *The Canon of Medicine* (Al-Qanun fi't-Tibb), which was used as the standard medical textbook in the Islamic world and Europe up to the 18th century.

2.8. The Medical School of Salerno

In spite of the surgical tradition of the medieval Salernitan School (Salernitana Medical School) and the foundation of the first universities, for a long time anatomical research did not provide a significant improvement of knowledge. Nevertheless, its members reintroduced the ancient anatomical knowledge by re-translating major ancient works from the Arabic and/or Byzantine language, for instance Nicola de Deopreprio di Reggio, also called Niccolò Greco, who lived in the first half of the 14th century. He was ordered by the king of Naples, Roberto d'Angiò, to translate the works of Galen he had obtained from the Byzantine Emperor Andronikos [III Palaiologos] (de Renzi, 1857). These translations have been praised to be much better than previous ones from the Arab language. A still confused description of the lymphatic system appeared in the works of some physicians of the Salernitan School in the 11th century, such as Cofone [il vecchio], who wrote "*and there is the vena chilis, into which capillary veins enter, which cannot be seen because of their extreme smallness*" (Medici, 1857; Natale et al., 2017).

3. The European Renaissance and the 17th century

Both the Catholic Church and the Coran prohibited dissections of human cadavers; in this situation, it is understandable that the knowledge of anatomy progressed very slowly. Under the papacy of Boniface VIII, excommunication threatened everyone who unearthed corpses to dissect them. Therefore, it proved necessary to wait for the particularly isolated works of the Italians and the beginning of the Renaissance (Ferrandez, 2006).

De Lassus revealed that Mondino in 1306 and 1315 dissected the corpse of a woman and wrote a very brief treatise on anatomy. Later on, in 1377, the Duke of Anjou officially authorized the doctors of Montpellier to use the bodies of executed criminals for dissections. Pope Clement VII allowed the surgeons in the kingdoms of Leon and Castile to dissect corpses for study purposes in 1386, and Pope Sixtus IV expressly granted permission for anatomical sections in 1482 (Schmugge, 1989). In 1556, Emperor Charles V asked the theologians of the University of Salamanca if it was possible for Catholics to open human cadavers, and the Spanish doctors responded that this was useful and, therefore, lawful (Ferrandez, 2006).

Interestingly, while most specialists in the history of medicine seem to agree that the seventeenth century is the true time of discovery of the lymphatic vessels of some parts of the body, some previous texts already described them.

3.1. Niccolò Massa

Niccolò Massa (1485–1569), in 1537 mentor of Vesalius in the Venetian hospitals as a surgeon and anatomist, observed lymph vessels in the fat surrounding the kidneys (Lind, 1975; Suy et al., 2016a). His description, published in 1536 (Massa, 1536), posed some problems since the vessels were inconstant (Ferrandez, 2006).

3.2. Charles Éstienne

In 1545, Charles Éstienne (1504–1564) published *De dissectione partium corporis humani libri tres* (Éstienne, 1545). Éstienne was an early exponent of scientific anatomy in France. He had the usual humanistic training of his time in Paris. He seems to have spent some time in Italy studying in Padua, where he became interested in medicine (1530–1534). After that period he returned to Paris and started working in his family's printing business. He performed his dissections and his anatomic researches in co-operation with Etienne de la Riviere, who was his classmate in the University of Paris from 1535 until 1539, when they finished their anatomy manuscript. Eventually, Éstienne acquired his medical degree at the University of Paris in 1542 (Markatos et al., 2017).

In the above-mentioned book, Éstienne described the abdominal viscera and their vasculature as well as the veins and arteries, called "lactes", which he named "primary veins", thanks to which the chyle from the stomach moves to the porta hepatis. One of the figures (Fig. 1) artistically represents the mesentery, and its legend makes clear reference to the "lactes" located in proximity to the mesenteric arteries ("*Venae atque arteriae in mesenterio, lactes*

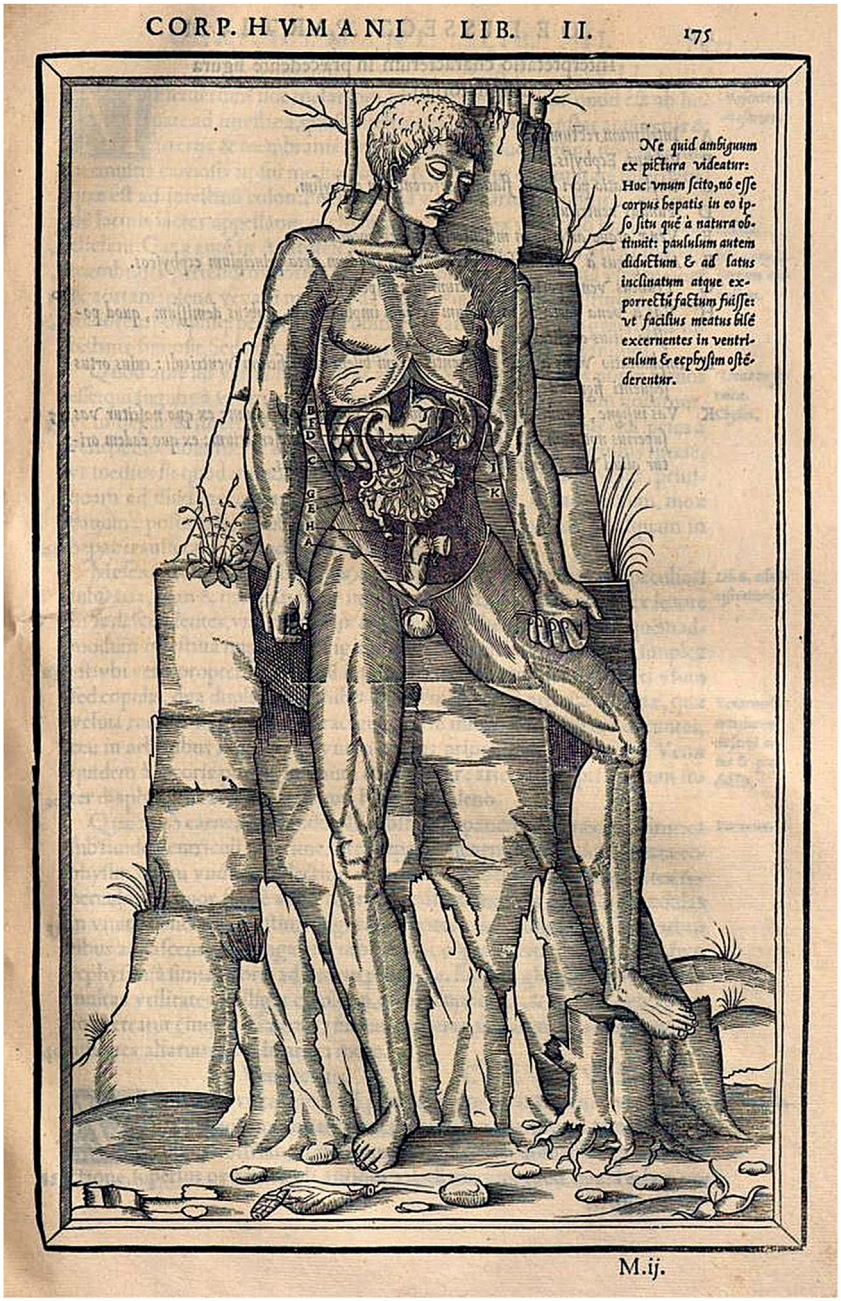

Fig. 1. Charles Éstienne (1545): *De dissectione partium corporis humani libri tres*, liber II [Three Books on the Dissection of the Parts of the Human Body, Book II].
[...] E: Venae atque arteriae in mesenterio, lactes vocatae. [...] G: Truncus venae portae: & initium suae dispersionis. H: Vasàvena porta in intestinum rectum implantatum, subtus demissum, quod postea latius explicabitur. [...]
[. . .] E: Veins and arteries in the mesentery that are called lacteals ('*lactes*'). [. . .] G: trunk of the portal vein and the beginning of its dispersion. H: The vessel from the portal vein that is sent down and implanted into the rectum, which will later be explained more extensively. [. . .]

vocatae"). (Ferrandez, 2006) As Éstienne clearly distinguished the portal vein, he may really have described the lymphatic vessels.

3.3. Andreas Vesalius

Andreas Vesalius (1514–1564), the famous anatomist, at least took particular notice of a lymphatic node "*about in the middle of the fore part of the oesophagus, [. . .] as having something particular in it, and not to be found in other lymphatic glands.*" (Cruikshank, 1786).

When describing the mesentery, Vesalius explicitly writes "*Its [the mesentery's] function of binding the intestines to the spinal column is not the only reason why the substance of the mesentery is membranous; there is another important reason, and that is so that it may bind firmly together all the veins that run from the gate of the liver to the intestines and all the arterial offshoots that run from the great artery [i.e. aorta] to the intestines, supporting them all firmly and securely so that when the person leaps or falls they are not bruised or ruptured. The larger trunk of the portal vein, in the area close to the kidneys where the mesentery grows out from the spinal column, passes between the two membranes of the mesentery; it is accompanied by an artery [i.e. coeliac trunk] that, taking origin from the great artery before the latter sends branches to the kidneys, is destined to spread into the intestines. Hither also come two nerves, one on each side, that grow out from the branches that come from the sixth pair of cerebral nerves [i.e. N. vagus] and extend along the roots of the ribs. This means that this large trunk of the portal vein, the artery just mentioned, and*

the two nerves reach the center of the mesentery, and then travel in safety by means of a numerous array of progeny through the entire area of the mesentery to the intestines. [. . .] The mesentery admits no veins other than the trunk of the portal vein mentioned earlier.

I do not understand what Galen means when he claims that the intestines and mesentery receive veins that do not end in the liver and when he says elsewhere that branches spread from the hollow vein to the intestines. [. . .]

The mesentery has something else in addition to fat. Nature in her wisdom realized that the crowd of vessels offshoots contained between the membranes of the mesentery required that the glandulous body for which the Greek names are pancreas and kallikreas be placed under and around every one of their divisions so that none of them should be left unstrengthened or liable to be weakened by movement; for she was aware that anything that divides into branches is very liable to damage at the point of division. She therefore constructed the large glandulous body at the center of the mesentery (Figs. 2 : L; 3 : L) where the first division of the vessels takes place, and this body conveys in safety the prime and most important branches of the vessels. Throughout the rest of the mesentery she placed a glandule (Figs. 2 M; 3: M; 4 : F, G) at every division of the vessels to strengthen and sustain the division." (Vesalius, 2007)

Lymphatic structures outside the abdomen were neither mentioned by Vesalius (Fulton, 1938) nor by the artists Leonardo da Vinci (1452–1510) or Michelangelo (1475–1564) (Kanter, 1987).

3.4. Ambroise Paré

Ambroise Paré (ca. 1510–1590), the famous Parisian surgeon, also noted Galen's hypothesis on the development of the chylos: "*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 veins' to the portal vein.*" (Schuchhardt et al., 2003).

3.5. Gabriele Falloppio

Gabriele Falloppio (1523–1562) was a pupil of Vesalius. He vivisected humans sentenced to death by the administration of poison. In them he observed the lymphatics (not named as such) as vessels "*coursing over the intestines full of yellow matter, going to the liver and lungs*" (Ambrose, 2006), and furthermore "*in the flat part of the liver there are little openings that end in the pancreas and in the surrounding glands. These little openings transport an oily, yellow and bitter juice.*" (Natale et al., 2017).

3.6. Bartolomeo Eustachi

About 1563, Bartolomeo Eustachi (1520–1574), a Roman professor of anatomy, described the thoracic duct (*vena alba thoracis*) with one-way valves in horses, but he was unable to identify its termination and 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.*" (Eustachius, 1564, Antigramma XIII; Natale et al., 2017). He is said, by some, to have ascribed to this vein the function of nourishing the thorax; but he himself expressly disavowed any such idea (Cruikshank, 1786). He was also able to detect valves in the thoracic duct (Trapnell, 1965). His report, illustrated with no less than 47 copper plates, was filed away in the Vatican Library and forgotten until 1714, when it was finally openly re-published by Giovanni Maria Lancisi (1654–1729), after Thomas Wharton had included the text in his *Adenographia* in 1656 (Suy et al., 2016a).

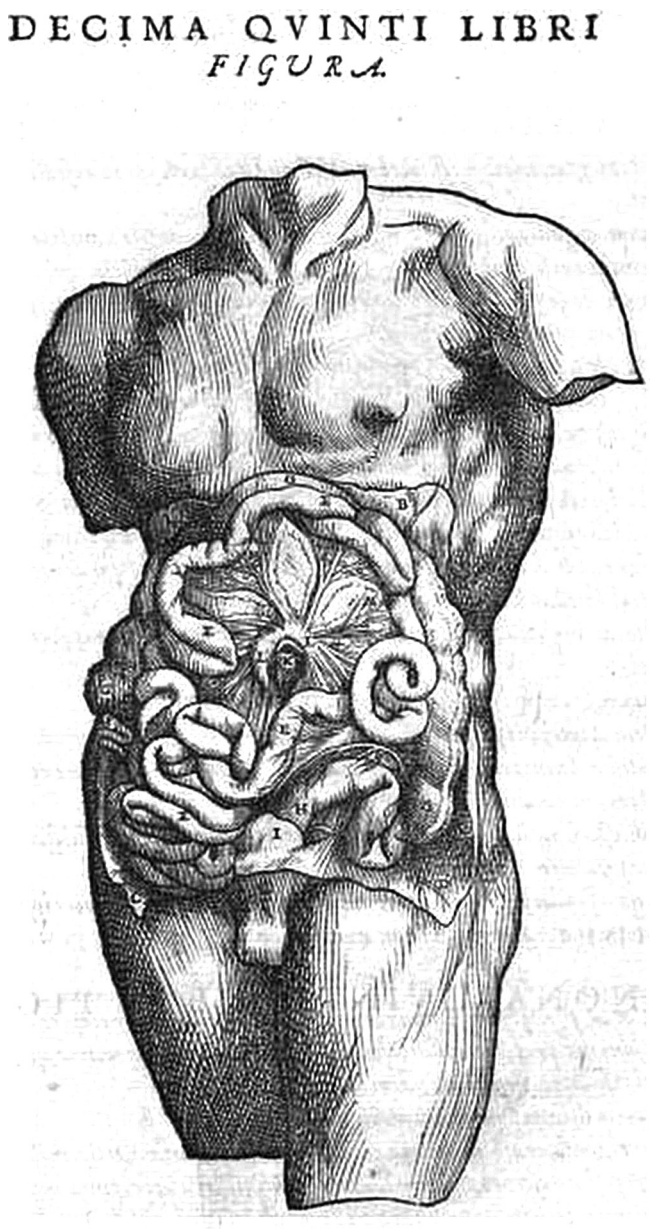

Fig. 2. Andreas Vesalius (1555): *De humani corporis fabrica libri septem*. liber V. fig. 10, p. 564 [Seven Books on the Fabric of the Human Body, book V, fig. 10, p. 564].
[...] L,L Corpus glandulosum, mox in ipsa uasorum distributione positum, quae meserterýcentro inseruntur. M,M Glandulae uasorum distributionibus interiectae, quas uasa ipso per mesenterium moliuntur progressu.[...]
[. . .] L,L Glandular body positioned in nearly the same distribution as the vessels inserting into the center of the mesentery. M,M Glands which are placed between the distribution of the vessels, working themselves upwards by progressing through the mesentery. [. . .]

3.7. Johannes Costaeus

Johannes Costaeus (Joannes de Costa or Giovanni Costeo; 1528–1603), a professor in Bologna, introduced the term '*venae lacteae*' (lacteal veins) for small white vessels in breasts which he had detected (Costeo, 1595; Aselli, 1628).

Fig. 3. Andreas Vesalius (1555): *De humani corporis fabrica libri septem*. liber V. Figura 11, p. 565 [Seven Books on the Fabric of the Human Body, book V, fig. 11, p. 565].
[. . .] L,L Hiquoquae characteres, similiter atquae in decima, glandulosum corpus notant, totius mesenterýmaximum. M,M Glandulae illis interpositae uasorum dissectionibus, quae iam intestinis appropinquant. [. . .]
[. . .] L,L Here, too, the characters designate, as in fig. 10, the glandular body, the largest in the whole mesentery. M, M The glands are penetrated by these dissections of the vessels which already approach the intestines. [. . .]

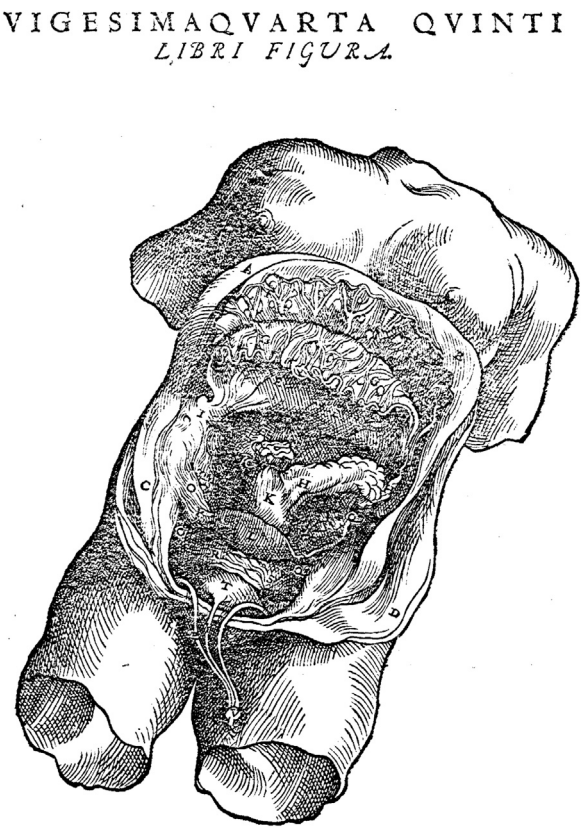

Fig. 4. Andreas Vesalius (1555): *De humani corporis fabrica libri septem*. liber V. Figura XXIV, p. 579 [Seven Books on the Fabric of the Human Body, book V, fig. 24, p. 579].
[...] F,F G,G Altera mesenterýmembrana notatur, ab altera quam G & G insigniui diuulsa. Utraquae autem membrana uasorum per mesenterium seriem, & glandularum uasorum distributionis interpositarum naturam indicat. [...]
[. . .] F,F G,G Another membrane of the mesentery is shown, which I distinguished from the other by the signs G & G. But both indicate a series of vessels running through the mesentery, and the nature of the distribution of interposed glands and vessels. [. . .]

3.8. Gaspare Aselli

One of the central figures in the research of the lymphatics is Gaspare Aselli (or Asellio; Latinized Casparius Asellius; 1581–1626). He was an Italian surgeon and anatomist and is noted for the discovery of the lacteal vessels of the lymphatic system (Wikipedia contributors, 2017c). In 1622, Gaspare Aselli discovered the lacteals; and this is how he described his discovery: "*On the 23rd of July of that year (1622) I had taken a dog in good condition and well fed, for a vivisection at the request of some of my friends, who very much wished to see the recurrent nerves. When I had finished this demonstration of the nerves, it seemed good to watch the movements of the diaphragm in the same dog, at the same operation. While I was attempting this, and for that purpose had opened the abdomen and was pulling down with my hand the intestines and stomach gathered together into a mass, I suddenly beheld a great number of cords as it were, exceedingly thin and beautifully white, scattered over the whole of the mesentery and the intestine, and starting from almost innumerable beginnings. At first I did not delay, thinking them to be nerves. But presently I saw that I was mistaken in this since I noticed that the nerves belonging to the intestine were distinct from these cords, and wholly unlike them, and, besides, were distributed quite separately from them. Wherefore struck by the novelty of the thing, I stood for some time silent while there came into my mind the various disputes, rich in personal quarrels no less than in words, taking place among anatomists concerning the mesaraic veins*[4] *and their function. And by chance it happened that a few days before I had looked into a little book by Johannes Costaeus written about this very matter. When I gathered my wits together for the sake of the experiment, having laid hold of a very sharp scalpel, I pricked one of those cords and indeed one of the largest of them. I had hardly touched it, when I saw a white liquid like milk or cream forthwith gush out. Seeing this, I could hardly restrain my delight, and turning to those who were standing by, to Alexander Tadinus, and more particularly to Senator Septalius, who was both a member of the great College of the Order of Physicians and, while I am writing this, the Medical Officer of Health, 'Eureka' I exclaimed with Archimedes, and at the same time invited them to the interesting spectacle of such an unusual phenomenon. And they indeed were much struck with the novelty of the thing*" (translated by and cited from: Foster, 1924). Aselli repeated his experiment some days later but to his disappointment the demonstration failed. Considering the circumstances, he found out that the second experiment was done with a dog that had been fed a longer time ago, whereas the first dog was fed just before the vivisection. A third repetition with a dog soon after it had been fed confirmed the initial results, as the lacteals were filled with chyle again (Anderson, 1933). He saw these vessels not only in dogs but in a variety of other quadrupeds such as cats, sheep, cows, pigs, and even in a horse but – most probably – not in humans (Aselli, 1628; Cruikshank, 1786). Aselli detected the presence of valves in these vessels hindering a backward flow and later identified the thoracic duct but failed to recognize its connection to the lymphatics (Cruikshank, 1786; Ambrose, 2006). He ascertained that these vessels were channels for conveying the chyle away from the intestine; but, influenced

[4] Archaic expression for 'mesenteric veins'.

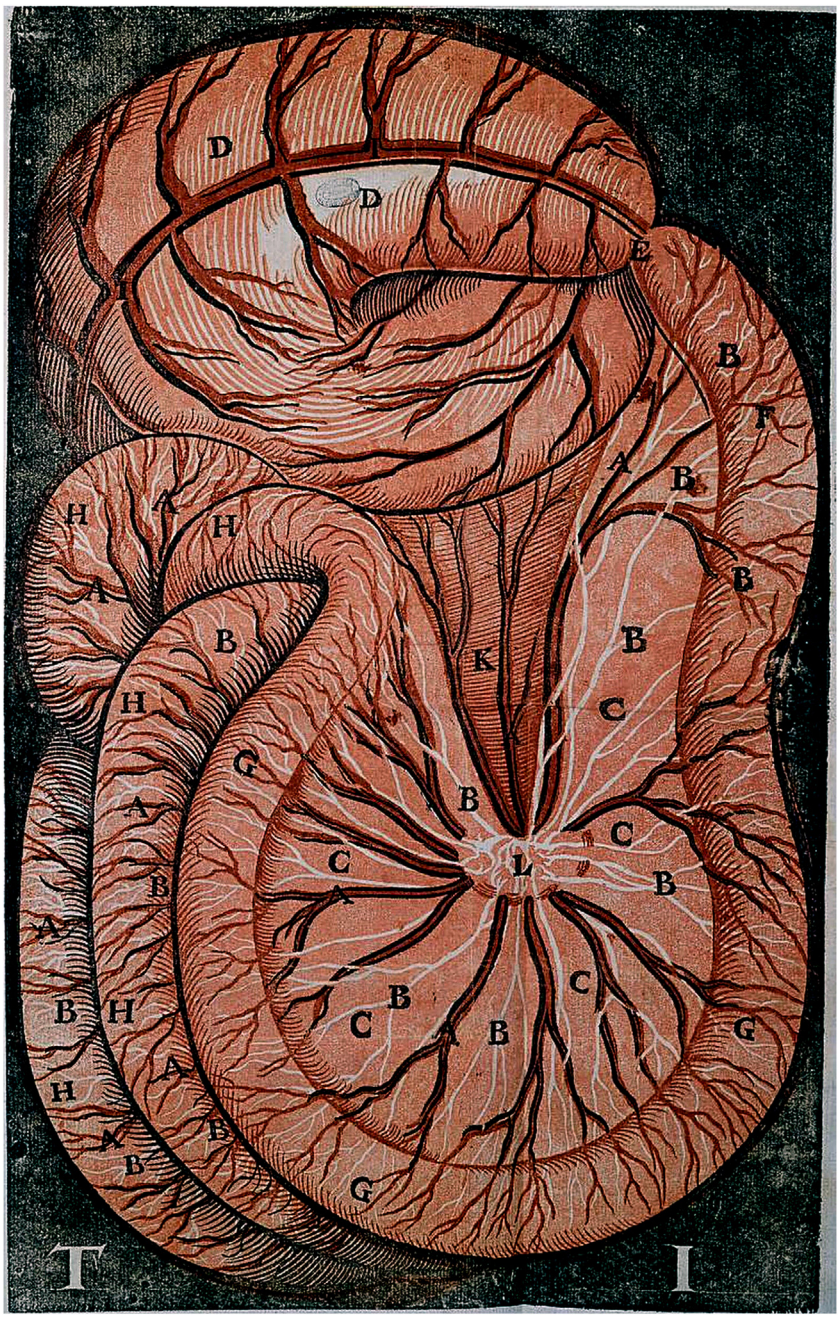

Fig. 5. Gaspare Aselli (1628): *De lactibus sive lacteis venis, quarto vasorum mesaraicorium genere*. Tabula prima [On the Milk Vessels or Milk Veins, the Fourth Sort of Vessels in the Mesentery, Fig. I].
A: Venae Mesaraicae vulgatae, Portae rami, cum Arterÿs mesaraicis. B: Venae Lacteae discurrentes per mesenterium ad intestina. [...] L:παγκρέαζ@ portiuncula: in quam Venae lacteae, inter se implexa insinuantur, fermâcapreolorum.
A: The ordinary veins of the mesentery, the branches of the portal vein, with the arteries of the mesentery. B: The milk veins running through the mesentery to the intestines. [. . .] L: The pancreas, the small opening into which the entwined milky veins insert.

by the then accepted view that all absorbed food was carried to the liver, he went wrong as to the ultimate course taken by these vessels. He thought that he could trace them into the liver, where the food presumably was "concocted" into blood, as Galen's ancient physiology affirmed (Ambrose, 2006). Nevertheless, Aselli himself described and drew the cluster of lymph nodes lying in the mesentery but named them 'the pancreas'; this cluster of lymph nodes was afterwards often addressed as 'the pancreas of Aselli' (Figs. 5–7) (Foster, 1924). Beside the incorrect description, the fourth figure of Aselli's work (Fig. 8) shows that the 'lacteals' correctly arise from the liver and confluence in the porta hepatis. This shows how overwhelmingly convincing Galen's work was.

Aselli's results were published posthumously by his two friends, Senator Septalius and Alexander Tadinus, (Eales, 1974) – Aselli died in Milan[5] in 1626 – initially as 'dissertatio' in Milan in 1627. A second edition was published 1628 in Basel (Aselli, 1628), and a third edition in 1640 in Leyden (Aselli, 1640; Anderson, 1933).

[5] According to the Italian Wikipedia version already in 1625 (contributori di Wikipedia, 2016)

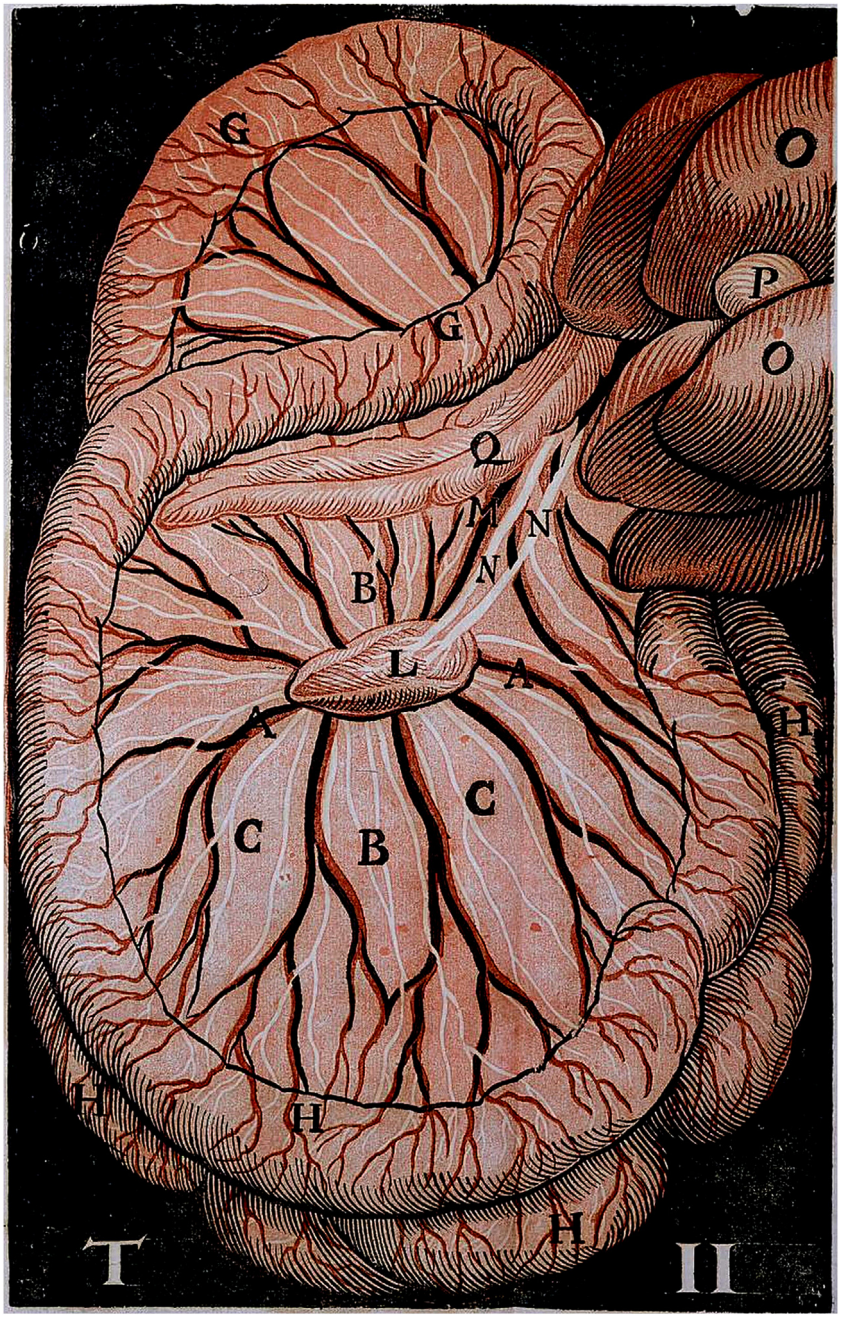

Fig. 6. Gaspare Aselli (1628): De lactibus sive lacteis venis, quarto vasorum mesaraicorium genere. Tabula secunda [On the Milk Vessels or Milk Veins, the Fourth Sort of Vessels in the Mesentery, Fig. II].
A: Venae mesaraicae vulgatae cum Arteriis. B: Venae Lacteae. [. . .] L: Implicatio Lactearum in pancreate. [. . .] N: progressus Lactearum ex Pancreate ad Hepar. [. . .]
A: The ordinary veins of the mesentery, with the arteries. B: The milk veins. [. . .] L: The entanglement of the milk veins in the pancreas. [. . .] N: The course of the milk veins from the pancreas to the liver. [. . .]

3.9. Nicolas-Claude Fabri de Peiresc and Pierre Gassendi

In 1628 Nicolas-Claude Fabri de Peiresc (1580–1637) and Pierre Gassendi (1592-1655) described the mesenteric lymphatics in "*the body of a highly fed malefactor 2 h after his execution*" (Ambrose, 2006). Fabri de Peiresc, Principal Court Judge of Aix-en-Provence and famous astronomer, was kindly disposed toward scientific investigation and had read Asellius' book (Gans, 1962). "*Informed by his friend, L'Abbé Pierre Gassendi of the discovery of Aselli, Peiresc, a wise and penetrating spirit, versed, as we know, in the study of various sciences, designed from 1628, the project, very audacious for his time, to check, if possible, the existence of human chylifera in the corpse of a sentenced person. Having obtained several copies of Aselli's work 'De venis lacteis', he had them distributed to some of his friends' doctors and gave them instructions for the operation he was planning. Moreover, he had prepared himself for this task by dissecting the viscera of the abdomen in animals of various kinds.*" (Bugnion, 1926). The autopsy of the condemned took place six years after the idea was born (1634) and is related as follows: "*For this purpose (that is, for the purpose of observing the chyliferae) Peiresc gave ample food to a man condemned to the rope, when his judgment had not yet been announced and he was in a quiet state, so that there was time enough to form a chyle which had become milk when the operation was done. An hour and a half after the execution the corpse was transported with*

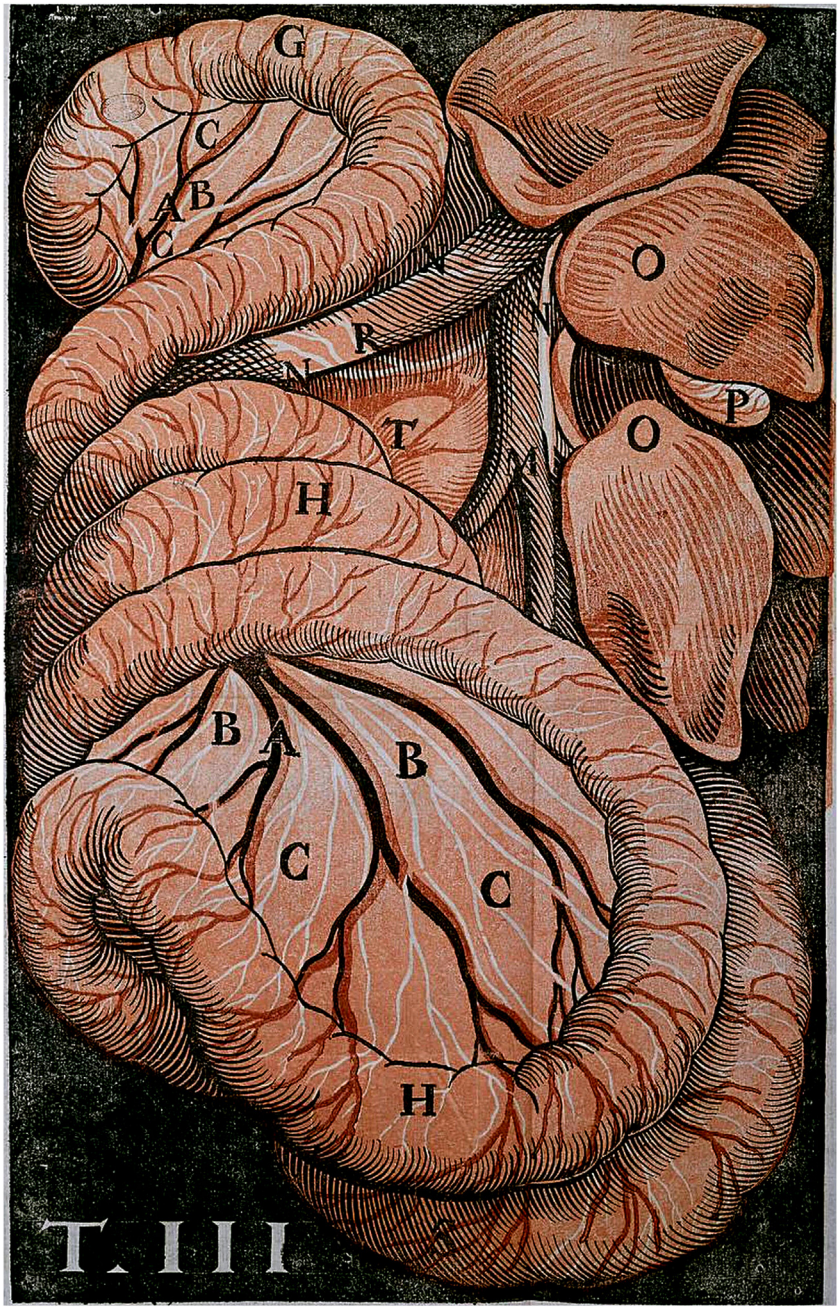

Fig. 7. Gaspare Aselli (1628): *De lactibus sive lacteis venis, quarto vasorum mesaraicorium genere*. Tabula III [On the Milk Vessels or Milk Veins, the Fourth Sort of Vessels in the Mesentery, Fig. III].
A: Venae & Arteriae Mesaraicae. B: Lacteae venae. [. . .] N: Lactea juxta Cavam ascendens ad Hepar. N+Eadem Lactea ad venam Portae propagata, eamqua coronans.
A: The veins and arteries of the mesentery. B: The milk veins. [. . .] N: The milk vein ascending beside the vena cava to the liver. N + The same milk vein propagated to the portal vein, surrounding it.

extreme rapidity to the theatre of anatomy, and in the belly which was opened on the field appeared the white veins from some of which milky liquor was drawn" (Bugnion, 1926). Thus, when the autopsy was performed an hour and a half after the subject's death, the venae lacteae of Asellius stood out clearly (Gans, 1962).

3.10. Jacques Mentel

In 1629, Jacques Mentel (1599–1671), a physician and professor at the Faculty of Medicine of Paris, reported that mesenteric lymphatics terminate in the thoracic duct before gaining access to the bloodstream (Chikly, 1997). Like Aselli, he dissected live dogs before his students for his investigations (Guerrini, 2015). In fact, Mentel never published an account of his findings but in a letter attached to the second edition of Pecquet's book (Mentel, 1654) he reported his observations of 1629 (Suy et al., 2016b).

3.11. Johann Vesling

In 1634, Johann Vesling (1598–1649) in Padua identified both the lacteals and the thoracic duct in human cadavers but also failed to recognize their confluence (Ambrose, 2006). In 1647, he produced detailed drawings of the human mesenteric lacteals in his Syntagma anatomicum (Vesling and Blasius, 1677), but ignored the

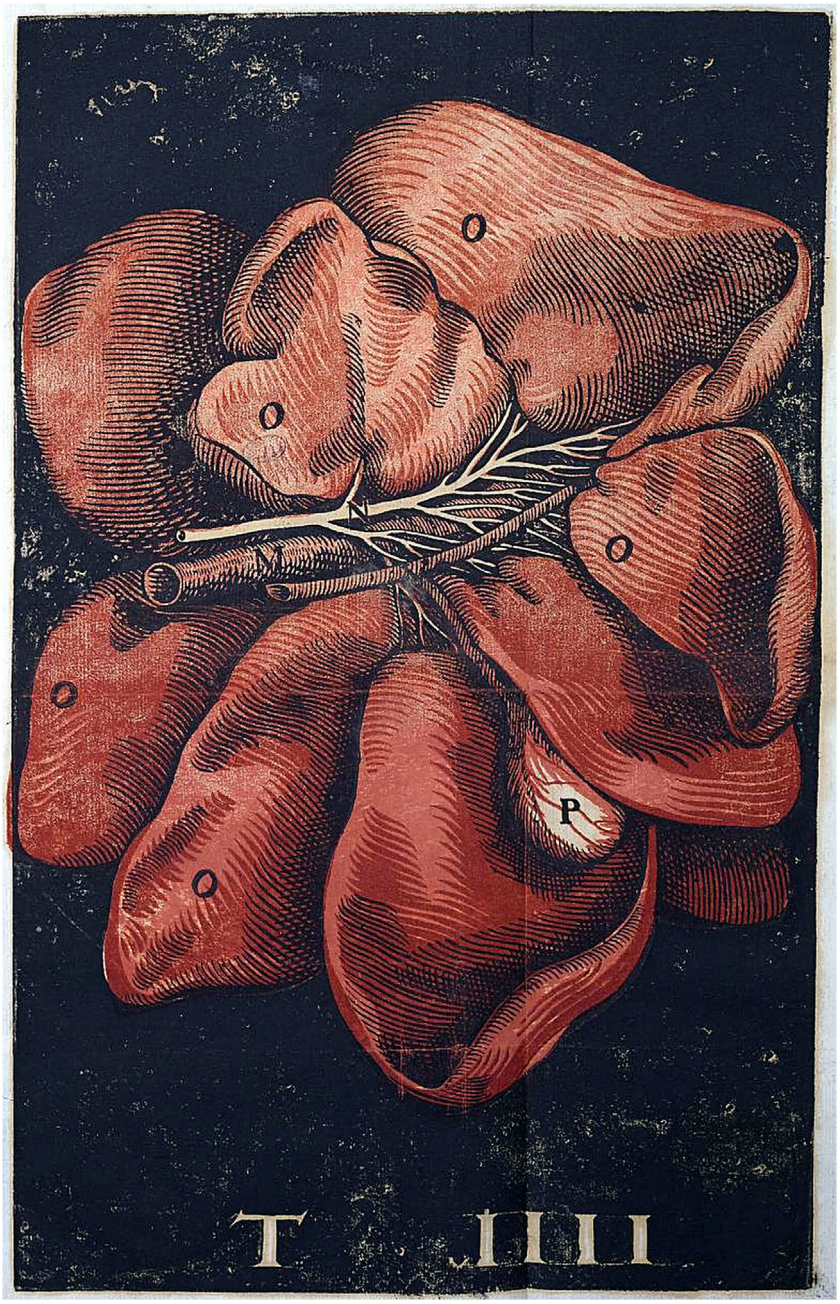

Fig. 8. Gaspare Aselli (1628): *De lactibus sive lacteis venis, quarto vasorum mesaraicorium genere*. Tabula quarta [On the Milk Vessels or Milk Veins, the Fourth Sort of Vessels in the Mesentery, Fig. IIII].
M: Vena Portae. N: Lactearum in Hepar insertio.
M: The portal vein. N: The insertion of the milk vessels into the liver.

destination of the thoracic duct. It also seems that he was the first to see the lymphatics of the liver although he took them for lacteals (Cruikshank, 1786).

3.12. Nathanael Highmore

In the chapter *De Venis Lacteis* of his *Corporis humani disquisitio anatomica* [. . .], Highmore (1613–1684) described elaborately the discovery by Aselli, and, with the knowledge of Aselli's book, that he found the lacteals in the dissection of a human body in 1637, and also – "idem & ipse" – in 1639 (Highmore, 1651, pp. 36–42). Highmore, a British surgeon and anatomist, who had studied at Oxford, had indeed discussed vessels dispersed throughout the gastro-intestinal tract, which he called lacteals, but which were obviously serous lymph vessels (Suy et al., 2016b), and he showed the difference of these vessels and the mesenteric veins (Trapnell, 1965). Highmore's treatise was – by the way – the first to recognize Harvey's new circulatory theory.

3.13. Alexander Read

In the fourth edition of *The manual of the anatomy, or dissection of the body of the man*, published in London in 1650, Alexander Read (1580–1641) summarized the knowledge of the time (Read, 1650). The chapters nine and ten, respectively, deal with the "mesentery" and "the lacteal veins". This edition was published twenty-five

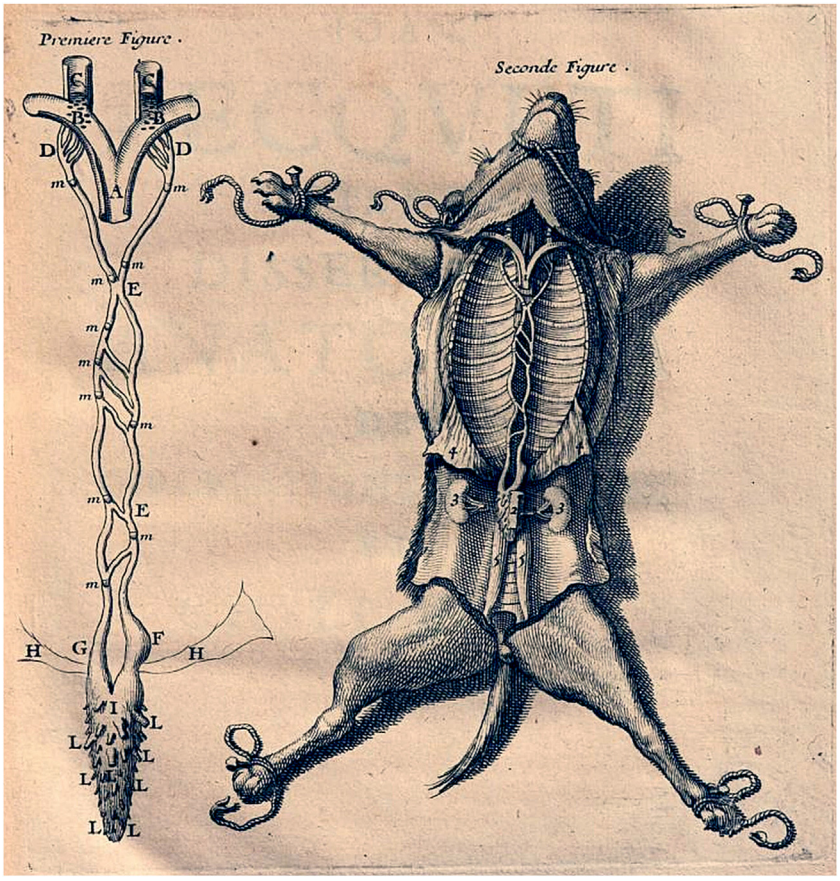

Fig. 9. Jean Pecquet (1651): *Experimenta nova anatomica*... Premiere e Seconde Figure [New Anatomical Experiments..., Figs. 1 and 2].
Premiere Figure: A: [Vena] Cava; BB: Iugularium axillariumque venarum concursus, ubi chyli scaturigines intra cavam, seu lactearum ostiola punctis designantur; CC: Iugularium valvuae influenti in cavam chylo ascensu interdicentes; DD: Lacteorum vasorum ad scaturigines distributio; EE: Diversi, pro naturae ludentis arbitrio, vasorum lacteorum concursus; F: Ampulla, que intra thoracem, juxta illaesum diaphragma sinistrorsum saepius apparuit. G: Alveus dextrorsum ad diaphragma excrescens; HH. Residua diaphragmatis portio; I: Chyli receptaculum; LLL: Mesentericarum lactearum trunci [...]; mmm: variae intra thoracem valvulae chylo concedentes ad cavam transitum [...]
Seconde Figure: 1. [Vena] Cava; 2. Superstitis aortae inter renes chyli receptaculo adhaerescentis portio; 3. Renes; 4. Dissectum diaphragma; 5. Psoas seu lumbares musculi
Fig. 1 A: The vena cava; BB: The confluence of the jugular and the axillary veins, where the course of the lymphatic fluid into the vena cava or the point-shaped small openings of the milk veins are drawn; CC: The valves of the jugular vein which block the ascent of the lymph flowing into the vena cava; DD: The branching of the milk vessels up to their junction [with the brachiocephalic vein] EE: Different junctions of the milk vessels according to the arbitral decision of the play of nature; F: The ampulla which appears more often on the left side inside the thorax beside the unharmed diaphragm; G: A channel leading to the diaphragm on the right side; HH: the residual part of the diaphragm; I: The receptacle (collection vessel) of the lymphatics [Cisterna chyli], LLL: The trunks of the mesentery milk vessels [...]; mmm: different valves inside the thorax which permit the lymph's transition to the vena cava
Fig. 2 1: The vena cava; 2: The part of the preserved aorta between the kidneys which is attached to the cisterna chyli; 3: The kidneys; 4. The dissected diaphragm; 5: The psoas or the lumbar muscles.

years after Aselli's description and just a year before the discovery of Pecquet. It clearly states the existence of the lacteal vessels in reference to their discoverer but they are described transporting the chyle of the mesentery towards the liver. At the time Read described a Galenic-type physiology, well anchored in the spirit of the 17th century. One year later, Jean Pecquet put things in their place (Ferrandez, 2006).

3.14. Jean Pecquet

Aselli's discovery was not so much noticed in his time; a quarter of a century later Jean Pecquet (1622–1674), a French scientist from Dieppe, published his *Experimenta nova anatomica* (Pecquet, 1651). Herein Pecquet described the "receptacle of the chyle" (cisterna chyli) and its continuation as the thoracic duct, which pours its content into the venous system at the junction of the left jugular and subclavian veins (Fig. 9). Pecquet not only described these structures accurately but showed that Aselli's mesenteric lacteals pour their contents into the receptacle, and that therefore the chyle is not delivered to the liver directly (Foster, 1924; Natale et al., 2017). In order not to be accused of fraud he had Adrien Auzot and Peter Mersenne, two reliable members of the Academie Parisienne, witness his experiments. According to their letters, included in his dissertation, his work had their full endorsement (Suy et al., 2016b).

Pecquet had been attracted to the subject already in 1647/1648 as medical student at Montpellier and was familiar with Aselli's work. While removing the heart of a dog, he noticed cloudy whitish fluid (chyle) issuing from the superior vena cava. Pressure on the abdomen increased its flow and led him to trace its source along the thoracic duct to a chyle-filled distension at its lower end (at L2), which he termed chyli receptaculum (now termed the cysterna chyli). Further investigations led him to conclude that the contents of the mesenteric lymphatics do not feed the liver (as Galen claimed) but flow through the thoracic duct and enter the venous system at the junction of the left subclavian and jugular veins; actually, he depicted the chyli receptaculum and the valves of the thoracic duct (Ambrose, 2006). Nevertheless, Pecquet was unable to describe the network of the lymphatic vessels outside the abdominal and thoracic cavities (Natale et al., 2017).

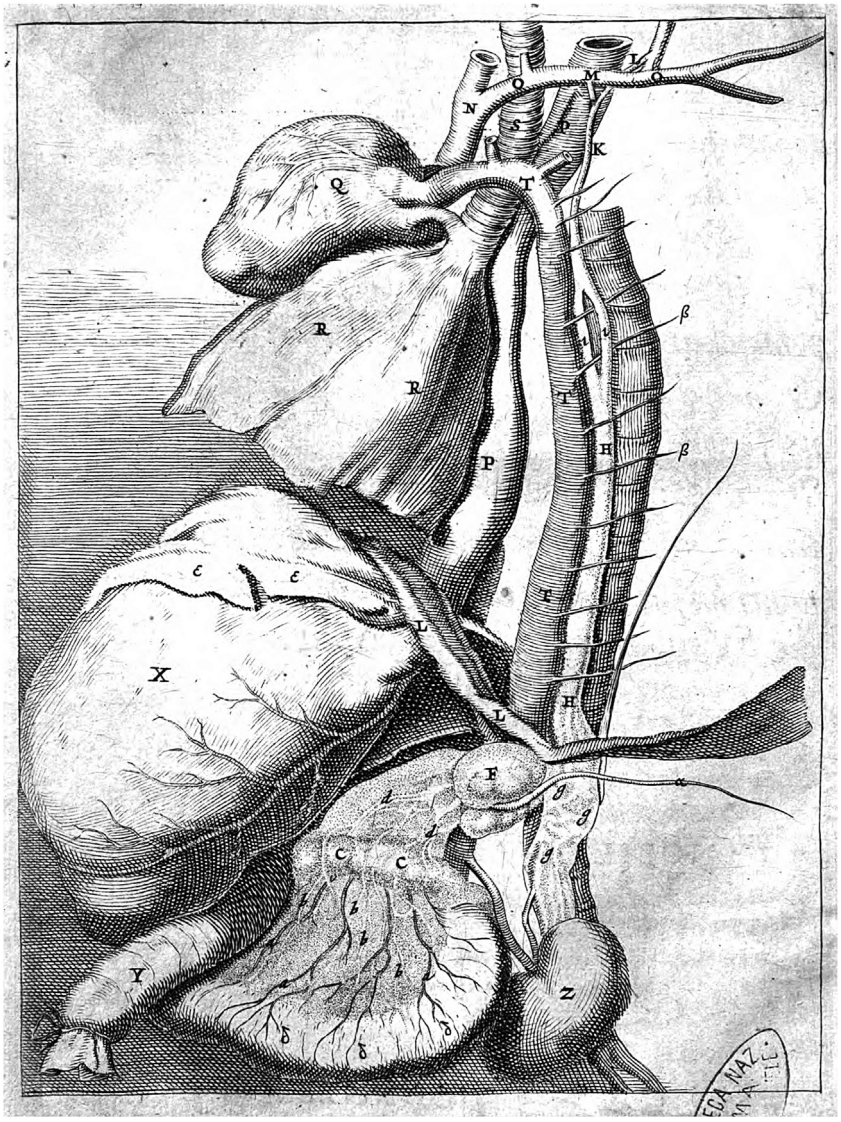

Fig. 10. Johannes van Horne (1652): *Novus ductus chyliferus* . . . [A new lymph channel . . .].
[. . .]; bbb: Venae lacteae per mesenterium disseminatae; CC: Glandula mesenterii maxima, Asellio quoque Pancreas dicta; dd: Duo rami insignes per medium ramum conjuncti, a dicta glandula ad renalem pergentes; [. . .] ggg: Anafractus, gyri, plexusque quamplurimi arteriae magnae trunco incumbentes; HH: Ductus chyliferus novus per thoracis longitudinem ascendens; ii: Ejusdem bifurcatio intra quartam & sextam thoracis vertebram; K: Portio ductus chyliferi oesophago incumbens, ubi cor sueravit; L: Ductus insertio in jugularem sinistram; M. Ejusdem ingressus in axillaris principium seu subclaviam; [. . .]
[. . .]; bbb: The milk vessels (which are) distributed in the mesentery; CC: The largest gland of the mesentery, also named pancreas by Asellius; dd: Two remarkable branches, joined together by a middle branch, which reach from the said gland to the kidney; [. . .] ggg: windings, loops and plexus resting mostly on the trunk of the largest artery; HH: A new thoracic duct ascending through the length of the thorax; ii: Its division between the fourth and sixth thoracic vertebrae; K: The opening of the thoracic duct resting on the oesophagus where the heart is attached; L: The insertion of the duct into the left jugular vein; M: Its (the duct's) insertion into the beginning of the axillary vein or the subclavian vein; [. . .]

3.15. Jan van Horne

These results were confirmed just one year later by the Dutch anatomist Johannes (Jan) van Horne (1621–1670) in the *Novus ductus chyliferus*, where he described the lymphatic valves of the thoracic duct (van Horne, 1652; Natale et al., 2017).

Unaware of Pecquet's dissertation, he presented his findings as "a new and quite unexpected doctrine concerning the entirely new path of the nutriment now detected, by which the milky liquor, known as chyle, expressed from food, is asserted to be carried not to the liver as writers have recently said but directly to the heart, a doctrine which is demonstrated by the decisive influence of reasons and by very much experience." He described how he discovered a milky bag (saccum lacteum) above the left kidney connected through lacteals to a large mesenteric glandular body. The drawing, performed during the vivisection, shows the milky bag, the mesenteric chyle vessels and glands, an intertwined clump of lacteals, the thoracic chyle duct and all the internal organs (Fig. 10). According to van Horne the chyle undergoes its final concoction and deposits its excrements in the clump of lacteals, thus rendering them harmless to the heart. He described the efferent thoracic chyle duct as a "certain vessel turgid with milk" that passes through the diaphragm towards that part of the vena cava known as the subclavian vein in man and the axillary vein in dogs. Backflow in the chyle duct was prevented by valves, since blowing from the duct into the subclavian vein produced bubbles in the blood; otherwise blowing from above into the duct was impossible, because the valves in the duct prevented it. After a series of experiments with ligatures to demonstrate that none of the lacteals runs to the liver, he boldly declared that "unless by a quirk of nature, no chyle was diverted to the liver".

In the late 1650s, van Horne altered his opinion on the transport of chyle towards the heart. In his review of the history of the human anatomy, first published in 1660, he argued for a division of the chyle. Only the best part of the chyle was carried to the heart by the thoracic duct; the rest was mixed with the blood in the reddish [portal] veins that took it to the liver, the vena cava and, finally, the heart (Suy et al., 2016b).

Van Horne, professor of anatomy from 1650 to 1670, was among the teachers of Niels Stensen at Leyden University (Baumann, 1927), but also of Frederik Ruysch, whom he encouraged to examine the lymphatic system (Ijpma and van Gulik, 2013).

3.16. Thomas Bartholin

Thomas Bartholin (1616–1680) is remembered as one of Denmark's most renowned medical professors, since he was a very skilled anatomist and charismatic teacher. In his youth, while studying medicine in Leyden (1637–40), Bartholin read Aselli's paper from 1627 and soon located for himself the '*venae lacteae*' during canine dissections. In 1650, Thomas Bartholin autopsied a waiter who had choked to death on a piece of meat, and thus, like Fallopius a century before, observed the mesenteric lacteals in a person. Upon learning of Pecquet's description of the flow of lacteal fluids in dogs, in the next year Bartholin dissected two criminals within an hour and a half after their execution and confirmed the French anatomist's report of the lacteals connecting to the thoracic duct. However, he rejected one of Pecquet's conclusions and maintained instead (and incorrectly) the Galenic doctrine that some chyle must go to the liver. In early 1652 he published a short account of these studies entitled *De lacteis thoracicis in homine [. . .]* (Fig. 11). In further studies on dogs and cadavers over the following months Bartholin recognized what seemed like two sets of bloodless vessels located in the mesentery, both entering the thoracic duct. Some were the familiar vessels filled with cloudy fluid (fat globules) coming from the small intestines (Aselli's *venae albae et lacteae*), while others with a clear watery fluid seemed connected to the liver. The latter troubled him since they did not appear to drain the intestines. When these latter vessels were ligated, the section proximal to the liver filled with clear fluid, indicating that they were transporting fluid (lymph) from the liver to the thoracic duct. He named these vessels *vasae lymphaticae*, from which the widely used term for the system was derived later on. Bartholin now corrected his earlier mistake and concluded that the mesenteric vessels do not flow into the liver but instead drain only into the blood stream via the thoracic duct. In May 1653 he published *Vasa lymphatica, nuper Hafaniae in animantibus inventa et hepatis exsequiae* (Bartholin, 1653). In this book he proclaimed the "dethroning" of the liver as the destination of mesenteric lymph, whether cloudy or clear. Bartholin had previously noticed elsewhere in the body similar thin, delicate vessels containing a clear watery fluid. These vessels seemed so widespread as to suggest a distinct system analogous to the veins existing throughout the body (Fig. 12). Bartholińs "vasa lymphatica" became the basis of todayś terminology ("lymphatics") (Ambrose, 2006).

3.17. Olof Rudbeck

In 1651, the lymphatic system attracted the attention of a Swedish medical student, then unfamiliar with either Pecquet's just published report or Bartholin's current investigations. In Uppsala, 20-year-old Olof Rudbeck (1630–1702) observed a "whey-like fluid" draining from the supraclavicular notch of a butchered calf. He traced the source back to the thoracic duct and to its enlargement around L2, which he named the *vesicula chyli* (the little bladder of chyle = *cysterna chyli*). Within a year he examined 300 animals and, contrary to the standard teaching, became convinced that no chyle feeds into the liver. Indeed, he noted that clear fluid (lymph) passes from the liver in small vessels which join with mesenteric lacteals to enter the thoracic duct. He called these small vessels *ducti hepatici aquosi* (watery hepatic ducts). In the lungs and retroperitoneal kidneys he also observed tiny vessels appearing to drain tiny glands (= the lymph nodes, then called conglobate glands). These and other such vessels he termed vasa *glandularum serosa* (the aqueous vessels of little glands). Thus, in early 1652 Rudbeck stated that lymphatic drainage occurs in parts of the body outside the abdominal and thoracic cavities and postulated a drainage system throughout the body (Ambrose, 2006).

In April 1652, Rudbeck demonstrated his findings to Queen Christina of Sweden, her court, and academicians in the castle of Uppsala. In May 1652 he defended his university thesis, which summarized his anatomical findings. According to medieval practice, in the 17th century his public defense was still viewed as "the date of communication of a discovery to the world" (Larsell, 1928). Finally, during the summer of 1653, Rudbeck published a monograph reviewing his studies, *Nova excercitatio anatomica exhibens Ductus Hepaticos Aquosos et Vasa Glandularum Serosa* (Fig. 13) (Rudbeck, 1653). In June 1652 Rudbeck received and first read Pecquet's report from 1651. Rudbeck's demonstration before Queen Christina led her to fund his additional studies in Holland. On his way there in August 1653, in a Hamburg bookstore, he encountered Bartholin's book Vasa Lymphatica, just published in May 1653, and only then learned of the Danish professor's observations. In that same year in Copenhagen, Bartholin became aware of Rudbeck's findings via an abstract of his dissertation, and in February 1654 received a copy of the young graduate's book (Ambrose, 2006). Bartholin himself seemed to be content to share his discovery with Rudbeck and Joyliffe (Cruikshank, 1786).

However, subsequently, a hot and long lasting "paper-war" between Bartholińs followers and Rudbeck ensued. This dispute concerned three issues of priority: (1) Who was the first to discover that the mesenteric lacteals connect with the thoracic duct? (2) Who did first determine that mesenteric chyle does not flow into the liver but into the blood stream via the thoracic duct? (3) Who recognized first that the lymphatic system is widespread throughout the body? (Ambrose, 2006). Ambrose is of the opinion that "Pecquet" is the answer to the questions one and two; even Bartholin agreed to that (Bartholin, 1652). The answer to question three is not so easily found: whereas Rudbeck presented his results first, Bartholin first published his studies in May 1653 (nearly exactly one year after Rudbeck's defense of his thesis).

3.18. George Joyliffe

George Joyliffe (1621–1658), a physician in Cambridge, distinguished between lacteal and non-lacteal vessels and named the latter lymphatics (Natale et al., 2017). Unfortunately, his works are lost and we can only rely on citations by his contemporaries (Barrowman and Tso, 2010). In the controversy over scientific priority he was supported by Francis Glisson. In his famous book *Anatomia hepatis* (Glisson, 1654), Glisson claims that his student Joyliffe as early as 1653 discovered a fourth class of vessels, different from veins, arteries and nerves [the lymphatic system], in the whole body or at least in most of its parts long before Rudbeck and Bartholin (Cruikshank, 1786), and that these vessels contain an "*aqueous humor*". Joyliffe deemed that the function of these vessels was to carry "humor" throughout the body (Chikly, 1997).

[6] This section on Niels Stensen is solely based on the detailed and extensive book by Kardel and Maquet (2013). References to Stensen's work comprise – whenever possible – the original publications and the reference to the collective edition of

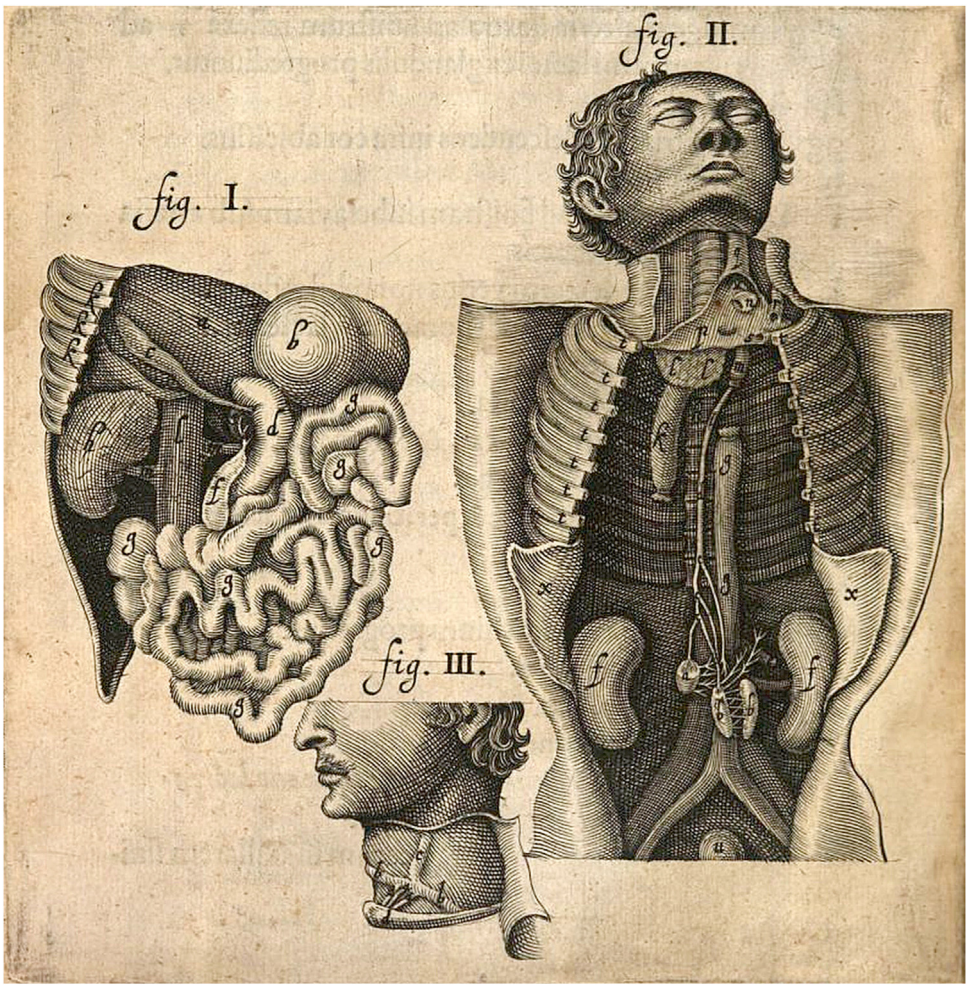

Fig. 11. Thomas Bartholin (1652): *De lacteis thoracicis in homine brutisque nuperrime observatis, historia anatomica.* Figures 1–3 [The thoracic ducts in humans and animals which were examined recently . . ., Fig. 1–3].
Fig. I Receptaculum seu compages novarum glandularum in suo situ exhibitur, eique annexa: [. . .] e: Pancreatis pars sub duodeno, ad quam sparguntur rami lactei ex glandulis receptaculi; f: Glandulae lumbales receptaculi in suo situ junctae; [. . .] i: Ramuli lactei ex glandulis in pancreatis superficie sparsi; [...]
Fig. II. Glandulae novae lumbares separate earumque rami lactei ad axillarem, exemptis visceribus, monstrantur: a: Glandula superior lactea nova; bb: Glandulae duae inferiores separatae, ramique lacteis invicem conjunctae; ccc: Rami lactei ex glandulis adsecendentes; d: Solitarius ramus thoracicus; Emulgens arteria dextra ad sinistrum reflexa, ad quam rami lactei ex glandulis progrediuntur; [...] i: Lactea thoracica ad sinistram subclaviam sub arteria subclavia repens; [...] n: Valvula lacteae thoracicae, & interna lacteae insertio; [. . .]
Fig. III: Externa in alio capite humano lactearum insertio visitur: a: Tripartita lactearum thoracicarum in axillarem sinistram insertio; [. . .]
Fig. I: The receptacle or the arrangement of the new glands and its appendices are shown in its place: [. . .] e: The part of the pancreas below the duodenum to which the branches of the milk vessel are scattered from the glands of the receptacle; f: the lumbar glands of the receptacle converging in its place; [. . .] i: Small lacteals coursing superficially from the glands to the pancreas; [. . .]
Fig. II: Separate new lumbar glands and their branches are shown near the axillary vein after removal of the viscera: a: the superior new milk gland; bb: two separate inferior glands, and branches (that are) alternately connected with the milk branches; ccc: milk branches departing from the glands; d: the solitary thoracic branch; the leaving/right artery, to which the milk branches from the glands are advancing, turning to the left (side); [. . .] i: the thoracic milk vessel moving to the left subclavian vein below the subclavian artery; [. . .] n: the valve of the thoracic duct and the inner insertion of the thoracic duct; [. . .]
Fig. III: The external insertion of the thoracic milk vessels in another human head is shown: a: the insertion of the thoracic milk vessels, divided into three parts, into the left axillary vein; [. . .]

3.19. Niels Stensen[6]

Niels Stensen (aka Nicolaus Steno aka Nicolaus Stenonis, 1638-1686) was a pupil and mentee of Thomas Bartholin at Copenhagen University, Gerald Blaes at Amsterdam's Athenaeum in the spring of 1660, where he discovered the parotid duct,[7] and later on of Franz de la Boë (latinized Sylvius) and Jan van Horne at Leiden University (1660-1663). Sylvius supported Stensen's studies by readily attending his dissections, consigning cadavers to him and inviting others to witness the investigations. During these studies, Stensen recognized that the then customary name "Parotis" actually designated two different "glands", one of which pours saliva through the duct which he discovered, whereas the other, like usual lymph nodes without an excretory duct (termed conglobate glands), belongs to the system of lymphatic vessels (Kardel and Maquet, 2013, 72f). Stensen enumerated his following new findings: 1. all lymph vessels were connected to glands but the proper locations of formation of the lymph are unknown. 2. the lymph vessels which belong to the "conglobate glands", the actual lymph vessels, discharge their content back into the venous system, directly or through the "conglobate glands". [. . .] 4. all the glands are organs in which the lymph vessels disperse their roots (Kardel and Maquet, 2013, p. 106).

Stensen's publications by Vilhelm Maar '*Nicolai Stenonis Opera Philosophica*' (OPH; Maar, 1910)

[7] The parotid duct had already been discovered in 1655 by Walter Needham (ca. 1631–1691), who, however, had not published his findings at that time.

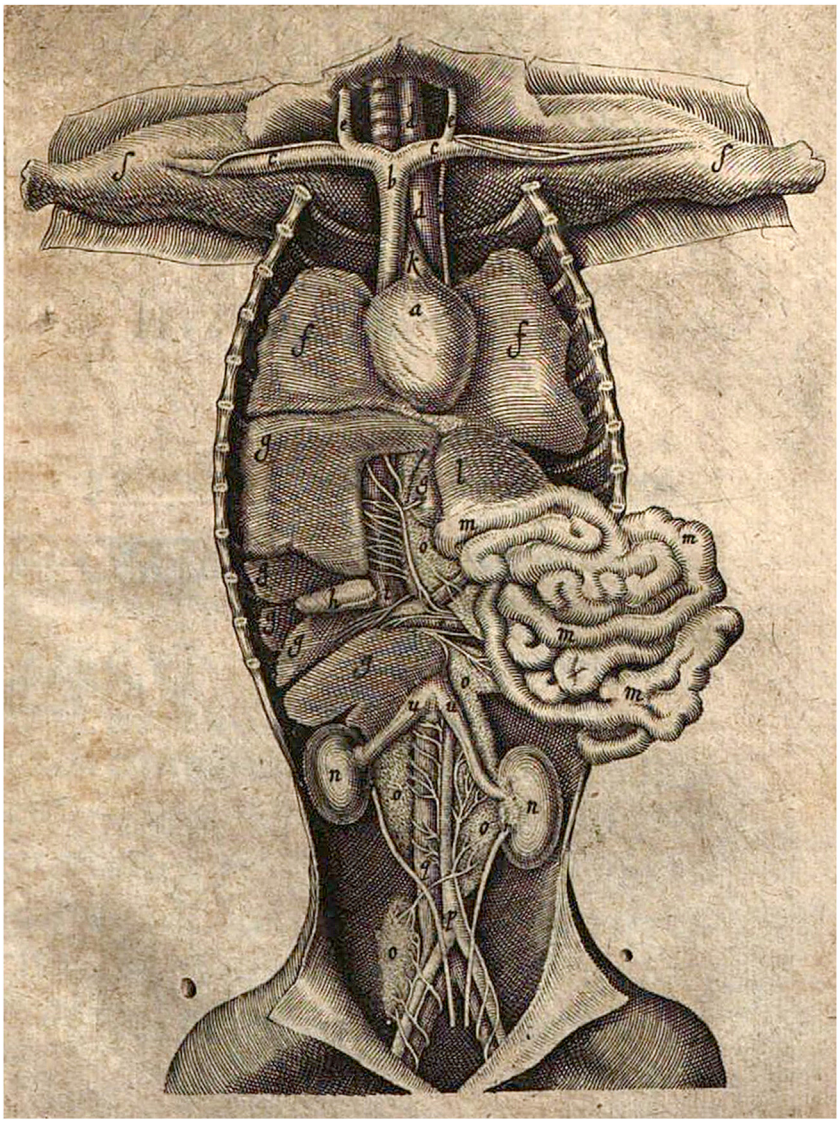

Fig. 12. Thomas Bartholin (1653): *Vasa lymphatica, nuper Hafniae in animantibus inventa* . . . [The lymphatic vessels (lymphatics), recently found in animals in Copenhagen]. *Figura exhibentur vasa nova lymphatica in cane dissecto, qvae ut discernas, reliqvas partes literis signatas ita distingue: [. . .] i: Vena lactea thoracica axillari sinistrae inserta; oooo: Pinguedo, quam vasa lymphatica penetrant, sub qua etiam prope emulgentes receptaculum situm est, & hic inde lacteae glandulae*
In the figure the new lymphatic vessels, dissected in a dog, are shown for your recognition; the other parts are marked by letters so that they may be distinguished: [. . .] i: The thoracic milk vessels inserted into the left axillary vene; oooo: The fat penetrated by the lymphatic vessels below which the receptacle is situated beside the nearly emptied lymphatic vessels, and here, therefore, the milk glands

In his letter to Thomas Bartholin '*On the First Discovery of an External Salivary Duct and on the Experiments of Bils*' 1661, Stensen also described "some new lymphatic ducts" in the head of a calf and several dogs and, furthermore, he mentioned "another duct which I saw in the thorax to be different from the thoracic duct as far as position and color of the contents are concerned, of which I observed nothing except a fairly long duct in the left side of the thorax situated beyond the internal branch of the ninth pair of nerves and rising on to the jugular glands" (Stensen, 1667a; Maar, 1910, OPH 1, Vol. I, 3–7). Furthermore he described the situation around the cisterna chyli in a dog one day after initial vivisection: "The [previously cranially ligated] thoracic duct, then hardly visible, was now also turgid and showed several small branches returning, after a short parting, to the trunk from which they originate. But what is most important in this matter: a vessel from the receptacle to the inguinal gland was seen completely full of milk, although some of the rivulets which from another source go to the same vessel disclosed lymph of aqueous colour." Stensen extended his descriptions in a first book edition in the same year (Stensen, 1661; Maar, 1910, OPH 2, Vol. I, 11–51) and a second, even more extended, edition in 1662 (Stensen, 1662). Therein he described [in a dog] the confluence of lymphatics 'from the head and neck, from the arms as well as from the external and internal parts of the thorax' into the 'bifurcation of the vena cava in a jugular and an axillary branch'. Furthermore he described that 'not only the ascending thoracic duct joins the descending duct of the neck but that many vessels also converge to the same place from the back as well as from the forelegs [i.e upper extremity], together with some from the thorax [. . .], and almost conspire with each other.' Stensen then elaborated the concept of the antegrade lymphatic flow directed by valvulas and retrograde flow when brute force or (artificial) obstacles occur.

In the letter on '*Various New Observations in the Eyes and Nose, etc.*', written in September 1661, Stensen described that he repeated some experiments of Bils concerning the flow of the chyle but could not repeat Bils' results, i.e. that the chyle should flow towards the liver (Stensen, 1667c; Maar, 1910, OPH 3, Vol. I, 55–58). This dis-

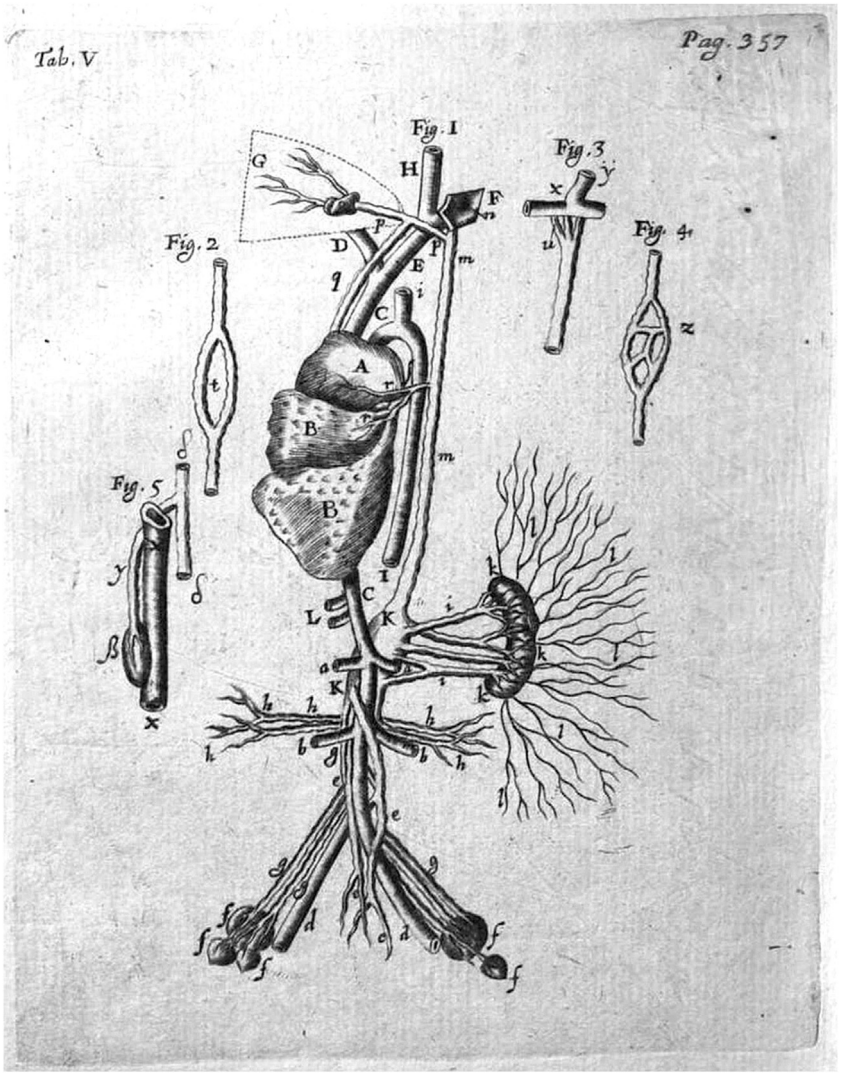

Fig. 13. Olof Rudbeck (1653): *Nova exercitatio anatomica, exhibens ductus hepaticos aquosos, & vasa glandarum serosa [. . .]* Tabula II [New anatomical exercise showing the ductus hepaticos aquosos (watery hepatic duct) and the watery vessels of the glands . . ., Figure 2].
Fig. 1 : [. . .] E: Vena axillaris sinistra; F: Pars ejusdem aperta ut in conspectum veniret venae chyliferae insertio; [. . .] K: Vesicula chyli; eeee: vasa serosa quae sub intestino recto ad vesiculam chyli tendunt; fffff: glandulae ad crurales venas sitae; ggg: harum glandularum vasa serosa vesiculam prospicientia; hhhh: ejusdem generis vasa, inter abdominis musculos progredientia, que similiter vesiculam chyli ingrediuntur; kkk: pancreas glandulosum; lll: venae lacteae mesenterii inter pancreas & intestina; mm: ductus chyliferus; n: ejus in venam axillarem insertio; o: glandulae sterni; pp: harum, ductus serosus ramo chylifero inhians; q: ramulus hujus ad costas progrediens; r: glandulae cordis; ss: harum glandularum vas serosum, quod sub corde ductui chylifero inseritur.
Fig. 2 Ostendit bifurcationem ductus chyliferi sub corde, ut plerumquae; illam invenit
Fig. 3 : [. . .]; y: ductus chyliferi triplex insertio
Fig. 4 z: ramificatio varia ductus chyliferi, [...]
Fig. 1 : [...] E: The left axillary vein; F: A part of it was opened to show the insertion of the lymphatic vein; [...] K: The lymph vesicle; eeee: the translucent vessels (vasa serosa) moving under the intestine to the lymph receptacle; fffff: the glands beside the crural veins; ggg: the translucent vessels of these glands heading to the vesicle; hhhh: vessels of the same kind running among the abdominal muscles and likewise into the lymph vesicle; kkk: the glandulous pancreas; lll: the lacteal veins of the mesentery between the pancreas and the intestines; mm: the lymphatic duct; n: its insertion into the axillary vein; o: the sternal glands; pp: their ductus serosus moving into the lymphatic duct; q: a small branch of it moving to the ribs; r: the glands of the heart; ss: the vas serosum, inserting into the lymphatic duct below the heart
Fig. 2 shows the bifurcation of the lymphatic duct below the heart, as usual; it inserts into it
Fig. 3 a triple insertion of the lymphatic duct
Fig. 4 another ramification of the lymphatic duct

pute was continued by 'Response to Vindications for Rehabilitation of the Liver' (Stensen, 1662, second of four treatises; Maar, 1910, OPH 4, Vol. I, 61–73), involving also van Horne, Pecquet, and even Bartholin.

The thoracic duct was again a topic in Stensen's letter on the '*Origin of Sweat from Glands. On the Insertion and Valvula of the Thoracic Duct and of the Lymphatics*' (Stensen, 1667b; Maar, 1910, OPH 7, Vol. I, 101–103). Therein Stensen described that the orifice of the thoracic duct 'in the vena cava is provided with a fairly large and delicate valvula opposing regurgitation of the blood. This same valvula also closed the orifice of the lymphatic duct descending from the neck.'

In 1662–1663, Stensen worked in collaboration with his friend and fellow student Jan Swammerdam on the '*Diversity of lymphatic ducts*', finally published in 1675 (Stensen, 1675; Maar, 1910, OPH 12, Vol. I, 139–142). Swammerdam is acknowledged for providing Fig. 1. '*The diversity observed in dogs near the junction of the lymphatic ducts with the vena cava on the left side of the neck is found either in the branches of insertions, [. . .] which are many here, few there, or in the small rings, [. . .] which are completely absent in some dogs, are*

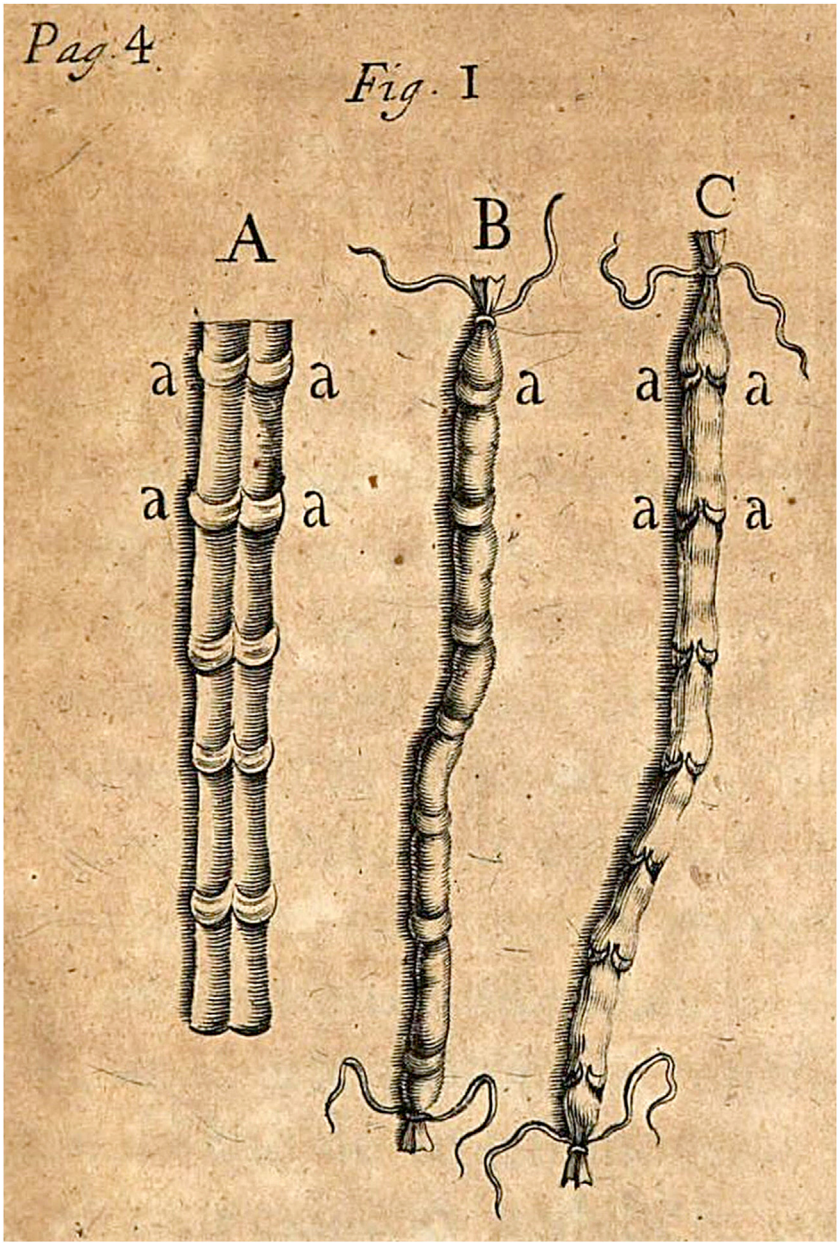

Fig. 14. Frederik Ruysch (1665) *Dilucidatio valvularum in vasis lymphaticis et lacteis* Figure 1 [An explanation of the valves in milk vessels and lymphatic vessels].
Vasa lymphatica a parte antica, a latere, & secundum longitudinem dissect. cum suis valvulis exhibet. A: Vas lymphaticum secundum longitudinem dissectum; B: Vas lymphaticum a latere; C: Vas lymphaticum ab antica parte; aaaaa: valvulae semilunares in dictis vasis
The lymphatic vessels from anterior, from the side and dissected lengthwise with their valves. A: The lymphatic vessel dissected lengthwise; B: The lymphatic vessel from the side; C: The lymphatic vessel from anterior; aaaaa: semilunar valves of the said vessels

present in a certain number in most, are fewer in others still, sometimes narrow, sometimes fairly wide [. . .]'.

3.20. Frederik Ruysch

In 1665, Frederik Ruysch (1638–1731), Lecturer in Anatomy of the Amsterdam Guild of Surgeons, and the city's municipal surgeon and obstetrician, published his beautifully illustrated thesis *Dilucidatio valvularum in vasis lymphaticis et lacteis* (Ruysch, 1665; Gans, 1962; Barrowman and Tso, 2010). It contained the results of detailed studies on the valves of the lymphatics that Ruysch had examined mainly by dissection but probably also by intravascular injections (Barrowman and Tso, 2010). According to Gans (1962), Ruysch wrote: "*. . . clearer than the afternoon light, I saw the valves, double everywhere, very swiftly, a growing moon attached to the sides of the vessels, similar to those found in the cavity of the veins, but more in number and ranker*" (Fig. 14).

The artist Adriaen Backer was commissioned to paint Ruysch's anatomy lesson performed on March 29th, 1670. In that painting, *The Anatomy Lesson of Dr. Frederik Ruysch*, Ruysch performs an anatomical dissection of the inguinal lymph nodes. Ruysch also founded his own anatomical museum in which he exhibited about 2000 of his permanent anatomical specimens, among them several specimens with prepared lymphatics. This collection was sold in 1717 to the Russian Tzar Peter the Great and shipped to St. Petersburg (Russia) (Ijpma and van Gulik, 2013).

3.21. William Harvey

Surprisingly, the most famous English scientist William Harvey (1578–1657), the discoverer of the systemic blood circulation illustrated in the celebrated *Exercitatio anatomica de motu cordis et sanguinis in animalibus* (1628), ignored, at least in part, the progress in research on the lymphatic circulation, and he still accepted the double function of the portal vein (blood and chyle transport, alternatively) and denied the presence of chyle in lacteals and its passage from the thoracic duct to the subclavian vein (Natale et al., 2017).

Funding

No financial support.

Ethical statement

Not applicable for this article.

Acknowledgements

We want to remind and honor those people whose corpses were used for investigating the anatomy of lymphatics by several authors.

This project would not have been possible without Google Books, who digitized the ancient original books and provides open access to this literature.

References

Alexander, J.S., Ganta, V.C., Jordan, P.A., Witte, M.H., 2010. Gastrointestinal lymphatics in health and disease. Pathophysiology 17, 315–335.
Ambrose, C.T., 2006. Immunology's first priority dispute—an account of the 17th-century Rudbeck–Bartholin feud. Cell Immunol. 242, 1–8, http://dx.doi.org/10.1016/j.cellimm.2006.09.004.
Anderson, H., 1933. GASPAR ASELLIUS: the discoverer of the lacteals. Can. Med. Assoc. J. 28, 666–667.
Aselli, G., 1628. De lactibus sive lacteis venis, quarto vasorum mesaraicorium genere, novo invento Gasparis Asellii, Cremonensis Antomici Ticinensis, Dissertatio. Henric. Petrinus, Basel.
Aselli, G., 1640. De lactibus sive lacteis venis, quarto vasorum mesaraicorium genere novo invento Gasparis Asellii, Cremonensis Antomici Ticinensis, Dissertatio. Qua sententiae anatomicae multae, vel perperam receptae convelluntur, vel parum perceptae illustrantur. J. Maire, Leyden.
Barrowman, J., Tso, P., 2010. Gastrointestinal lymphatics. Compr. Physiol. (Suppl 16), 1733–1777, http://dx.doi.org/10.1002/cphy.cp060148.
Bartholin, T., 1652. De lacteis thoracicis in homine brutisque nuperrime observatis, historia anatomica. M. Martzan, Kopenhagen.
Bartholin, T., 1653. Vasa lymphatica, nuper Hafniae in Animantibus inventa, et Hepatis exseqviae. Hakius, Kopenhagen.
Baumann, E.D., 1927. HORNE (Johannes van). In: Molhuysen, P.C., Blok, P.J., Kossmann, F. (Eds.), Niew Nederlandsch Biografisch Woordenboek (NNBW). N. Israel, Amsterdam, pp. 624–625.
Bugnion, E., Dec. 1925. Arch d'Anat 5 1926. La dècouverte des chylifères de l'homme faite en 1634 par quelques médécins aixois, grâce à l'initiative du sénateur de Peiresc. Notice Historique présentée à'Academie d'Aix-en-Provence., pp. 619.
Casley-Smith, J.R., 1972. The role of the endothelial intercellular junctions in the functioning of the initial lymphatics. Angiologica 9, 106–131, http://dx.doi.org/10.1159/000157923.
Chikly, B., 1997. Who discovered the lymphatic system. Lymphology 30, 186–193.
contributori di Wikipedia, 2016. Gaspare Aselli. In: Wikipedia, L'encyclopedia libera, last update: 26 luglio 2016. http://it.wikipedia.org/w/index.php?title=Gaspare_Aselli&oldid=82230788. (visited: 8 giugno 2017).
Costeo, G., 1595. De lactis serique natura et in medicina usu. Rossius, Bologna.
Craik, E., 2009. The Hippocratic Treatise On Glands: Edited and Translated with Introduction and Commentary. Brill, Leiden, Boston.
Crivellato, E., Ribatti, D., 2007. A portrait of Aristotle as an anatomist: historical article. Clin. Anat. 20, 447–485, http://dx.doi.org/10.1002/ca.20432.
Crivellato, E., Travan, L., Ribatti, D., 2007. The Hippocratic treatise' On glands': the first document on lymphoid tissue and lymph nodes. Leukemia 21, 591–592, http://dx.doi.org/10.1038/sj.leu.2404618.
Cruikshank, W., 1786. The Anatomy of the Absorbing Vessels of the Human Body. G. Nicol, London.
de Renzi, S., 1857. Storia documentata della scuola medica di Salerno, 2nd ed. Gaetano Nobile, Napoli.
Eales, N.B., 1974. The history of the lymphatic system, with special reference to the Hunter-Monro controversy. J. Hist. Med. Allied Sci. 29, 280–294, http://dx.doi.org/10.1093/jhmas/XXIX.3.280.
Éstienne, C., 1545. De dissectione partium corporis humani libri tres. Simon de Colines, Paris.
Eustachius, B., 1564. De Vena sine Pari. In: Eustachius, B. (Ed.), Opuscula anatomica. Luchinus, Venetiis [Venice], pp. 262–311.
Ferrandez, J.-C., 2006. El sistema linfático. Médica Panamericana, Buenos Aires, Madrid.
Foster, M., 1924. Lectures on the History of Physiology during the Sixteenth, Seventeenth and Eighteenth Centuries. University Press, Cambridge.
Fraser, P.M., 1969. The career of Erasistratus of Ceos. Rendiconti del Istituto Lombardo 108, 518–537.
Fulton, J.F., 1938. The early history of the lymphatics: With particular reference to Bartholin, Rudbeck and Joyliffe. Bull. Hennepin Co. Med. Soc. 9, 5–10.
Gans, H., 1962. On the discovery of the lymphatic circulation. Angiology 13, 530–536, http://dx.doi.org/10.1177/000331976201301106.
Glisson, F., 1654. Anatomia hepatis, cui praemittuntur quaedam ad rem anatomicam universe spectantia. Et ad calcem prois subjiunctur nonnulla de lymphae-ductibus nuper repertis. Gardianis, London.
Golzari, S.E., Kazemi, A., Ghaffari, A., Ghabili, K., 2012. A brief history of elephantiasis. Clin. Infect. Dis. 55, 1024–1025.
Guerrini, A., 2015. The Courtiers' Anatomists: Animals and Humans in Louis XIV's. University of Chicago Press, Paris.
Highmore, N., 1651. Corporis humani disquisitio anatomica; in qua sanguinis circulationem in quavis corporis particula plurimis typis novis, ac aenygmatum medicorum succinctâ dilucidatione ornatam prosequutus est Nathanael Highmorus. Samuel Broun, Den Haag.
Ijpma, F.F., van Gulik, T.M., 2013. Anatomy lesson of Frederik Ruyschöf 1670: a tribute to Ruysch's contributions to lymphatic anatomy. World J. Surg. 37, 1996–2001, http://dx.doi.org/10.1007/s00268-013-2013-x.
Kanter, M.A., 1987. The lymphatic system: an historical perspective. Plast. Reconstr. Surg. 79, 131–139.
Kardel, T., Maquet, P., 2013. Nicolaus Steno: Biography and Original Papers of a 17th Century Scientist. Springer, Berlin, Heidelberg.
Langslow, D., 2012. Rufus of Ephesos. In: The Encyclopedia of Ancient History. John Wiley & Sons, Inc.
Larsell, O., 1928. Olof Rudbeck the elder. Ann. Med. Hist 10, 301–313.
Lind, L.R., 1975. Studies in pre-Vesalian anatomy: biography, translations, documents. American Philosophical Society, Philadelphia.
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. Clin. Anat. 24, 807–816, http://dx.doi.org/10.1002/ca.21194.
Maar, V., 1910. Nicolai Stenonis Opera Philosophica. Vilhelm Tryde, Copenhagen.
Markatos, K., Chytas, D., Korres, D., Laios, K., Androutsos, G., Chronopoulos, E., 2017. Charles Estienne (1504–1564): his life, work, and contribution to anatomy and the first description of the canal in the spinal cord. World Neurosurg. 100, 186–189, http://dx.doi.org/10.1016/j.wneu.2016.12.126.
Marmelzat, W.L., 1991. Galen on "glands" and "spongy flesh": with special reference to an ancient mechanico-biophysical theory for superficial lymph node function. J. Hist. Med. Allied Sci. 46, 419–439, http://dx.doi.org/10.1093/jhmas/46.4.419.
Massa, N., 1536. Liber introductorius anatomiae siue dissectionis corporis humani. F. Bindoni & M. Pasini, socios, Venice.
May, M.T., 1968. Galen and the Usefullness of the Parts of the Body. Cornell University Press, Ithaca, NY.
Medici, M., 1857. Compendio storico della scuola anatomica di Bologna dal rinascimento delle scienze e delle lettere a tutto il Sécolo 18 con un paragone fra la sua antichità e quella delle scuole di Salerno e di Padova. Volpe e del Sassi, Bologna.
Mentel, J., 1654. Epistola ad Joannem Pecquetum. In: Pecquet, J.P. (Ed.), Nova experimenta antomica. Cramoisy, Paris, pp. 141–150.
Natale, G., Bocci, G., Ribatti, D., 2017. Scholars and scientists in the history of the lymphatic system. J. Anat. 231, 417–429, http://dx.doi.org/10.1111/joa.12644.
Pecquet, J., 1651. Ionannis Pecqveti Diepaei Experimenta nova anatomica, quibus incognitum hactenus Chyli Receptaculum, & ab eo per Thoracem in ramos usque Subclavios Vasa Lactea deteguntur. S. & G. Cramoisy, Paris.
Read, A., 1650. The Manual of the Anatomy, Or, Dissection of the Body of Man. E. Tyler, London.
Reveron, R.R., 2014. Herophilus and Erasistratus, pioneers of human anatomical dissection. Vesalius 20, 55–58.
Rudbeck, O., 1653. Nova excercitatio anatomica, exhibens ductus hepaticos aquosos, & vasa glandarum serosa, nuc primum inventa, æneisque figuris delineata: Eucharius Lauringerus.
Ruysch, F., 1665. Dilucidatio valvularum in vasis lymphaticis et lacteis. Harman Gael, Den Haag.
Schmugge, L., 1989. Leichen für Heidelberg und Tübingen. In: Schwab, D., Giesen, D., Listl, J., Strätz, H.-W. (Eds.), Staat, Kirche, Wissenschaft in einer pluralistischen Gesellschaft. Duncker & Humblot, Berlin, pp. 411–418.
Schuchhardt, C., Wittlinger, H., Rabe, H., 2003. Eine Kleine Geschichte der Lymphologie. Viavital, Köln.
Sheldon, J., 1784. The History of the Absorbent System: Part the First, Containing the Chylography. John Sheldon, London.
Stensen, N., 1661. Anatomica de glandulis oris, &, nuper observatis inde prodeuntibus vasis. Johann Elsevir, Leiden.
Stensen, N., 1662. Nicolai Stenonis observationes anatomicæ, quibus varia oris, oculorum, & Narium vasa describuntur, novique salivæ, lacrymarum & muci fontes

deteguntur, & Novum nobilissimi Bilsii De lymphæ motu & usu commentum examinatur & rejicitur. Jakob Chouët, Leiden.
Stensen, N., 1667a. De prima ductus salivalis exterioris inventione & Bilsianis experimentis (Epist. XXIV). Thomæ Bartholini Epist. Medicin. Cent. Hafniae, III., pp. 86–95.
Stensen, N., 1667b. Sudorum origo ex glandulis. De insertione & valvula lactei thoracici & lymphaticorum (Epist. LXV). Thomæ Bartholini Epist. Medicin. Cent. Hafniae, III., pp. 262–266.
Stensen, N., 1667c. Variae in oculis & naso observationes novae &C. (Epist. LVII). Thomæ Bartholini Epist. Medicin. Cent. Hafniae, III., pp. 224.
Stensen, N., 1675. Lymphaticorum varietas. Thomæ Bartholini Acta Medica et Philosophica Hafniensia II:240–241.
Strkalj, G., Chorn, D., 2008. Herophilus of Chalcedon and the practice of dissection in Hellenistic Alexandria. S. Afr. Med. J. 98, 86–89.
Suy, R., Thomis, S., Fourneau, I., 2016a. The discovery of lymphatic system in the seventeenth century. Part I: the early history. Acta Chir. Belg. 116, 260–266, http://dx.doi.org/10.1080/00015458.2016.1176792.
Suy, R., Thomis, S., Fourneau, I., 2016b. The discovery of the lymphatics in the seventeenth century. Part III: the dethroning of the liver. Acta Chir. Belg. 116, 390–397, http://dx.doi.org/10.1080/00015458.2016.1215952.
Trapnell, D.H., 1965. Man's understanding of the lymphatics, with particular reference to the lung. Proc. R. Soc. Med. 58, 37–40.
van Horne, J., 1652. Novus ductus chyliferus. Nunc primum delineatus, descriptus et eruditorum examini expositus. F. Hack, Leiden.
Vesalius, A., 2007. On the Fabric of the Human Body, Book V: The Organs of Nutrition and Generation. A Translation of De Humani Corporis Fabrica Libri Septem. In: Richardson, W.F., Carman, J.B. (Eds.), Norman Anatomy Series, vol. 4. Norman Pub.
Vesling, J., Blasius, G., 1677. Syntagma anatomicum. Frambotti, Padua.
Wikipedia contributors, 2016. Herophilos. In: Wikipedia, The Free Encyclopedia, last update: November 30, 2016. https://en.wikipedia.org/w/index.php?title=Herophilos&oldid=752279660. (visited: May 9, 2017).
Wikipedia contributors, 2017a. Erasistratus. In: Wikipedia, The Free Encyclopedia, last update: January 15, 2017. https://en.wikipedia.org/w/index.php?title=Erasistratus&oldid=760261524. (visited: May 9, 2017).
Wikipedia contributors, 2017b. Galen. In: Wikipedia, The Free Encyclopedia, last update: June 27, 2017. https://en.wikipedia.org/w/index.php?title=Galen&oldid=787830547. (visited: June 28, 2017).
Wikipedia contributors, 2017c. Gaspare Aselli. In: Wikipedia, The Free Encyclopedia, last update: April 9th, 2017. https://en.wikipedia.org/w/index.php?title=Gaspare_Aselli&oldid=774556259. (visited: April 27th, 2017).
Wikipedia contributors, 2017d. Rufus of Ephesos. In: Wikipedia, The Free Encylopedia, last update: June 28, 2017. https://en.wikipedia.org/w/index.php?title=Rufus_of_Ephesus&oldid=787886222. (visited: June 28, 2017).
Wiltse, L.L., Pait, T.G., 1998. Herophilus of Alexandria (325–255 B.C.). The father of anatomy. Spine (Phila Pa 1976) 23, 1904–1914.