On the unlocked secrets of the lymphatics and lymphatic circulation

A short tale of how eminent scientists walked from there to here

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"Progress in science depends on new techniques, new discoveries and new ideas, probably in that order" Sydney Brenner, The Times, 1986

The glory of having discovered the lymphatic vessels belongs undoubtedly to the Italian Gaspare Aselli from Cremona; he established itself as an excellent anatomist and surgeon, also military, in Milan, where the first true description of the lymphatic system can really begin; later, he moved to Pavia, where in 1624 he obtained the chair of anatomy (Figure 1).

On the 23rd of July 1622, urged by some of his friends, he submitted to vivisection a fed dog, with the purpose of highlighting the recurring nerves and movements of the diaphragm.

"While pulling down with my hands the intestines and the stomach gathered together into a mass to discover the abdominal fascia of the diaphragm, I was attracted by the presence of numerous white cords, exceedingly thin and beautifully white, branched throughout the mesentery and on the peritoneal surface of the intestine, and starting from almost innumerable beginnings" - he described.[1]

At first, those filaments could have been considered nerves. But it was enough to record one of the less subtle ones, so that a whitish mood, similar to milk or cream, could emerge. He invited who was standing by to observe the interesting spectacle of such an unusual phenomenon and they indeed were much struck with the novelty of the thing.

It is characteristic of the perspicacity of Aselli and the correctness of his conclusions that, when on the following day he performed vivisection on another dog and failed to discover the same phenomenon, he thought that his failure might be due to the fact that this animal had been dissected with an empty stomach, as compared of the preceding day.

He repeated the same experiment in a third, few hours before well-fed dog and was once more able to observe the mesenteric lymphatic vessels as at the first time. He was able to demonstrated

Figure 1. Gaspare Aselli, (1581-1626). Engraved portrait of Aselli by the Milanese painter and engraver Cesare Bassano (1584-1648) (Published on KOS, by courtesy of Franco Maria Ricci Editore). The excellent Italian anatomist and surgeon Gaspare Aselli from Cremona is, above all, known for his discovery of the intestinal lacteal vessels of the lymphatic system when he was in Milan (1622). He moved later to the University of Pavia, where he was a professor, obtaining the chair of anatomy (1624). Aselli passed away at the age of forty-five due to an acute and malignant fever.

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them hereafter in various mammals and he definitively proposed the term "vasa lactea" to designate the pale circulatory pathways that appeared so distinguishable by veins with their red fluid.

He definitively described his findings in his "Anatomica Ticinensis Dissertatio De Lactibus Sive Lactis Venis, Quarto Vasorum Mesaraicorum Genere", published in Milan in 1627, after his death (Figure 2).[2]

The Aselli's treatise contained four striking color woodcuts that were the first illustrations of lymphatics and probably the first in color in all medical literature; they show the white lacteals running in the mesentery from borders of the small bowel to lymph nodes, still believing the lymphatic flow ran towards the liver, to be here transformed into blood (Figures 3-6). The lymphatic system from then was studied intensively.

It seems that Vesalius had discovered the thoracic duct as first: he, however, failed to recognize its significance and termed it "vena alba thoracis".[1]

So, chyle vessels in man were first demonstrated by Pecquet in 1651 on the body of an executed criminal; Pecquet described also the thoracic duct and the cisterna chyli as a lacunar lymphatic structure situated in front of the vertebral column, still known as Pecquet's cistern or "receptaculum chyli".[1,3]

It is to Rudbeck, student at Uppsala, and Bartholinus, professor of mathematics at Copenhagen, that credit is due for having assembled the accumulated pieces of mosaic and recognized the lymphatic system as such.

A very violent dispute regarding the question of priority flared up between Rudbeck and Bartholinus, as unfortunately they worked on the new tiny vessels separately from each other; they accused one another of plagiarism with the question of the lymph

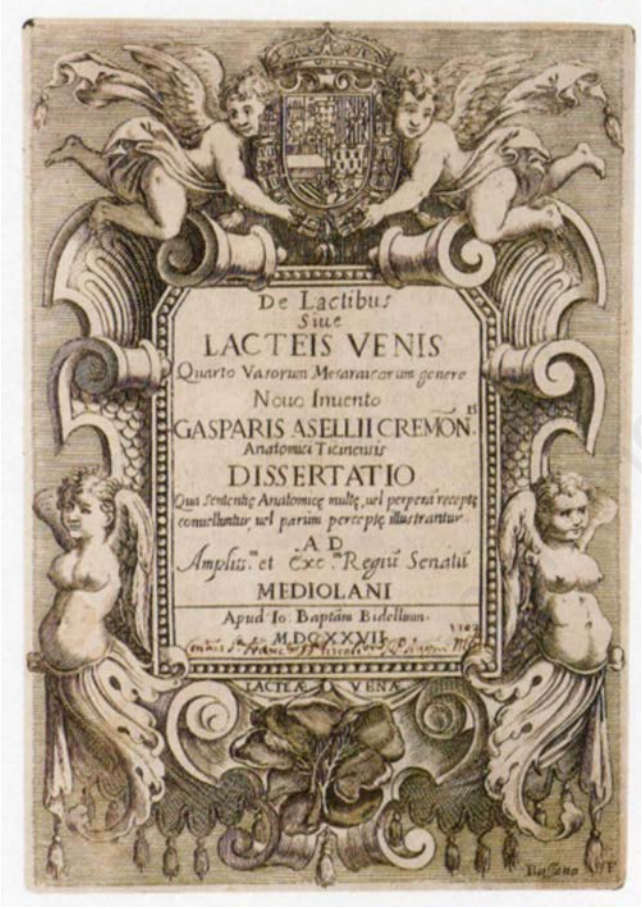


Figure 2. Gaspare Aselli, (1581-1626). Title page of *De Lactibus, Sive Lacteis Veins Quarto Vasorum Mesaraicorum Genere, Novo Invento Gasparis Aselli Cremonensis Anatomica Ticinensis Dissertatio*. Engraved by the Milanese painter and engraver Cesare Bassano (1584-1648) (Published on KOS, by courtesy of Franco Maria Ricci Editore). Immediately following his discovery in 1622, during repeated dog vivisection, Aselli began a systematic study of the course and significance of the chylous vessels. '*De Lactibus Sive Lacteis Venis*' resulted in a remarkable treaty with his findings' report. It was published in 1627, almost two years after his death, in Milan at the press of Giambattista Bidelli through the efforts of Nicolas Fabry de Peiresc by his friends Senator Settala and Alessandro Tadino.

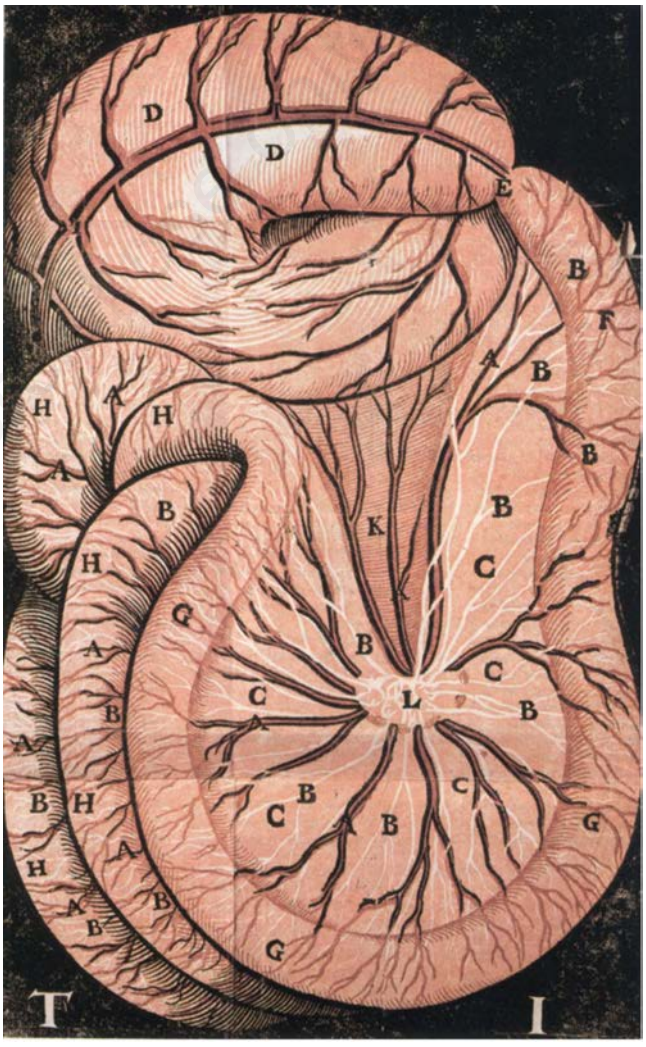


Figure 3. Gaspare Aselli (1581-1626). *De Lactibus*. Table one of four folding chiaroscuro woodcuts printed in black, red, and two shades of brown (Published on KOS, by courtesy of Franco Maria Ricci Editore). In the *De lactibus*, colored illustrations used to more accurately distinguish the different types of vessels depicted were published for the first time in the history of illustrated medicine in the specific interest of the scientific accuracy of the written text.

vascular apparatus as a fluid-conveying system which exists side by side with the arterial and venous systems and its relationship with liver and liver functions (Figure 7).[1]

In his work *De Lacteis Thoracis,* issued in 1652, Bartholinus noticed that the lymphatic vessels running to the liver were not chyle vessels and not emptying themselves in the liver but emerging from it and still though that the liver was the hematopoietic organ *par excellence*.[4,5]

Subsequent investigations convinced him, however, of the incorrectness of this theory and in his following paper *Vasa Lymphatica Nuper Hafniae Inventa,* published in 1653, drawing the proper conclusions he ceased to consider the liver as a center of blood production; but, for the first time, in the title appears the term *vasa lymphatica*, with which we are still familiar.[1]

In 1654, Glisson seems to have been the first to suggest that the lymphatic vessels had a different function, from absorbing the chyle.[6]

Knowing that the contents of the lymphatics joined with the chyle of the thoracic duct, he concluded that the lymphatics could have an absorbent function and serve "to take something from the parts in which they are grafted, undoubtedly a watery mood, as commonly found there".

For more than a century, researchers and clinicians eluded the fictions of this second circulatory system, and adventurous and speculative ideas found a fertile soil in the scanty physiological and pathological knowledge of that age.

It was the progress of methodology which played an important part in the further development of the knowledge concerning the lymphatic system.

A new method in the history of these researches was that of mercury injection, a discovery of Nuck (1692) which made it possible to examine preparations in their connection and to preserve the preparations so injected; this technique of injection in conjunction with dissection of human cadavers produced detailed and accurate anatomical studies on the topography of lymph vessels (Figure 8).

The studies of Nuck facilitated the fundamental works of William Hunter and his brother John (1762), his pupil Cruikshank

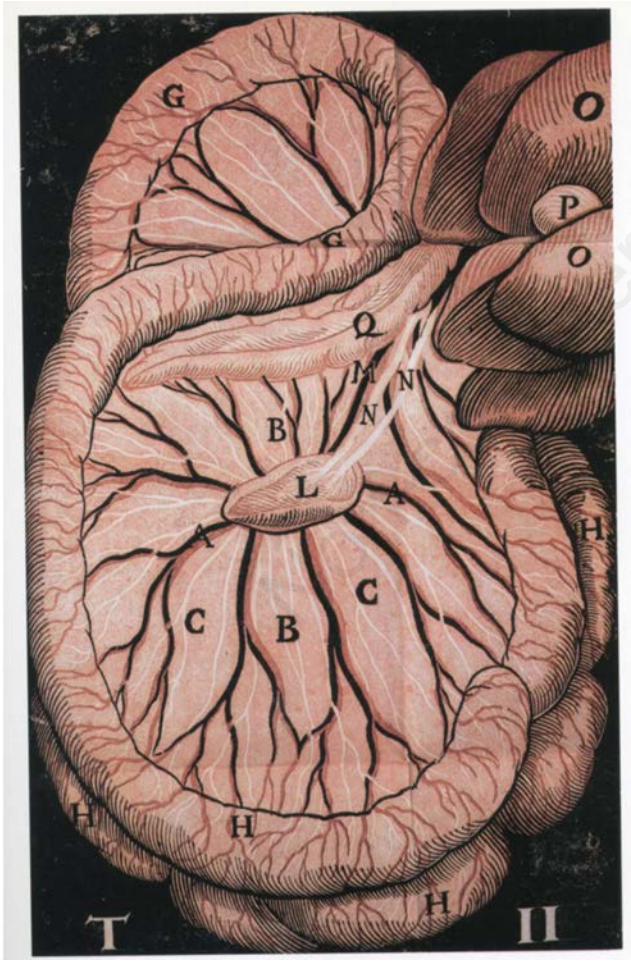


Figure 4. Gaspare Aselli (1581-1626). *De Lactibus*. Table two of four folding chiaroscuro woodcuts printed in black, red, and two shades of brown (Published on KOS, by courtesy of Franco Maria Ricci Editore). As appears in the original *De Lactibus* edition and in few others, the striking woodcuts, have been attributed either to Cesare Bassano or to his associate Domenico Falcini.

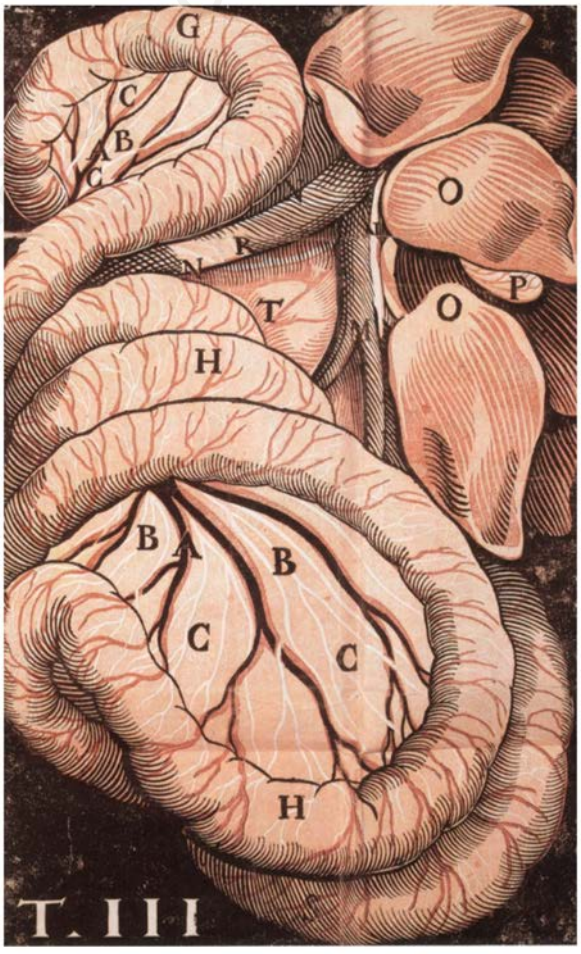


Figure 5. Gaspare Aselli (1581-1626). *De Lactibus* Table three of four folding chiaroscuro woodcuts printed in black, red, and two shades of brown (Published on KOS, by courtesy of Franco Maria Ricci Editore). In 2023, at the Danish antiquarian booksellers market, the first fine copy edition of *De Lactibus* with anatomical illustrations printed in color and dated 1627 was sold for over 100.000 €.

(1789) and, above all, Mascagni, eminent *In Regio Senarum Lyceo Publico Anatomes Professore* (1787).[1,7-9]

In his last anatomy class, William Hunter claimed to have proven "that only the lymphatic system absorbs, not the veins, and that it serves to collect and channel whatever is produced - or to mix it with blood - from the skin, intestinal canal and any cavity and surface".[1,7]

Hunter had in mind a wide range research on the lymphatic system, but he had died before he could accomplish it.

During their investigations, the researchers injected the lymphatics in all parts of the human body, and the masterfully illustrated tables they derived from their experiments are still appropriate. But to indicate the superiority of Mascagni's portrayal of lymphatic network, is of particular interest to remind his method of investigation: he injected mercury into the peripheral minute lymphatic vessels with finely drawn-out glass cannulae, but kept the bodies to investigate immersed in warm water both to prevent hardening of the lymphatic vessels and to favor the progression of contrast medium, due to dilation of the mercury.[10,11]

The preparations of the Hunter brothers still survive at the Anatomy Museum, The Hunterian in Glasgow, and at the Hunterian Museum in London in the buildings of The Royal College of Surgeons; the plates of Mascagni from his monograph *Vasorum Lymphaticorum Corporis Humanis Historia Et Ichonographia* (1787) all remain amazing witnesses of the detailed knowledge which were acquired.[1]

The importance of the lymphatic absorption system in relation to the pathology of the body was increasingly emphasized. Scientists began to think also that toxic substances and infections were caught at the level of the lymphatic glands - whose removal could produce healing -, and they ended up thinking that the glands were intermediate stations through which infections would then spread to the rest of the body.

As for our particular context, during a period of approximately seventy years (1760-1830) after the specific pathological examination of diseased organs and tissues became a science thanks to the contribution of its Italian founder Giovanni Battista Morgagni - so called "His Anatomical Majesty" -, the study of the gross pathology of tumours was carried on largely by some outstanding surgeons as in France (Le Dran and Laennec), and in England (John Hunter – the younger brother of William –, Hodgkin, and Cooper).[1,12]

As they became good clinical diagnosticians of the external forms of cancer, as skin, breast, and others, warmly advocating their local surgical excision, the progress made in the description and classification of cancer far outweighed all that had been gained since the beginning of history of tumors.

In this context, Morgagni correlated, as best he could, the clinical record with the autopsy findings, in an effort to explain the cause of death anatomically. Unfortunately, he showed a serious lack in understanding cancer namely the fact that he knew nothing of the process of metastasis, so the French surgeon Le Dran was probably the first to believe that the lymphatic vessels were responsible for the spread of cancerous forms. Le Dran was considered "The Most Enlightened Cancer Surgeon of the Eighteenth Century".[13]

In a rare 1882 copy of Gustav Jacob Henle's treatise on general anatomy, I have found a direct source of the state of the art of the time on the lymphatics.[14]

Henle thus commented on the ways of highlighting this system of channels: "The ordinary means that work to make them evident do not allow to fill them with mercury without resorting to violence or without offending the parties. The cannula is randomly introduced into the skin and into the cellular tissue; it happens first a sprain, after the trunks of the lymphatics are filled as often happens for some accident, following an extravasation of blood".

Moreover, it confirmed their function as absorbing structures and intuited how the lymphatic network can rightfully play an important role in receiving and transporting pathological elements.

"This capillary lattice seems to immediately soak in the liquid that surrounds them. The fluid contained in the lymphatic vessels and that which soaks the interstices of the organs and the serous cavities are identical. As the lymphatic vessels take over the blood plasma, they form a necessary link in the chain of circulation. The first admission of lymph, for example in the lymphatic root is a purely physical act; but the propulsion that occurs there is the result of a vital action."

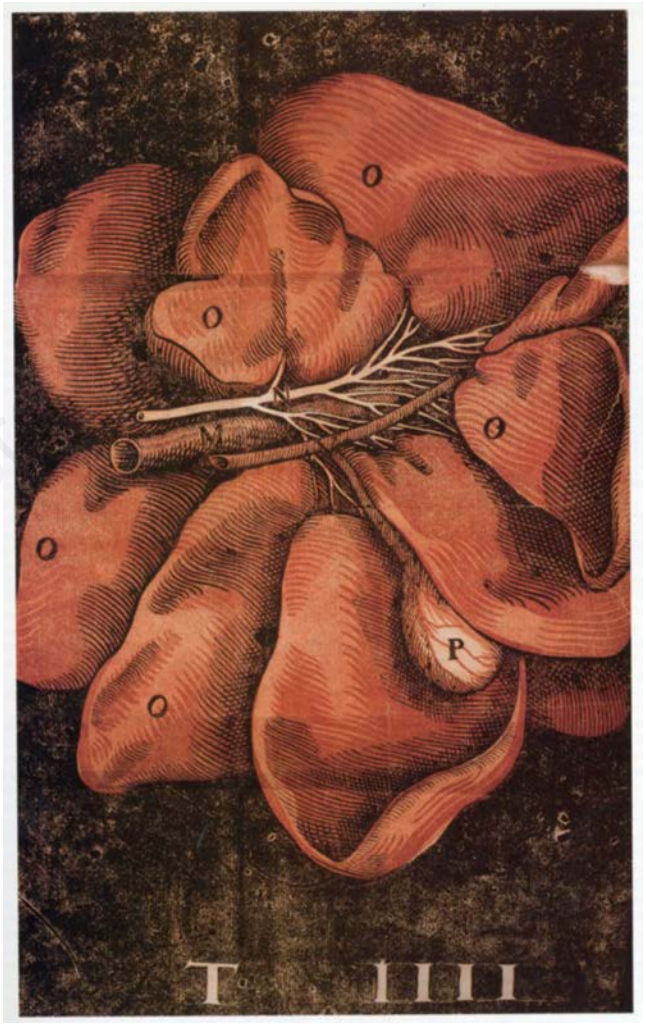


Figure 6. Gaspare Aselli (1581-1626). *De Lactibus*. Table four of four folding chiaroscuro woodcuts printed in black, red, and two shades of brown (Published on KOS, by courtesy of Franco Maria Ricci Editore). Medical historians believe that Aselli wrote in a more dynamic manner and with greater physiologic insight than his predecessors, whose approach had been essentially teleologic and descriptive. Within the antique market of rare books, it appears that Aselli's work was reprinted in Basel in 1628, in Leiden in 1640, and in Amsterdam in 1645. In the later editions, the illustrations were reduced in size and printed in black only from copperplate engravings.

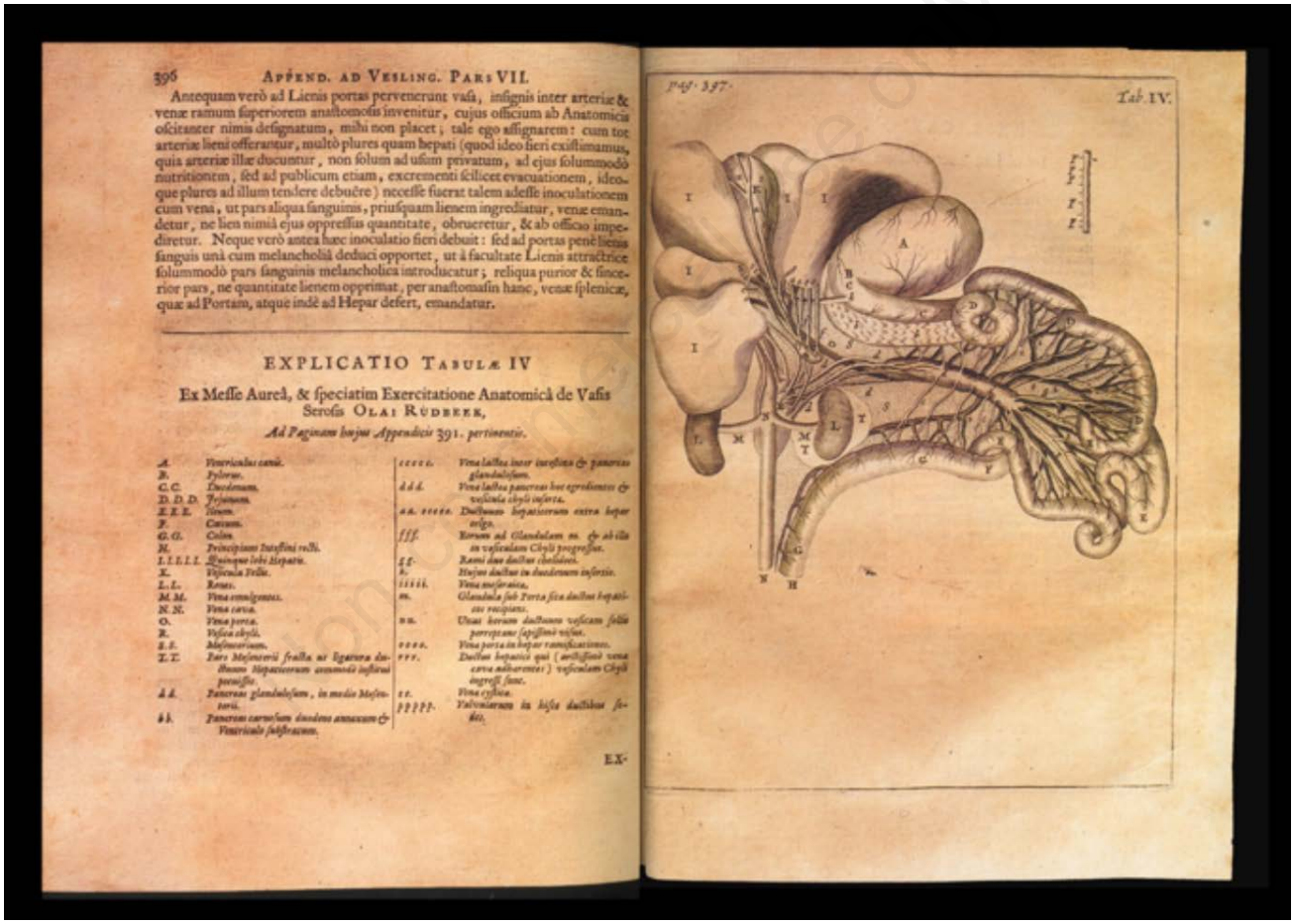
And, he finally stated that "there is no doubt that the lymphatics absorb, the swelling and inflammation of the lymphatic glands that receive their trunks from inflamed parts, are irrefutable evidence in favour of the absorption of lymphatics".

This can serve as proof of how the nineteenth century enlisted many passionate about the art of revealing the gross and microscopical anatomy of entire lymphatic system in details; any discovery will be useful in future in interpreting the mechanisms of lymphatic dispersion of cancer cells.

And indeed, in 1896 Starling was able to demonstrate the first proof that lymph is formed from the blood by filtration through the blood capillary membrane, having understood that the blood capillaries leak protein; and the lymphatics return most of it to the blood; and either direction or rate of fluid transfer depend upon hydrostatic pressure in the blood capillaries and the osmotic pressure of the plasma proteins, respectively.[15]

In any case, however, the outstanding leader in this field was Philibert Constant Sappey, professor of anatomy and president of the Académie Nationale de Médecine in *Paris*, who carried out a long series of investigations of the lymphatics, using adult cadavers. By injections with mercury and an improved technique, he had the merit to complete our knowledge of the peripheral lymphatic capillary networks and the lymphatic pre-collecting and collecting ducts and lymph nodes, demonstrating the complementary nature of the lymphatic system with respect to the blood vascular system and, above all, their important role in neoplastic diseases.[16]

Other clinical and anatomical investigations were the focus of the studies of Poirier (1909), with particular reference to the changes in the regional lymphatic organs in cancer of the tongue, and Rouvier (1932), in his classical text on the anatomy of the lymphatic system.[17]



396 APPEND. AD VESLING. PARS VII.

Antequam verò ad Lienis portas pervenerunt vasa, insignis inter arteriæ & venæ ramum superiorem anastomosis invenitur, cujus officium ab Anatomicis oscitanter nimis defignatum, mihi non placet; tale ego assignarem: cum tot arteriæ lieni offerantur, multò plures quam hepati (quod ideo fieri existimamus, quia arteriæ illæ ducuntur, non solum ad usum privatum, ad ejus solummodò nutritionem, sed ad publicum etiam, excrementi scilicet evacuationem, ideoque plures ad illum tendere debuêre) necesse fuerat talem adesse inoculationem cum vena, ut pars aliqua sanguinis, priusquam lienem ingrediatur, venæ emandetur, ne lien nimiâ ejus oppressus quantitate, obrueretur, & ab officio impediretur. Neque verò antea hæc inoculatio fieri debuit: sed ad portas penè lienis sanguis unà cum melancholiâ deduci opportet, ut à facultate Lienis attractrice solummodò pars sanguinis melancholica introducatur; reliqua purior & sincerior pars, ne quantitate lienem opprimat, per anastomosin hanc, venæ splenicæ, quæ ad Portam, atque indè ad Hepar defert, emandatur.

EXPLICATIO TABULÆ IV

Ex Messe Aureâ, & speciatim Exercitatione Anatomicâ de Vasis Seroſis OLAI RUDBECK,

Ad Paginam hujus Appendicis 391. pertinentis.

A.	Ventriculus cani.	*ccccc.*	Venæ lacteæ inter intestina & pancreas glandulosum.
B.	Pylorus.	*ddd.*	Venæ lacteæ pancreas hoc egredientes & vasculum chyli inferta.
C.C.	Duodenum.	*eee. eeeee.*	Ductuum hepaticorum extra hepar origo.
D.D.D.	Jejunum.	*fff.*	Eorum ad Glandulam m. & ab illa in vasculum Chyli progressus.
E.E.E.	Ileum.	*ggg.*	Rami duo ductus choledochi.
F.	Cæcum.	*h.*	Hujus ductus in duodenum insertio.
G.G.	Colon.	*iiiii.*	Vena mesaraica.
H.	Principium Intestini recti.	*m.*	Glandula sub Porta sita ductus hepatici recipiens.
I.I.I.I.I.	Quinque lobi Hepatis.	*nn.*	Usus horum ductuum vesicam fellis peregrinæ supplisse visus.
K.	Vesicula Fellis.	*oooo.*	Vena porta in hepar ramificatione.
L.L.	Renes.	*rrr.*	Ductus hepaticus qui (multisidâ vena cava adhærente) vasculum Chyli ingressi sunt.
M.M.	Vena emulgentes.	*ss.*	Vena cystica.
N.N.	Vena cava.	*ttttt.*	Valvulæ in hisce ductibus sitæ.
O.	Vena porta.		
P.	Vesica chyli.		
Q.Q.	Mesenterium.		
T.T.	Pars Mesenterii fralla ut ligatura ductibus Hepaticorum communis inserui potuisse.		
d.d.	Pancreas glandulosum, in medio Mesenterii.		
b.b.	Pancreas carnosum duodeno annexum & Ventriculo subjectum.		

EX-

Figure 7. Olof Rudbeck (1630-1702). Table taken from *Nova exercitatio anatomica in Joannis Vestling, Syntagma anatomicum* (Published on KOS, by courtesy of Franco Maria Ricci Editore). Note in Explicatio Tabulae IV, the references to the *Vene Lacteae* marked by the letters *ccccc* and *ddd* which indicate them in the table on the right side of the image. Olof Rudbeck the Elder, Swedish botanist and physician, architect, educator, composer and gifted with a strong singing voice, is one of Uppsala University's most outstanding and eclectic figures throughout the centuries. The young Rudbeck realized what has been called 'the first scientific discovery by a Swede', the lymphatic system and the circulation of lymphatic fluid in the human body. A Danish scientist, anatomist and mathematician, Thomas Bartholin had made roughly the same discoveries at the same time, and the two naturally disagreed about which one of them had been first. At any rate, Rudbeck had performed a scientific feat and as a young man made a name for himself among the learned in Europe. In 1660, he was appointed as one of the chairs of the Faculty of Medicine in Uppsala (at that time, there were only two). In the early 1660s he had the Theatrum Anatomicum built as an anatomical theatre for dissections of human cadavers.

There is still reason to be grateful to all those lymphatic-obsessed dreamers, to their rivalries and their irrepressible need to unravel the mysteries that motivate all scientific endeavors. It was really an honor to get their work out of the darkness and bring it back to the light.

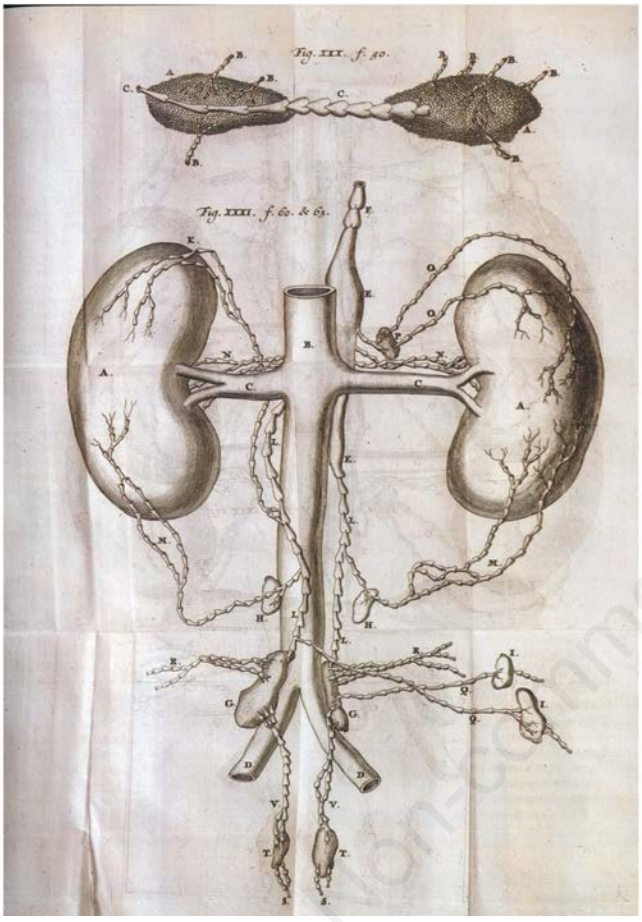


Figure 8. Anton Nuck (1650-1692), also called Antonius Nuck van Leiden. Table taken from *Adenographia curiosa et uteri anatome nova,* Lugduni Batavorum [Leiden]: Apud Jordanum Luchtmans. The first edition is dated 1691. (Published on KOS, by courtesy of Franco Maria Ricci Editore). This figure is one of 9 folding engraved plates. Note the quality of the *adenographia* of the numerous structural components of the lymphatic system, including lymphatic capillaries, afferent lymphatic vessels, lymph nodes, efferent lymphatic vessels, and various lymphoid organs. The one-way valves of the collecting lymphatic vessels are represented in an amazing manner. Anton Nuck, professor of anatomy at Leiden, was distinguished for his investigations of the glands and lymphatics. He also described the inguinal canal, called after him the "canal of Nuck." His treatise was also recognized as a milestone in obstetrics and gynecology: he first described the lymphatic network of the ovary and provided the experimental ligature of uterine horns after copulation in dogs, observing pregnancy afterward, implantation having taken place above the ligature itself. The value of a rare first copy of the *Adenographia* is currently close to 2.000 €.

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