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A forgotten debate in the history of medicine: vascular anastomoses, from open functional relationships to tight structural connections

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Abstract. According to current anatomical nomenclature, vascular anastomoses are direct connections between blood vessels. The Greek word '*anastomōsis*' means 'opening' and conveys the idea of 'patency' rather than 'connection'. *Anastomōsis*, and the related term *sunanastomōsis*, originally referred to a mere approximation of the mouths of adjacent blood vessels – especially arterioles and venules – facing each other at their terminal ends. These vessels were not strictly connected and did not form anatomical units in the proper sense. Over time, however, the term *anastomōsis* underwent a significant semantic change and now denotes a closed, structured anatomical connection. How and when did this semantic shift occur? The aim of the present study was to evaluate the concept of *anastomōsis* in different historical periods from Antiquity to the Seventeenth century and to investigate how this entity gradually lost its original meaning of mere functional opening to acquire the notion of true anatomical structure.

Keywords: modern anastomosis, anatomy, physiology, history.

INTRODUCTION

Vascular anastomoses are direct connections between blood vessels (Standring, 2005). The term implies a state of structural, physical continuity between the vascular components involved. Anastomoses can be divided into arteriovenous anastomoses, anastomoses between arteries and anastomoses between veins. Arteriovenous anastomoses occur between smaller arteries and veins, with no capillary section between them. Connecting vessels may be straight or tortuous, and often have a thick muscular tunic. They are widespread in the body and are most common in the skin of the nose, lips, ears, the nail-beds of the fingers and toes, nasal and digestive mucosa, and erectile tissue. Arteries can also be connected by an anastomosis, allowing to supply the area of the other. An end-to-end anastomosis occurs when two arteries communicate directly with each other. An anastomosis by convergence occurs when two arteries converge and merge. Transverse anastomoses are also described. Anastomoses also occur between veins. They form connecting

channels or lead to venous plexuses. Anastomoses may be macroscopic or microscopic. In any case, they denote direct connections between distinct blood vessels.

Vascular anastomoses have played a crucial role in the history of medicine and science. In Antiquity, as well as in Middle Ages and the Renaissance, according to Galen's teachings, they were assumed to be critical sites for the exchange of material, namely refined blood and *pneuma*, between small, invisible arterioles and venules in the organs of the body. During the sixteenth and seventeenth centuries, anastomoses were considered as the main route for blood passage from the venous to the arterial compartment. In a circulatory perspective, Harvey first conceived of them as one of the two routes by which blood would pass from the veins to the arteries.

The term 'anastomosis' is derived from the Greek word '*anastomōsis*' (ἀναστόμωσις). It means 'opening' and conveys the idea of 'patency' rather than 'connection'. The cognate verb '*anastomoō*' (ἀναστομόω) means 'to provide with a mouth', 'to open', also 'to be opened, dilated'. *Anastomōsis* and the related term *sunanastomōsis* (συναναστόμωσις) were used by the great anatomist and physician Erasistratus of Iulis on Ceos, who lived in the earlier half of the third century BC. According to von Staden, "*Sunanastomōsis* is apparently one of Erasistratus' many neologisms, formed with a characteristically Hellenistic double prepositional prefix" (von Staden, 1975). Aristotle had already used the formula "τῶν φλεβίων ἀναστομωθέντων", to refer the tiny blood vessels that opened on the surface of the skin as a result of intense heating of the body (Aristotle, *De partibus animalium*, III.5, 668b5). Modern scholarship has interpreted ancient *anastomōseis* as closed, continuous structures. They have been equated with capillaries, which are microscopic endothelial tubes directly linking arterioles to venules, or with connecting vascular channels. Harris stated that Erasistratus "seems to have invented rather than discovered the capillary system", and Furley compared the *anastomōseis* to "invisibly small channels" which connected the arteries to the veins at the extremities of both (Harris, 1973; Furley, Wilkie, 1984). This misleading view is no longer tenable. Recently, David Leith has provided textual evidence for a new interpretation of the *anastomōsis* construction in the teaching of Erasistratus. According to Leith's analysis, Erasistratean *anastomōseis* (Galen, *De venae sectione adversus Erasistratum*, 3, K.11.153 = fr. 198 Garofalo, 1988), contrary to what the term would imply according to modern anatomical nomenclature, do not denote the connection and physical continuity between invisible arterial and venous structures but merely involve a proximity of the terminal openings (ἔσχατα στόματα) placed at the extremities (πέρατα) of adjacent arterioles and venules He argues that this minute openings or mouths placed at the extremities of the invisible arteries and veins of the triplokia "are not joined together at their ends, but lie alongside one another in every part of the body" (Leith, 2015). There is thus a small interspace, or *hiatus*, between the adjacent vessels. Erasistratus conceived of the vascular system as consisting of two distinct and separate branches: the *pneuma*-transporting arteries and the blood-conveying veins (ps.-Aristotele, *De spiritu*, 5, 483b28-31, 484a2-3; Lewis, Gregoric, 2015). There were no connexions between the two districts. The *pneuma* flows exclusively in the arterial compartment and the blood in the venous. The two substances never meet and mix under physiological conditions. Arteries and veins originate in the left and right ventricles, respectively. Both kinds of vessels divide and branch again and again to their way to the various organs of the body, gradually diminishing in size and eventually becoming invisible. At their outermost periphery, the subsensible arterioles and venules, perceptible only to reason, lie side by side and next to the invisible nerves, intertwined and embedded in ubiquitous elemental structures called the *triplokia tōn angeiōn* (τριπλοκία τῶν ἀγγείων), the 'triple web' of elastic vessels. The microscopic artery and vein of the *triplokia* terminate with tiny orifices or mouths lying alongside one another (παρακειμένων ἀλλήλοις τῶν στομάτων). Normally, these *stomata* remain closed and the blood is held in the small veins (Lonie, 1964; Harris, 1973; Garofalo, 1988; Vallance, 1990; Vegetti, 1998). When *pneuma* escapes from the arterial district or a plethora condition occurs in the venous system, there is an 'opening' of the *stomata* (*anastomōsis*) at the venous terminations and blood runs rapidly into the arterial conduits. Thus, an 'open' pathway develops between venules and arterioles, which necessarily causes disease. In Erasistratus' theory of the *triplokia*, terminal vessels are not directly joined. They do not form a 'closed', structured anatomical connection. Such a spatial arrangement is expected to imply functional significance. In Erasistratus' doctrine of the *anastomōseis* there seems to be no place for any physiological function, since in the normal state there are no *anastomōseis* at all. In the ordinary condition, the terminal *stoma* of the imperceptible vein of the *triplokia* remains closed and the nourishing blood is poured out in the surrounding *parenchuma* – that is the flesh of the organ – at the side of the vein (κατὰ τὰ πλάγια). Thus, the *anastomōsis* appeared to play a role only in pathology and was closely connected with it. So, we assume that the Erasistratean *anastomōsis* is to be conceptualized not so much as an anatomical structure but as a functional condition.

The term *anastomōsis* then did not initially imply physical continuity between the vessels involved. It was not intended to denote a connecting vascular channel. How and when did this semantic shift occur? In what way did the Erasistratean *anastomōseis* become the modern anastomoses? The aim of this paper was to evaluate the meaning of the concept of *anastomōsis* in different historical periods from Antiquity to the Seventeenth century and to explore how this entity gradually lost its sense of mere functional opening to acquire the notion of true anatomical structure.

THE ANTIQUITY

Around the time of Erasistratus, about the first half of the third century BCE, we have the interesting testimony of the pseudo-Aristotelian author of *De spiritu*. He asserts that the air-ducts (*artēriai*) and the nutriment-ducts (*phlebes*), which extend along the ribs "are connected by contact" (τὰς δὲ φλέβας καὶ τὰς ἀρτηρίας συνάπτειν εἰς ἀλλήλας) and exchange substances, because "the *pneuma* needs the liquid and the liquid needs the *pneuma*" (Ps.-Galen, *Introductio sive medicus*, 9, K.14.697-698; Manetti, 2011; Galen, *De usu partium*, VII.8, K.3.538; *De anatomicis administrationibus*, II.11, K.2.337; *De facultatibus naturalibus*, II.6, K.2.105; *De venae sectione adversus Erasistratum*, 3, K.11.153 = frs. 86, 87, 88, 90, 148, 198 Garofalo; Leith, 2015). In this case, there seems to be a real contact (συνάπτειν) and not a mere proximity between the vessels. The last sentence probably implies a general physiological view of the author and suggests that these connections may be present throughout the human body. Remarkably, the author of this short treatise does not use the word *anastomōsis*, or related terms, to refer to this type of vascular connection. This would suggest that what was called *anastomōsis* did not mean a tight junction by contact of the vessels, but a loose proximity of their endpoints. This seems to be important testimony, because given the general lack of ancient textual accounts, it appears the only one that departs from the teaching of Erasistratus and clearly implies the notion of a close connection between opposing vessels.

In the second century AD, Galen derives the idea of *anastomōseis* from Erasistratus. In his doctrinal system, however, these vascular arrangements acquire new functional roles. They perform a crucial task even under normal conditions, exchanging small quantities of *pneuma* and blood of the finest and purest quality through the orifices of the thinnest, invisible arterioles and venules. In this way, a peripheral relation will be established between arteries and veins, symmetrical to the central one given by the pores in the *septum interventriculare*, and the advantages derived from respiration and pulse would be beneficial not only to the heart and arteries, but also to the veins.

The idea of *anastomōseis* or *sunanastomōseis* – Galen seems to use both terms without any significant difference – came to Galen from the empirical observation that animals slaughtered by severing a major arterial vessel bled out quickly and completely. He interpreted this observation by postulating the existence of *anastomōseis*, or 'openings', between the extremities of the vessels (τὸ πέρας ἀνεστομωμένων τῶν ἀγγείων), veins and arteries (Galen, *De facultatibus naturalibus*, III.15, K.2.207; *De usu pulsuum*, 5, K.5.165; *De methodo medendi*, V.2, K.10.311; Furley, Wilkie, 1984). Blood flows from the venous quarter into the arterial compartment through "small orifices" found at the ends of blood vessels. In *De methodo medendi* (V.2, K.10.311), Galen mentions τὸ στόμιον, "the tiny mouth" of the blood vessel participating in anastomōsis, and the small size of the vessels involved, "δι' ἀναστόμωσιν ἀγγείων μικρῶν". In *De usu partium* (VI.10, K.3.455-456) the Pergamene asserts that arteries and veins "open their orifices" (συνανεστόμωνται) in every part of the body, and exchange blood and pneuma "precisely through certain invisible and narrow passages" (διά τινων ἀοράτων τε καὶ στενῶν ἀκριβῶς ὁδῶν). Galen insists on the concept of the invisibility of these passages (ἀόρατα), which are so small that they "escape sight" and become "subsensible" (Galen, *De usu partium*, VI.21, K.3.510; *De usu pulsuum*, 5, K.5.165; Furley, Wilkie, 1984).

How was the structure of these *anastomōseis* conceived by Galen's doctrine? He leaves the matter somewhat unsettled. This problem is called into question in *De locis affectis (*V.7, K.8.351-352), where Galen describes the intrahepatic arrangement of the vascular branches of the portal vein and the hollow vein (the vena porta and vena cava of the modern anatomical nomenclature). He says that both vessels terminate with very small endings, which arrive at the same places in the liver flesh and form imperceptible *sunanastomōseis*. Indeed – Galen adds – no one doubts that there are invisible passages between these vessels, through which the nourishment conveyed by the portal vein is received by the branches of the hollow vein, being taken up by the very extremities of the latter. Thus the intralobular sinusoidal capillary system (Standring, 2005) was unknown to ancient Greek physicians and conceptualized as consisting of anastomōseis. This point is closely related to Galen's concept of sanguification, that is, the production of venous blood suitable for nourishing the body. As for

his related ideas about the movement of the nutritive blood in the liver, it is sometimes difficult to reconcile the assertions he makes in different places and presents in different contexts for different purposes (Galen, *De usu partium*, IV.3-5 and 12, K.3.269-273 and 298-300). In Galen's physiology, the flesh of the liver is the principal instrument of hemopoiesis and the source of the veins. Both the hollow vein and the portal vein originate in this viscus. The nature of the liver flesh is very similar to coagulated blood. Thus, the juice of the *chyle* absorbed from the stomach is transformed by the *parenchuma* of the organ and gradually converted into mature blood. Whether this process takes place within the hepatic vessels or whether it requires the spread of the *chyle* juice through the liver flesh and its re-entry as mature blood into the thin vessels connected with the hollow vein, Galen did not state openly. The second hypothesis, however, seems to have been favoured by the Pergamene. In *De usu partium* he states that "the veins of the convex part [of the liver] are not connected (οὐ συνάπτονται) with those of the concave part". If their extremities are not joined together there must necessarily be an interruption between their *stomata*. The structure of liver *anastomōseis* is further discussed by Galen in *De facultatibus naturalibus* (II.5, K.2.93-94 = fr. 146 Garofalo). Here, the Pergamene reports a passage from the first book of the *General Principles* of Erasistratus, in which the Alexandrian physiologist speaks of the structural architecture of the common space into which the subdivisions of vena porta conduct the unpurified blood, and from which the bile ducts take the bile, and the branches of vena cava receive the purified blood. Says Erasistratus:

As there are two kinds of vessels opening at the same place, one kind leading to the gall-bladder and the other to the vena cava, it follows that of the nutriment conveyed upwards from the alimentary canal, that part which fits both kinds of *stomata* is received into both kinds of vessels, a part being conveyed into the gall-bladder and the rest passing over into the vena cava. (Galen, *De usu partium*, IV.13, K.3.301)

According to Galen's commentary, it is difficult to say what we are to understand by the words "opening at the same place" (εἰς τὸ αὐτὸ δ' ἀνεστομωμένων*)* which appear at the beginning of the passage. Galen asks whether it is meant that there is either a 'junction' (συνάπτειν) between the end of vena porta and two other vessel ends (biliary and vena cava), or we must suppose that there is, as it were, a common space for all three vessels, which is filled by portal vein, and empties into both the biliary duct and the branches of vena cava. Galen seems to support the latter hypothesis. *Anastomōseis* are openings of the vascular terminal *stomata*. They do not condition a connection by close contact or even continuity of the parts, but the mere proximity of the paired vascular orifices. Galen also uses the cognate verb ἀναστομόω to refer for instance to the dilation of the external uterine orifice and vaginal canal, in a context where the idea of a physical or structural connection is not present (Galen, *De facultatibus naturalibus*, III.3, K.2.150). The verb ἀναστομόω is attested with the same meaning already in the Corpus Hippocraticum (*De natura muliebri* 37, L.7.380.13; *De mulierum affectibus I* 11, L.8.44.1, 13, L.8.50.15; 52.5, 84, L.8.210.4, 89, L.8.214.9; *De mulierum affectibus II* 110, L.8.238.6, 115, L.8.248.23, 116, L.8.252.5; *De sterilitate mulierum* 221, 8.426.9,11,14).

The way in which the intrahepatic veins are connected was described in Antiquity in a mode that suggests the idea of an open type of vascular interaction. Unfortunately, there is much missing in the written medical record between the extant citations from the work of Erasistratus and the work of Galen. We do know that Aretaeus of Cappadocia in the I-II century AD mentions the thinnest, invisible endings of the portal vein, whose orifices in the liver parenchyma "lie together face-to-face" (κατὰ τὸ στόμα ξυγκέονται) with the *stomata* of the inconspicuous, terminal segments of the vena cava (Aretaeus, *De causis et signis acutorum morborum*, II.8). These structures probably correspond to the *anastomōseis* of Galen. As early as the fourth century AD, Oribasius (c.325-400) gives a simplified account of the interaction between the intrahepatic branches of vena porta and vena cava, which seems to depend on that of Galen. However, he does not mention the presence of *anastomōseis* and simply states that the nourishment transported from the digestive tract through the portal vein to the liver is converted into blood and "received back" (αὖθις … μεταλαμβάνεται) by the vein located at the convexity of the organ, called the vena cava (Oribasius, XXV.60). This linguistic formula actually suggests the presence of an open intrahepatic movement of blood. The bishop Nemesius of Emesa lives about the same time as Oribasius (c.340-400). He possesses a profound knowledge of the works of Galen and of ancient Greek medicine. Nemesius makes no mention of intrahepatic *anastomōseis* between the endings of vena porta and vena cava but insists on the close resemblance of the liver parenchyma to coagulated blood and on the property of the hepatic flesh to convert intestinal juice into mature blood (Oribasiusius, *De natura hominis*, vol. XL, ch. 23, col. 696, 25-26). These ideas support the notion that the crude intestinal fluid is poured out of the extremities of vena porta into the liver substance and re-enters the endings of vena cava as mature blood.

Still in the Byzantine Empire, the court physician Theophilus Protospatharius (VII century) writes that the terminal branches of vena porta and vena cava "converge" (συμβάλλουσιν ἀλλήλαις) in the liver parenchyma "through their tiny extremities" (κατὰ τὰς περατώσεις αὐτῶν στενοτάτος οὔσας)(Theophilus Protospatharius, *De corporis humani fabrica*, II.13). "Through these terminals – Theophilus explains – the vena cava receives (μεταλαμβάνει) the purified and concocted blood from vena porta". Since blood preparation – Theophilus clarifies in line of Galen's doctrine – involves a complex process of improvement and refinement of the attracted juice, which includes the elimination of toxic products through the bile ducts, his account supports the view of an open relationship between the intrahepatic venous terminals.

THE MIDDLE AGES

In the Middle-Ages, Greek medical doctrine was transferred to the Islamic world. Accordingly, the notion of the structure of the *anastomōseis* shifted from a Galenic context to a more composite cultural setting. In Islamic medical teaching, the doctrines of Hippocrates and Aristotle were held in high esteem and given equal status to the canon of Galen. This point was also taken up in the theme of the present study. Thus, the spatial organisation of the intrahepatic *anastomōseis* became the subject of different views. In the *Kitāb al-Mansūrī* or *Liber ad Almansorem*, al-Rāzī (died c.925) describes the subdivision of the portal vein into a myriad of tiny vessels distributed throughout the liver parenchyma (al-Rāzī, 1497). Remarkably, these channels look like thin hairs and, in the Latin translation of the Arabic text, "are connected" (*jiunguntur*) to the roots of vena cava, which also have a hair-like appearance. In this way, blood nourishment "moves" (*transeat*) from vena porta to vena cava. Al-Rāzī does not mention the presence of *anastomōseis* and advocates for the first time the concept of a continuous hepatic venous network. He may have been influenced by ancient Hippocratic writings, some of which insist on the idea of a structural continuity in the constitution of the human body, likened to the geometric figure of the circle (*De locis in homine I*, L.6.276.2; *De victu I*.19, L.6.492.24; *De alimento IX,* L.9.102.1; Pormann, Savage-Smith, 2010). On the other hand, Ibn Sinā (d. 1037) in the *Canon of Medicine* seems to support the Galenic doctrine of an open circulation. He states that the small intrahepatic subdivisions of vena porta "run to meet the openings" (*occurrentibus orificijs*) of the roots of vena cava (Ibn Sinā, 1493)(Liber Canonis, book I, fen 1, doctrina 4, ch. 7). Ibn Sinā equates *anastomōseis* with 'constrictions'(*co angustationes*) and maintains that the *chyle* enter them only when mixed with aqueous fluid, which serves as an efficient vehicle. This is the strict doctrine of Galen, the term '*coangustationes*' translating the Greek 'φλέβας στενάς'(*De usu partium*, IV.5, K.3.273). Thus, Ibn Sinā apparently considers the intrahepatic *anastomōseis* as the convergence of the orifices of adjacent blood vessels facing each other at their terminal ends. This concept will play an important role in further discussion about the structure of *anastomōseis* because of the great influence Ibn Sinā exerted on the development of scientific and medical culture in the Latin world of Middle-Ages and Renaissance. The *Canon of Medicine* was destined to become one of the most important books in the academic education of physicians for centuries (Siraisi, 1987). In the Islamic cultural sphere, we find two other relevant figures: Al-Majūsī and Ibn Rushd. In the *Kitāb al-Malīkī* or *Liber regius*, Al-Majūsī (*fl.* c. 983) simply states that the subdivisions of the vena cava "attract the juice of the nourishment" (*attrahunt succositatem cibi*) from the branches of vena porta (Al-Majūsī, 1492). In the *Book of General Principles* or *Colliget*, Ibn Rushd (d. 1198) writes that hairy subdivisions of the portal conduit "meet" (*obviatur*) the hairy branches of vena cava (Ibn Rushd, 1482). The *chyle* nourishment is pooled in the branches of the portal channel, concocted in the hepatic *venae capillares*, and then leaves the liver through the roots of the vena cava. We are dealing here with a closed conception of hepatic movement. The *chyle* does not have to be poured out into the liver flesh to be converted into blood but remains in the very thin intrahepatic vessels. Ibn Rushd was a highly praised scholar of Aristotle. One of the most distinctive teachings in Aristotle's biological canon was that blood has its natural place in the vessels and always flows in them, otherwise it putrefies (*Historia animalium*, III 2, 511b1; *De partibus animalium*, III 4, 665b13). Thus, Arab physicians and scholars have taken a variety of positions on the question of *anastomōsis* structure, possibly reflecting the different reception of ancient doctrines.

In the Western world, with the establishment of the early *studia* of academic medicine, we witness the rise and development of a lively debate on the nature of *anastomōseis*. Towards the end of the thirteenth and beginning of the fourteenth century, Petrus Turisanus (died c.1320), the pupil of Taddeo Alderotti, the author of the most important and influential fourteenth-century commentary on Galen's Tegni (technē iatrikē, Ars medica) and one of the most influential representatives of Scholastic medicine, wrote that arteries and veins

exchange blood and spirit through "aperture of invisible mouths" (*apertione orificiorum occultorum*) placed throughout the body. In this way, the arteries convey the spirit to the veins, and equally receive the blood through "strict and invisible passages" (*ex vijs strictis, latentibus visum*)(Turisanus, 1557). In these words Turisanus seems to have correctly interpreted the meaning of Galen's *anastomōseis* or *sunanastomōseis*, but when we move on to examine his notion of intrahepatic *sunanastomōseis* we find that he supports the concept of a close structural continuity in the hepatic vein architecture. He writes that the *vena chylis* (vena cava) reaches the convexity of the liver from the right cavity of the heart and then branches into countless divisions throughout the liver substance (Turisanus, 1557). At the concavity of the organ these veins unite into a single vessel called the vena porta. The organisation of the hepatic veins thus appears to be that of an uninterrupted system of conduits. Turisanus does not mention liver *sunanastomōseis* at all.

On the other hand, we find Peter of Abano (c.1257-1315), the eminent physician, philosopher, astronomer and astrologist of the same age, writing at the beginning of the fourteenth century that:

When the *chyle*, attracted by meseraic veins, reaches the thinnest branches of vena porta, it runs to meet (*occurrit*) the finest divisions of vena cava. The lower ramifications [of vena porta] saturate (*imbibunt*) the orifices (*orificia*) of the vein and impregnate (*potant*) the small branches of the upper vein [the vena cava]. In this way everything touches everything and more efficient digestion takes place by contact. The moistening power of the liver converts the chyle into blood by means of its instrument, heat (Peter of Abano, 1526).

Thus, unlike Turisanus, Peter of Abano supports the view of an open intrahepatic *chyle*-blood movement. Nourishment seeps out of the terminal openings of vena porta into the liver parenchyma and is converted into blood. This in turn infiltrates the fine roots of vena cava and is transported throughout the body. Between the finest ends of vena porta and the thinnest roots of vena cava there appear to be small interstices. Galen's doctrine of the hepatic *sunanastomōseis* is well present in this mediaeval account. Professor in Paris and Padua, the Aponensis knew Greek and Arabic very well. He spent many years in Constantinople and Near-Eastern countries, and had direct access to ancient Greek sources and Arabic translations. He displays a highly developed, exquisite philological skill. Thus, Peter of Abano interprets the spatial arrangement of Galen's *sunanastomōseis* as that of discontinuous structures.

Mondino de' Liucci (c.1270-1326), another student of Taddeo Alderotti, on the other hand, in his *Anothomia* of 1316, affirms Turisanus' concept of a continuity in the structural architecture of the hepatic veins. He neglects the liver *sunanastomōseis* and states that the lobes are formed by separate and scattered veins distributed in the liver substance "like a net" (*ad modum retis*); the space intermingled within the vascular texture is filled with the substance of the liver (Mondino de' Liucci, 1494). The double sets of hepatic veins thus appear to form continuous vascular channels producing a reticular structure. This position is also held by Henry de Mondeville (c.1260-1320), surgical anatomist at Montpellier, who makes no allusion to hepatic *sunanastomōseis* and describes the course of liver veins in essentially the same terms as Turisanus uses (Henry de Mondeville, 1892). Both Mondino and Henry de Mondeville advocated a pragmatic approach to medical issues and actively participated in the practise of human dissection, which began to develop in the academic medical *studia* in the first decades of the fourteenth century (Siraisi, 1990; Carlino, 1994).

In the second half of the fourteenth century, in the late Middle-Ages, the Italian philosopher and physician Jacobus Foroliviensis (Jacobus della Torre) (c.1364-1414) portrays an open organisation of intrahepatic blood flow. He is the representative of a more theoretical and philosophical approach to scientific problems. In the *Expositio et quaestiones in primum canonem Avicennae*, he writes that food enters the invisible channels (*per poros insensibiles*) of *vena chylis* after being excreted from the invisible *capillares* of vena porta, like seeping sweat (*resudando*)(Jacobus Foroliviensis, 1547). Professor of logic and medicine at the universities of Padua, Bologna, Ferrara and Siena, Jacobus was well acquainted with Arabic medical literature and Ibn Sinā's reception of Galen's work.

THE RENAISSANCE

In 1502, Gabriele Zerbi (c.1445-1505), professor of medicine and logic at the universities of Bologna and Padua, writes that "the branches of vena porta ascend toward the convex part of the liver and run to meet (*occurrunt*) the subdivisions of vena cava, which arises in the convex part of the liver. Its branches descend to encounter (*descendunt et obviant*) the branches of vena porta" (Zerbi, 1502). Zerbi's position is ambiguous. He does not openly admit that there is a structural connection between the two sets of veins in the liver parenchyma. He does, however, assert that these vessels "meet" or "encounter" each other. In this way, he seems to acknowledge Galen's intrahepatic *sunanastomōseis* as

a kind of continuous structure. In 1523, the Bolognese professor of anatomy and surgery Jacopo Berengario da Carpi (c.1470-1530), in his *Isagogae breves*, seems to explicitly advocate the concept of a close, structural connection between the hepatic branches of vena cava and vena porta. He states that "the thinnest branches of vena cava are joined or united (*coastomantur seu uniuntur*) with the branches of vena porta" (Berengario da Carpi, 1523). Here there is no simple opening of minute orifices between the smallest extremities of the hepatic veins but a true anatomical union. This view is accepted by the Venetian physician and anatomist Nicolaus Massa (1485-1569), who in 1536 claimed that "the thinnest branches [of *vena chylis* or vena cava] are actually united (*uniuntur de facto*) with the branches of vena porta" (Massa, 1536). Massa's assertion is strengthened by the addition of the locution '*de facto*' to '*uniuntur*'. He also provides experimental support for his statement. For, after soaking and boiling liver preparations – he explains – the tissue substance is easily detached from the veins; in this way the complex venous network of the liver parenchyma becomes clearly visible. With Massa we again encounter the concept of the hepatic venous network conceived by Mondino, which implies the existence of a continuous structural connection between the terminal branches of vena porta and vena cava.

We now come to a fundamental step in the development of the concept of anastomoses as closed, continuous structures. Following the model conceived by Berengario and Massa, Andreas Vesalius (1514-1564), in the 1543 edition of *De humani corporis fabrica*, adopts the idea that those subdivisions of vena cava which extend into the liver turn towards the branches of vena porta. In this way, the minute branches of both veins "close tightly together by small orifices" (*osculis inter se connivent*)(Vesalius, 1543). Accordingly, the extremely small vessels which form the roots of vena cava, receive (*transsumant*) the blood produced by the liver in the branches of vena porta and transport nourishment throughout the body. In the second edition of the *Fabrica* of 1555, Vesalius adds this phrase: "and in many places they [the extreme branches of vena porta and vena cava] meet (*congredi*) and unite as continuous structures (*continuari*)" (Vesalius, 1555). Vesalius' passage is crucial because he postulates, with all the force of his authority, the existence of tightly coupled orifices (*oscula*) that structurally connect the terminal subdivisions of vena porta with the terminal segments of vena cava. These *oscula* allow the establishment of a continuous, uninterrupted vascular organization. The word '*oscula*' supersedes the terms *anastomōseis* or *sunanastomōseis* and will become increasingly important in the future history of these entities. The old Greek terms seem now apt to acquire the meaning of a structural union.

Despite Vesalius' theorem, the questions of the mutual relationship between the venous segments in the liver parenchyma and the structural nature of hepatic anastomoses were still the subject of debate among anatomists around the middle of the sixteenth century. Humanistic medicine experienced an increasing revival in the first half of the sixteenth century thanks to the work of scholars, translators and book publishers, who made Galen's writings more widely available, and in a more complete and accurate form than before (Bylebyl, 1979). In addition, the recovery of the original Greek text of Galen's treatise *De anatomicis administrationibus* gave anatomy a whole new significance in academic medicine. Matthaeus Curtius' approach to the problem is much more cautious. Curtius (c.1475-1542) was a Galenist of strict observance and the prototype of the humanistic physician. In his *In Mundini Anatomen Explicatio* of 1550, he raises the question whether "the veins supplied by the vena porta are connected (*iungantur*) with those which proceed from vena cava" (Curtius, 1550). There is uncertainty (*dubitatio*) – he says – whether the *capillares venae* derived from the two principal veins would join together (*iungantur inter se*) in the liver flesh, so that what is contained in the former is conveyed into the latter. It is indeed clearly evident that the nourishment attracted by the portal vein flows in the *capillares venae* and passes through them into the vena cava. This may be done – Curtius explains – in two ways. Either there is a direct connection between the ends of the capillary veins (*venae capillares simul iungantur*), or, if the veins are not connected (*venae quidem non iungantur*), the nourishment is poured indirectly through the spongy flesh in the liver (*per porositates iecoris*) into the capillaries of vena cava. Curtius then quotes Galen's passage from *De locis affectis*, and concludes that "it is not possible to deduce from Galen's words whether [the veins in the liver] are reciprocally connected or not". This conclusion is taken up by the pupil of Realdo Colombo, the Spanish anatomist Juan Valverde de Hamusco (born c.1525), who in 1559 states that the blood passes from vena porta into vena cava "either by union (*congiungendosi*) of the heads of one root with the heads of the other root, or by percolation (*risudando*) of the blood into the substance of the liver and then into the roots of the great vein" (Valverde de Hamusco, 1559).

In 1571 Andrea Cesalpino (1524/25-1603) published his *Quaestiones Peripateticae*. According to the Aretine philosopher and physician, the blood moves from the arteries to the veins through abundant reciprocal '*oscula*' which "the ancient Greeks called anastomoses" (*Graeci*

Anastomosim vocant). These *oscula* are distributed all over the body, not only in the pulmonary vessels but also in the systemic blood vessels. "Everywhere – he writes – veins are connected with arteries" (Cesalpino, 1571). These small orifices (*oscula*) – he adds – are present all along the course of the veins and arteries (Cesalpino, 1571). He does not dwell on the exact architecture of such *oscula*, but it is clear from his description that he regards them as true anatomical constructions, involving a structural continuity of parts. This may be regarded as a consequence of Cesalpino's natural philosophy. He was, in fact, an intransigent Aristotelian, and maintained, in accordance with the Stagirite doctrine, that blood was to be found only within the heart and vessels. Outside the vessels – he argued – no blood was conceivable. This implies a close union of the *oscula* to prevent the escape of blood from the vessels. This point is clearly recognised in the section dealing with the hepatic vascular system. Here Cesalpino states that there are invisible "connections" (*nexus*) between vena porta and vena cava (Cesalpino, 1571). The overall structure, however, is that of a continuous venous network. Galen was mistaken – proclaims Cesalpino – when he considered the relationship between the last branches of vena porta and vena cava to be discontinuous. Cesalpino provides an attractive explanation that accounts for Galen's error. In Galen's experiments, animals were not killed by strangulation, as previously recommended by Aristotle, so that the connection of the hepatic veins was consequently lost. Thus, Galen's *sunanastomōseis* were discontinuous, interrupted structures. On the other hand, in Cesalpino's opinion blood always flows within the vessels. If it drips out of the vessels, it is inevitably subject to putrefaction or agglutination (Cesalpino, 1571). It is impossible, therefore, for the blood of the liver to escape from the veins and re-enter them. The hepatic veins, therefore, consist of a continuous vascular system. This can be clearly seen in accurately washed liver specimens when the blood has been completely removed: an extremely fine texture of the vascular networks (*veluti retis*) is observable.

In 1593 Cesalpino published the *Quaestiones Medicae*, together with the second edition of his *Quaestiones Peripateticae*. In this work, Cesalpino formulates interesting claims. He states that during sleep and in the course of arm ligature, much blood flows from the arteries to the veins through the *oscula*. In particular, he says that in this last condition, "the veins are so much connected (*adeo copulari*) with arteries through *oscula*, that as soon as the vein is cut, the darker venous blood gushes out first, than the more brilliant arterial blood" (Cesalpino, 1593). Here Cesalpino vividly describes a so-called thought experiment (*per imaginationem - Gedankenexperiment*). Venous blood never becomes arterial and always keeps its dark colour. However, Cesalpino's assertion underscores the role he attributes to the *oscula* that connect the arteries to the veins. In summary, Cesalpino conceptualises anastomoses as real, continuous anatomical structures through which blood flows from arteries to veins.

A further chief contribution to the shaping of a new concept of anastomoses was made by the anatomist Arcangelo Piccolomini (1525-1586). Piccolomini died in 1586, when his *Anatomicae Praelectiones*, a rich collection of original anatomical observations, were published. In the chapter devoted to the structure of the liver, in describing the distribution and behaviour of the branches of vena porta and vena cava, he writes:

Both in raw and cooked livers of larger animals, in which everything is more clearly seen than in smaller ones, I have looked very carefully for connections and adhesions of their [the veins] extremities, but still I have never been able to detect them. The roots of both veins are indeed scattered over the substance of the liver without any order, and in many places they do not come into mutual contact (*sese non tangunt*). But when the roots touch (*se tangunt*), it is not along a longitudinal axis, but along a transverse plane. In this way they are seen to form right angles. Indeed, so many roots of vena porta do not penetrate (*infigunt*) with their extremities into the terminal points of vena cava, but into the middle parts of its roots. Similarly, the numerous roots of vena cava, with their terminal segments, do not enter (*infigunt*) into the terminal points of vena porta, but into its roots in the middle parts. In this way the blood flows from the roots of vena porta to the roots of vena cava (Piccolomini, 1586).

He also asserts that the blood is produced in the ultimate branching segments of vena porta, because they are exceptionally more numerous and sensitive than those of vena cava. In summary, Piccolomini contends that (i) there are no mutual end-to-end connections between the branches of vena porta and those of vena cava; (ii) the junctional attachment between these vessels does not run along their longitudinal axes; and (iii) the chyle does not emerge from the roots of vena porta in the liver parenchyma to be absorbed by the roots of vena cava once it has been converted into blood. He strongly maintains that the link between the two sets of veins occurs by means of connections which run along transverse axes. Piccolomini calls these connections "anastomoses of the roots" (*harum radicum anastomoses*), or "kisses" (*exosculationes*) between vessels, or "openings from the one to the other" (*ex alterutris in alteras apertiones*)(Piccolomini, 1586). Remarkably, he improves his

textual account with an instructive figure sketching the course of vena cava, vena porta, their branches, and root extremities. This drawing depicts some terminal segments of vena cava entering the middle of some of the roots of vena porta, as well as some terminal segments of vena porta entering the middle roots of vena cava. The caption defines these short connections as "insertions and anastomoses" (*insertiones et anastomoses*). Three conclusions can be drawn from Piccolomini's illustration. They are of overriding importance for the conceptual shift of anastomoses from purely functional states to genuine structural entities. Thus, according to Piccolomini, i) the term anastomoses denotes proper anatomical arrangements involving continuity of parts. Moreover, ii) anastomotic vascular connections are not end-to-end but end-to-side connections. Finally, iii) Piccolomini's doctrine implies, in contrast to Galen's assumption, that anastomoses are not merely invisible, imperceptible structures that elude the gaze and can only be theoretically surmised by the eye of reason, but well-documented and observable vascular pathways. It is difficult to say what Piccolomini actually observed in his experimental studies because in the human liver and in the liver of mammals there are usually no end-to-side or other types of visible connections between the branches of the vena porta and the roots of the vena cava. Modern imaging techniques have shown that multiple intrahepatic communications between the branches of the porta and hepatic veins are rare disorders. Interestingly, they occur more frequently in the right lobe of the liver. Most often, they are congenital defects, but acquired intrahepatic portosystemic shunts resulting from trauma or portal hypertension have also been described (Park et al., 1990; Corness et al. 2006). William Harvey, as we will see in the next section, openly admitted that he was unable to recognize anastomoses in the liver, although he spent much time and effort trying to find them. Anyway, Piccolomini's theoretical contribution was fundamental in shaping the modern concept of anastomoses.

THE SEVENTEENTH CENTURY

The seventeenth century begins with a fundamental contribution to the disclosure of the structure of anastomoses by the Swiss anatomist, physician and botanist Caspar Bauhin (1560-1624), professor of practical medicine at Basel. In 1605 he published a first-rate book, *Theatrum Anatomicum*, in which he supports Piccolomini's conception of hepatic anastomoses as a continuous connection between the roots of vena porta and those of vena cava (Bauhin, 1605). Specifically, the roots of both veins join along a transverse plane of incidence (*per transversum per Anastomoses commissis*), according to an end-to-side connection pattern. Bauhin claims that in the concave part of the liver the branches of vena porta are abundant and outnumber those of vena cava. The reverse is the case in the convex part of the organ. Thus, in the lower part of the liver there are many more branches of vena porta which penetrate (*infigunt*) the middle segments of the roots of vena cava and in the upper part the reverse is true. The formation of blood moves from the concave part of the liver to the curved surface of the organ through a "*mirabilis plexus*" formed by the origins of vena porta and those of vena cava. The blood flows through these anastomoses, and then passes throughout the body. The description of a "*mirabilis plexus*" in the liver parenchyma – that is the presence of an interlaced vascular network formed by the origins of the vena porta and those of vena cava – is an interesting conceptual novelty in the development of the idea of modern anastomoses and represent a further step in the approach to the truth. Without any microscopic support, one could only imagine the structural configuration of invisible blood vessels. This implies a method of reductionism leading to an abstract simplification of the real vascular texture of the part. Bauhin presents the same illustration that was published by Piccolomini. It is particularly interesting that he mentions a unique giant anastomosis (*peculiaris et insignis Anastomosis*), which imitates a canal (*quae canalem aemulatur*) and presents itself as a common, continuous duct (*veluti communis et continuus ductus*) allowing the penetration of a rather large stylet. It is possible that this is a *ductus venosus Arantii* which has not yet been closed. Bauhin provides another illustration in which this conduit is clearly seen (Bauhin, 1605). Furthermore, Bauhin extends the scope of the term 'anastomoses' to include the vascular connexions (*extremis iunguntur*) on the anterior wall of the trunk between the branches of the internal mammalian veins and those of the inferior epigastric veins (Bauhin, 1605). These anastomoses are located around the umbilicus (*circa umbilicum per Anastomoses*) and provide connexions between the matrix and the *mammae*, a subject of great importance in the Hippocratic and Galenic mechanism of lactation. In modern texts of anatomy, these connexions are still considered part of the anastomotic apparatus between superior and inferior vena cava (Standring, 2005). In summary, Bauhin's contribution to the history of the semantic shift of the term *anastomōsis* from a purely functional meaning to a fixed, structural significance is highly relevant. In the Swiss anatomist's text, anastomosis denotes an elongated, continuous *trait d'union* representing a common structure between two

main vessels. Bauhin's opinion is shared by his pupil, the Danish anatomist Caspar Bartholin (1585-1629). In his *Anatomicae Institutiones corporis humani*, first published in 1611, he rejects the concept that an anastomosis is a relationship between separate vessels and defines intrahepatic 'anastomoses' as "conjunctions (*conjunctiones*) between the roots of vena porta and cava" (Bartholin, 1626). They can follow either an end-to-side or an end-to-end union pattern.

Fourteen years later, in 1625, the German anatomist Caspar Hofmann (1572-1648), professor of medicine at Altdorf, published a Commentary on Galen's *De usu partium*. Hofmann was an Aristotelian, strongly influenced by Cesalpino. One of his main beliefs was the nourishing property of arterial blood. Not only venous blood but also blood flowing in arteries imparts nutritive power. In this perspective, *anastomōseis* play a crucial role in Hofmann's physiology. Venous and arterial blood "communicate through reciprocal openings of the vessels" to produce one type of blood (Hofmann, 1625). He even asserts that "it is the purpose of nature to connect (*conjungere*) veins with arteries" (Hofmann, 1625).

[Nature] – he explains – connected (*coniunxit*) veins in which thicker blood flows with arteries in which finer blood runs through *anastomōseis*. In this way a unique quality [of blood] is produced in each part to be nourished, as similar as possible to the quality of the parts themselves, by mixing both kinds of blood (Hofmann, 1625).

This fundamental role of anastomoses in bodily processes is achieved by anatomical communications that structurally connect veins with arteries (*conjunctiones venarum et arteriarum*)(Hofmann, 1625). With regard to hepatic anastomoses, Hofmann states that the orifices of the terminal branches of vena porta and vena cava are reciprocally connected (*sibi invicem iungi*)(Hofmann, 1625). In this way – Hofmann asserts – a style which has penetrated the vena porta enters the region of the vena cava. Leaving aside the doubtful experimental authenticity of this last proposition, we can safely conclude that anastomoses in Hofmann's doctrine are genuine constructions characterised by physical continuity between connected parts.

Changing conceptions on the structure of anastomoses have critical importance for the development of the theory of circulation. In the XI chapter of his *Exercitatio anatomica de motu cordis et sanguinis in animalibus*, William Harvey (1578-1657) postulates a circular flow of blood, moving ceaselessly from the arteries to the veins either directly through anastomoses (*per Anastomosin immediate*), or indirectly through tissue permeability (*mediate per carnis porositates*), or in both ways (Harvey, 1628). In his masterpiece of 1628 he does not bother with structural details about anastomoses. But in the epistle to Paul Marquard Schlegel, dated 26 March 1651, in London, he has occasion to discuss with some minutiae the physical architecture of anastomoses, a subject he had scarcely touched upon before in *Exercitatio anatomica prima*, addressed to Jean Riolan (1580-1657) in 1649 (Harvey, 1649; Harvey, 1958). Riolan indeed claimed that blood in the great vessels flows through visible anastomoses (*per multas anastomoses vasorum*) from the arteries into veins (Riolan, 1649a; Riolan, 1649b). By the time of *Exercitatio anatomica prima* and the letter to Schlegel, Harvey had already abandoned the idea that anastomoses would play a significant role in the transfer of blood from the arterial to the venous compartments. He admits that he had failed to identify these elusive structures. Despite intensive efforts, he confesses to having found something comparable to (*quod aequipollet*) anastomoses in only three vascular compartments, namely, the cerebral plexus vessels, the gonadal vessels, and the umbilical vasculature. He admits that the anastomoses discovered at these sites have a different structure from that imagined by the Ancients. Indeed – he says – anastomoses had always been thought of as bidirectional transit devices. But the theory of blood circulation implies a one-way passage of the blood. From this point of view, he reports an important vivisection experiment. When in a living animal the aorta is ligated at its origin and the blood is withdrawn from the arteries, the veins nevertheless remain filled up with blood, because it cannot flow back into the arteries either spontaneously or forcibly. Harvey hypothesised that the arterioles enter the wall of the venules at an angle and run a short distance between their coats, much like the entrance of ureters into the wall of the vescica or of the bile duct into the wall of the duodenum. The reflux of blood from the venules into the arterioles is thus prevented. He also furnishes experimental proof of his statement. In the *Exercitationes de generatione animalium* Harvey reports that insufflation of air in the ovarian arteries causes dilatation of the ovarian veins, which is due to a transfer of air from the arteries to the veins, possibly by anastomoses (Harvey, 1651). The reverse, however, never occurs. He thus admits that under certain circumstances (*interdum*) there is a direct (*immediate*) transfer of blood from arteries to veins through anastomoses. The term anastomoses should be avoided, however, because it implies that "vessels may open equally on both sides, so that blood may pass freely on this side and on that" (Harvey, 1958). Harvey concludes his thesis in the hope that the old term 'anastomoses' will be finally discarded. It is an unfamiliar, inappropriate word for the purpose of circulation.

CONCLUSION

This study addresses a neglected piece of scientific and medical history, namely the controversy about the actual structure of blood vessel communications and the changing meaning of the term '*anastomōsis*' from Antiquity to the Seventeenth century. It is concerned with the distinction between the early conception an of open, functional state, as formulated by Erasistratus of Ceos, Aretaeus the Cappadocian, Galen and Oribasius, and the later developed notion of a closed, anatomical structure, as it prevailed and established in the Middle Ages and the Renaissance, into the modern period. The different views of ancient physicians on the structure of the *anastomōseis* in Antiquity cannot be properly reconstructed because of the great lack of preserved medical records. However, the testimony of the pseudo-Aristotelian author of *De spiritu* and the cautious approach to the problem of the structure of intrahepatic *anastomōseis* advocated by Galen himself in *De facultatibus naturalibus* may reflect an ongoing, unresolved controversy over the actual configuration of blood vessel connections. Nonetheless, the open and purely functional conception of the *anastomōseis*, as developed by Erasistratus, appears to have ultimately prevailed in Antiquity according to the extant record. Galen himself apparently adopted it. The first semantic shift of the term '*anastomōsis*' seems to have occurred in the Islamic cultural sphere toward the end of the ninth century and the beginning of the tenth, thanks to the work of al-Rāzī. He postulated an uninterrupted architecture of venous vessels in the liver parenchyma, claiming that the extremities of the porta and cava veins "are connected". In the Western world, Petrus Turisanus, Mondino de' Liucci and Henry de Mondeville, were the first to conceive of hepatic vasculature as a continuous structural network in the early fourteenth century. In the late Middle Ages and Renaissance, there was a lively debate on the structure of *anastomōseis* between representatives of the Arab-scholastic tradition and the humanistic tradition in the context of the evolving practice of human dissection. This debate involved such figures as Peter of Abano, Jacopo Berengario da Carpi, Nicolaus Massa, Matthaeus Curtius and Juan Valverde de Hamusco. Major contributions to the shaping of a tight, structural concept of *anastomōseis*/anastomoses were made by Vesalius, Cesalpino, Piccolomini and Bauhin. Harvey put an end to it. He linked the question of the spatial configuration of these entities with the question of blood circulation. The letter to Schlegel is an important document that attests Harvey's historical and linguistic awareness of the origin and concept exhibited by the term '*anastomōsis*'. For the Ancients, *anastomōseis* were conditions in which vessels faced each other mouth to mouth. Harvey states that this circumstance does not exist. Anastomoses are physically interconnected structures, with the terminal segments of arterioles penetrating the wall of the venules and running transversely for a short tract in order to prevent the reflux of blood. The conceptual and semantic shift from an open vascular state to a tight, structured anatomical connexion is complete. From now on, the word anastomoses will symbolise direct connections between blood vessels.

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