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Venous circulation and William Harvey: A historical review

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Abstract:

Greco–Roman concepts regarding the circulation persisted until the 1600s even though many were incorrect. It was held that blood flows in veins from the liver to the periphery where it is consumed. It was not until the 1500s that anatomists identified venous valves and explored their function. This, in part, allowed William Harvey to describe the circulation as we know it today. This study included review of the literature and translations of William Harvey's books including *De Motu Cordis* which were published in 1628. Harvey's description of the venous circulation started the intense exploration of venous physiology that continues today. The resultant concepts of venous reflux associated with varicose disease have allowed practitioners to develop contemporary management.

Keywords:

Circulation, Galen, Harvey, reflux, veins

Introduction

Physicians through Greco–Roman times developed concepts regarding the circulation that persisted unchanged for the next 1400 years. However, the ideas were predicated more on their fertile imaginations than scientific research. They considered that food is broken down in the liver to be converted into blood, blood is distributed through veins to the periphery, and it is consumed there with no return to the heart. This changed with William Harvey's description of the circulation in the early 1600s, in large part, because he understood venous valve function. This major awakening took another 100 years to be accepted, but the floodgates to the modern venous physiology and management of varicose disease had been opened.

Greco–Roman Concepts

Alcmaeon (born c. 510 BC) of Croton, a Greek city on the instep of Italy's boot, was an early pioneer for anatomical dissection and one of the first to distinguish arteries from veins.[1] He taught that sleep occurs when blood leaves the body's surface through veins, one wakens when blood returns, and death results when blood is completely withdrawn.

Hippocrates (460–370 BC) of Kos, a Greek island in the Aegean Sea, was the original "Father of Medicine."[2,3] The *Corpus Hippocraticum* was some seventy medical works that started from his teachings and was collected in the library of Alexandria in Egypt. He did not distinguish between arteries and veins and taught that blood is produced in the liver and spleen and: "… is distributed to all the body to which it gives warmth and life." He thought about a microcirculation: "We may compare the movement of the blood with courses of rivers returning to their sources after a passage through numerous channels."

Aristotle (384–322 BC), the "Father of Western Philosophy," was raised in northern Greece, moved to Athens to study with Plato, and then left at age 37 to spend 8 years tutoring the young Alexander the Great in Macedonia.[4] In *De spiritu* (on the

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life-bearing spirit), he taught that blood is essential for life and that *pneuma* derived from inspired air flows in blood through the arteries and veins to form the "soul,"[5] a belief also found in the *Bible*.[3]

Alexandria on the Egyptian Mediterranean coast developed into a major center for Greek civilization with a library thought to contain one million books. A medical school established there was led by three men who were to make major contributions through human dissection. Praxagoras (born c. 340 BC) was from the island of Kos.[6] Herophilus (335–280 BC) was born in Chalcedon, a town near the modern-day Istanbul, and was the "Father of Anatomy."[7] His younger associate Erasistratus (304–250 BC) came from the Greek islands and was the "Father of Physiology."[8]

They believed that *pneuma* from inspired air is the "life force" and the only content of arteries, food-enriched blood produced in the liver flows only in veins, and both *pneuma* and blood are distributed throughout the body to be consumed with no return to the heart. Their teachings held sway for the next 500 years. Erasistratus came closest to unraveling the circulation for he understood the pulmonary circulation.

Galen (AD 129–200/216) of Pergamon, a Greek city in what is now western Turkey, was one of the most prolific intellectuals of Greek antiquity.[9-11] He updated the Greco–Roman concepts showing that arteries do contain blood and not just air or *pneuma.* His teachings are summarized in Figure 1 as follows:

- Digested food from the stomach and intestines passes to the liver as chyle to be converted into blood
- Blood is carried to the right side of the heart through the vena cava. A small proportion passes to the lungs through the pulmonary artery to collect *pneuma* from inspired air which is taken to the left heart. A larger proportion passes to the left heart through pores in the interventricular septum
- Blood in the left heart passes back to the right heart through interventricular pores mixing with blood arriving from the liver
- Brighter arterial blood flows from the left ventricle to all parts to supply *pneuma*, particularly to the brain
- Darker blood formed in the liver passes away through the vena cava to peripheral veins and is consumed to form flesh
- Arterial and venous blood ebb and flow from the heart to the periphery with no return.

Venous Valves

Little changed after Galen for some 1400 years until the Renaissance. Anatomical drawings continued to show major veins arising from the liver with descriptions of their supplying blood to the periphery. These included sketches by Leonardo da Vinci (1452–1519) held in the Windsor Collection of Queen Elizabeth II [Figure 2],[12] drawings in *Tabulae Anatomicae* by anatomist Andreas Vesalius (1514–1564) in Padua [Figure 3],[13] and in *La dissection des parties du corps humain* by anatomist Charles Estienne (1504–1564) with surgeon Etienne de la Rivière (d. 1569) in Paris [Figure 4].[14] It was then that venous valves were first identified, and the probable first to describe them were either French anatomists in Paris or the Italian anatomist Giambattista Canano (1515–1579) from Ferrara.[15,16]

Frenchman Jacques Dubois known as Jacobus Sylvius (1478–1555)[17] was a demonstrator in anatomy at the *Universite de Paris* in the 1530s when he was joined by three students, Frenchmen Charles Estienne (Carolus Stephanus),[18] Loys Vassé (Ludovicus Vassaeus),[19] and Belgian Andreas Vesalius,[20] each to become eminent anatomists. They have been credited with describing venous valves, but as the four were working together, it seems unlikely that either could claim exclusive discovery. Sylvius wrote *Isagoge anatomica* published posthumously in which he described valves in the azygos, jugular, brachial, and crural veins, and the cava as it leaves the liver, and he called them *epiphyses venarum*.[17] Sylvius may have heard of them from Canano and did not claim their discovery. Estienne and de la Rivière published their book in 1546, and it described valves in hepatic vein termed *apophyses membranarum*;[21] the publication had been delayed due to a lawsuit over authorship and they had submitted relevant engravings

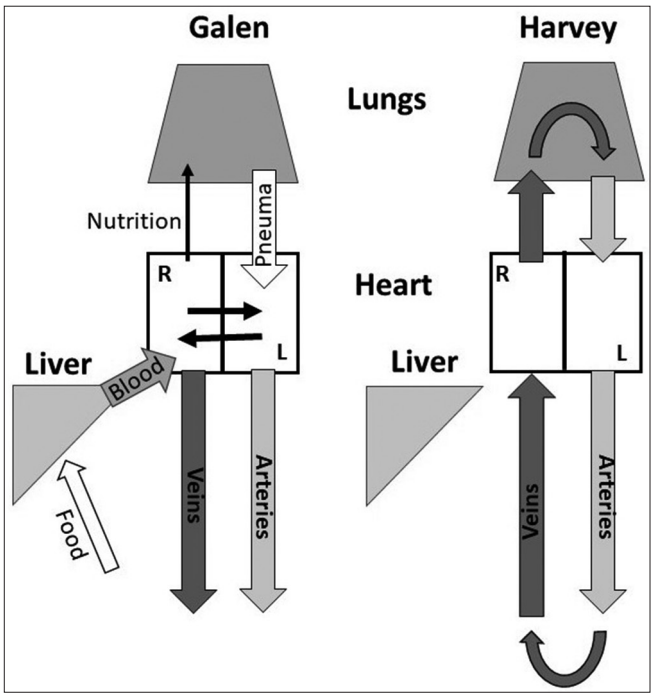

Figure 1: A diagram showing the differences between interpretations of the circulation by Galen (left) and Harvey (right). Adapted by the author from Voisin[11]

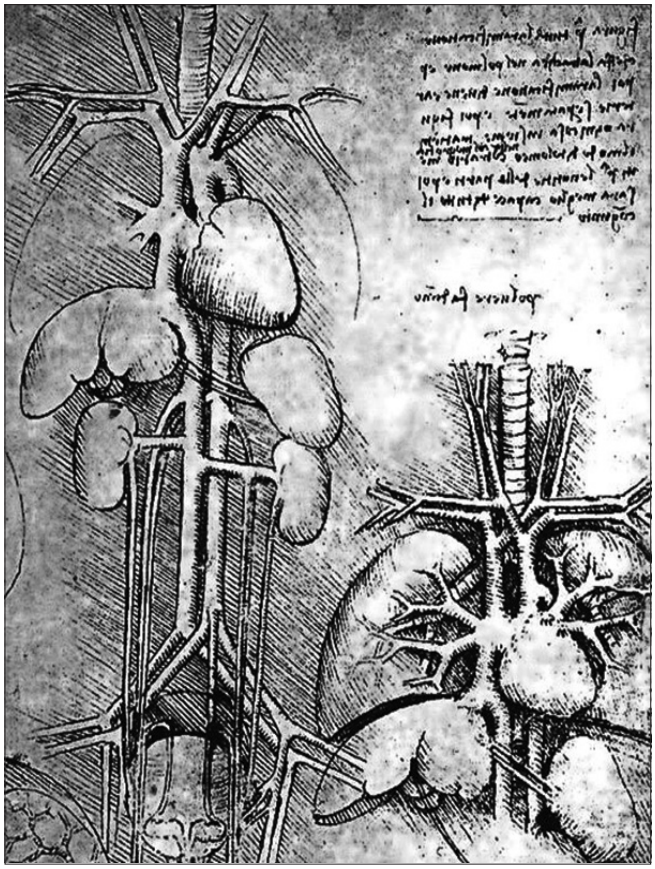

Figure 2: A sketch of the circulation by Leonardo da Vinci from the Windsor Folios in the Royal Collection at Windsor Castle, England.[12] It shows major veins coming from the liver as believed at the time. Courtesy of the Royal Collection Trust of Her Majesty Queen Elizabeth II, 2018

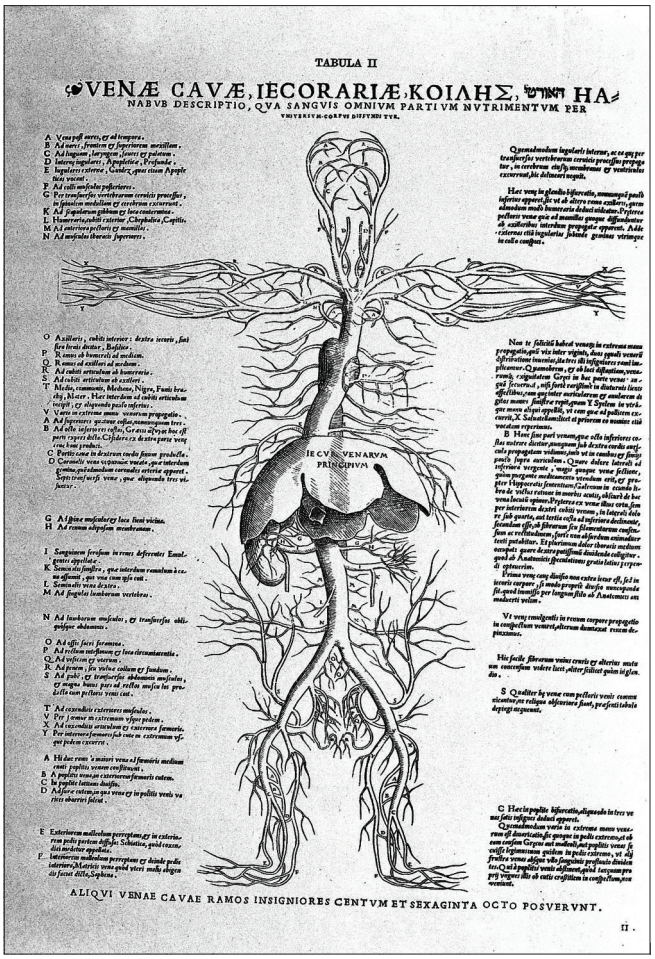

Figure 3: Vesalius' drawing of the vena cava from his *Tabulae Anatomicae*.[13] Two complete sets of the original edition exist: one in the Bibliotheca Nazionale Marciana in Venice and the other in the Hunterian Museum in London. Courtesy of the Wellcome Collection

to the *Faculté de Médecine* in the mid-1530s. Loys Vassé wrote *In anatomen corporis humani tabulae quatuor* (four tables on the human body anatomy) in 1541,[22] and his book has reference to venous valves. Vesalius wrote the most famous book of all, *De humani corporis fabrica libri septem* (the seven books on the structure of the human body), known as the *Fabrica*,[23] and it also had reference to venous valves but undoubtedly due to findings by others.

Canano met Vesalius in 1545 while both were visiting a sick friend in Regensburg, Germany, an Italian nobleman Francesco d'Este.[15] It is understood that Canano told Vesalius about discovering valves at the openings of the azygos and renal veins and in veins overlying the upper part of the sacrum. Canano did not publish these findings, and this account was only presented by others years later. Amato Lusitano (1511–1568) was a Portuguese Jewish physician who traveled throughout Europe to escape religious persecution before settling in Canano's Anatomy Department in Ferrara between 1542 and 1548. At a lecture in 1547 after Canano's retirement, Lusitano dissected 12 cadavers in the presence of many scholars and demonstrated valves in the azygos vein which he had undoubtedly learned from Canano. Lusitano published his work in *Curationum medicinalium centuriae septem*[24] in 1551, and this led to his being wrongly attributed with their discovery.

Hieronymus Fabricius d'Acquapendente (1537–1619)[25-27] was a professor of anatomy in Padua for 50 years. His fame as a teacher extended throughout Europe such that an estimated 10,000 foreign students studied with him. He was described as "kind and generous, learned and eloquent, sound in judgment and skillful in practice, earnest, and animated by a glowing enthusiasm." On the other hand, he was said to be argumentative with colleagues, dismissive of his German students for their accents, and in legal disputes with his illegitimate son. Fabricius was not the first to describe venous valves but was the most influential at the time for studying their function. He demonstrated valves in veins of the limbs to his students in about 1579, and this was published in

Anatomices et chirurgie, IV de venarum ostealis in 1603.[28] He observed that valves are found in peripheral veins but not in large veins of the trunk. He demonstrated that simple finger compression causes veins to appear as a series of regularly spaced knots on the surface. However, he accepted the concept that blood flowed away from the heart drawn by peripheral tissues and interpreted that venous valves acted to slow blood flow to allow its even distribution to prevent swelling and loss of nourishment. He explained varicose veins as being due to blood becoming denser to be held longer by valves, causing the veins to dilate.

Salomon Alberti (1540–1600), later to become a professor of anatomy at the University of Wittenberg, was one of the Fabricius' favored students, and with his permission, published his work in 1585 with excellent representations of valves in the leg and the structure of individual valves [Figure 5].[15]

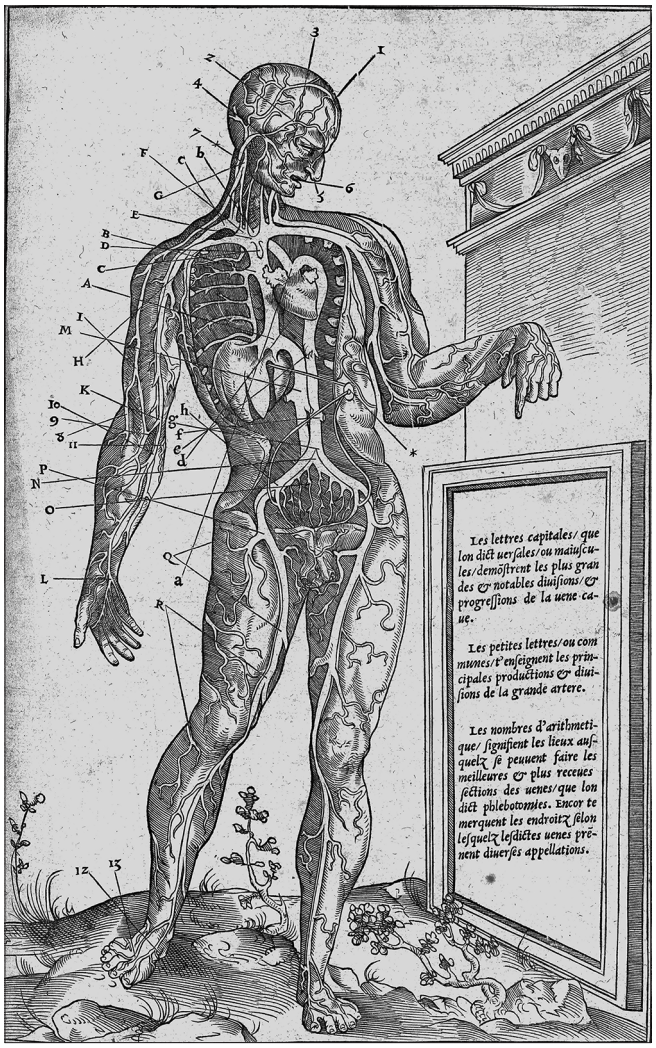

Figure 4: An illustration by Charles Etienne and Etienne de la Rivière, Paris, 1546, showing their concept of major veins and arteries in the abdomen, with veins drawn to originate from the liver.[14] Courtesy of BIU Santé, Paris

Discovery of the Circulation

The first accurate description of the circulation has been rightly attributed to one man, William Harvey, but much had been anticipated by others.[29,30] Cardiac function and the pulmonary circulation had been well studied, but there was little understanding of the venous circulation. Past concepts relied on reasoning rather than experiment, and it was here that Harvey used years of scientific endeavor with human and animal cadaver dissections and animal vivisection to piece together a complete picture.

William Harvey

William Harvey (1578–1657) [Figure 6][31-34] entered King's School, Canterbury, Kent, in 1588, the year that the Spanish Armada was defeated. He studied arts and medicine at Cambridge and then left to enroll with Fabricius in Padua in 1599, graduating in 1602. Harvey was one of the Fabricius' favorite students who said of him after his examinations that he: "… had shown such skill, memory and learning that he had far surpassed even the great hopes which his examiners had formed of him."[35]

While with Fabricius, Harvey learned much about venous valves that was to play an integral part in his later presentations. On return to England, he built up an exclusive private practice, became a Fellow of the College of Physicians in 1607 and a Fellow of the Royal Society, and was appointed physician to St. Bartholomew's Hospital in 1609 to attend once a week to diagnose and write prescriptions.

John Aubrey (1626–1697) was Harvey's protégé, friend, and biographer.[31,36] He said: "He was not tall; but of the lowest stature, round-faced, olivaster complexion; little eie, round, very black, full of spirit; his haire was black

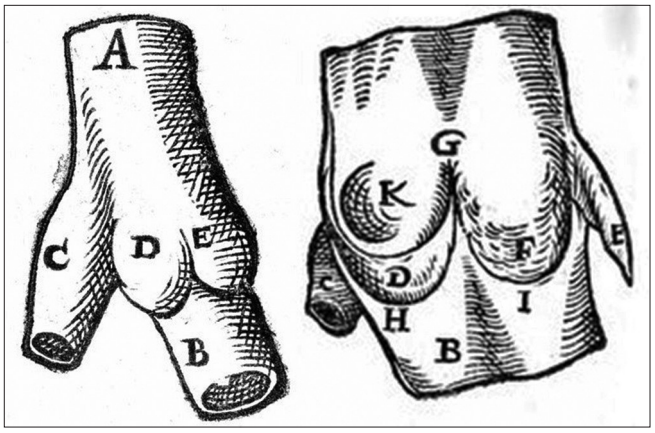

Figure 5: A drawing from Salomon Alberti's *De Valvulis*, 1585, from the Wellcome Collection. It shows the outside and inside of part of a leg vein, AB, with a muscle tributary vein; C, D, and E are the two cusps of a bicuspid valve in the main vein. These are probably the first drawings of a venous valve[15]

Figure 6: Portrait of William Harvey from the Wellcome Collection

as a raven, but quite white 20 yeares before he dyed." Harvey was said to be humorous, precise, immersed in his own thoughts but ready for a direct conversation, and contemptuous of women. According to Aubrey: "He was wont to say that man was but a great mischievous baboon."

Harvey was a rough diamond. Aubrey said that: "He was very cholerique; and in his young days wore a dagger … but this Doctor would be too apt to draw-out his dagger upon every slight occasion."[31,36] Harvey was forthright in pressing his arguments using what were colorful terms for the times in scientific works – although he was a contemporary of Shakespeare. Commentators have noted Harvey's "… racy English embedded in his Latin text;"[37] thus *mehercule* – by Hercules, and *Deus bone* – by God, considered profanity in puritanical England.[38] Profanity became a statutory crime for printed texts in 1606 subject to a fine of 10 pounds or three hours in the stocks, but Harvey was not liable to criminal charges because his book was published abroad.[38] One commentator considered that Harvey indeed viewed himself as Hercules, rather than cleaning out the Augean stables now clearing centuries of misconceptions about the circulation.[38]

King James I succeeded Queen Elizabeth I the year after Harvey returned from Padua, and Harvey became a committed royalist and physician to James I in 1618 and to Charles I in 1631. Hunting with King Charles allowed Harvey access to deer for dissection. When Civil War began in 1642, he accompanied Charles to Oxford where he was made "Doctor of Physic." He pursued his studies without mind to the fighting, but parliamentary troops ransacked his house in London with loss of all his medical records. Harvey resumed practice and continued writing but went into political exile after the king was executed in 1649. He died of a stroke in 1657 aged 79.

The Lumleian lectures

Harvey was invited in August 1615 at the age of 37 to present three Lumleian lectures to the Royal Society.[31] He gave these lectures in the week preceding Shakespeare's death and published them as *Praelectiones anatomicae* (anatomical lectures), 98 pages of notes preserved in the British Museum. Referring to previous legendary figures, he stated the intention was: "Not to praise or dispraise other anatomists, for all did well, and there was some excuse even for those who are in error."[31] But, he also stated that: " I have often wondered and even laughed at those who fancied that everything had been so consummately and absolutely investigated by an Aristotle or a Galen or some other mighty name, that nothing could by any possibility be added to their knowledge.[35] Further: "But while we acquiesce in their discoveries and believe, such is our sloth that nothing further can be found out, the lively acuteness of our genius languishes, and we put out the torch which they have handed on to us."[37]

The overall summary of his discovery was that: "… all of the blood in the left ventricle is sent into the arteries, round by the smaller veins into the venae cavae, and then to the right ventricle again. In this way, the circulation is complete."[37]

De Motu Cordis

Harvey published *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* (on the motion of the heart and blood in animals) in Latin in 1628, generally known as *De Motu Cordis*.[31,39] The first edition was a small book of 72 pages poorly printed on inferior paper with several mistakes, and only about seventy copies survive, all in institutions.[40-42] It was published in Frankfurt by William Fitzer to save costs. The first edition in English was not until 1653.

He was loath to publish his findings for well-founded fear of being ostracized to the detriment of his practice. Harvey expressed his concern in the book: "Not only do I feel a danger to myself from the malice of the few, but I dread lest I have all men as enemies so much does

habit or doctrine once absorbed, driving deeply its roots become second nature and so much does reference for antiquity influence all men." (Chapter VIII). According to Aubrey: "I have heard him say, that after his booke of the Circulation of the Blood came out, that he fell mightily in his practize, and that 'twas beleeved by the vulgar that he was crack-brained; and all the physitians were against his opinion, and envyed him."[29]

He wrote about every aspect of the adult and fetal circulations. In relation to the venous circulation (Chapter XIII), he wrote that venous valves: "… are usually two together, they face and touch each other, and their edges are so apt to join or close that they prevent anything from passing from the main trunk or larger veins to the smaller branches." Discussing the only figure in the book [Figure 7], he showed that: "If you will clear the blood away from the nodule of valve by pressing a thumb or finger below it, you will see that nothing can flow back being entirely prevented by the valve and that the part of the vein between the swelling and the finger disappears while above the swelling or valve it is well distended. But as soon as the finger is removed, the vein is filled from below." Referring to venous return: "The valves are present solely that blood may not move from the larger veins into the smaller ones lest they rupture or varicose and that it may not advance from the centre of the body into the periphery through them but rather from the extremities to the centre.… The quantity of blood forced up beyond the valve by a single compression may be estimated, and this multiplied by a thousand gives so much blood transmitted in this way through a single portion of the veins in a relatively short time, that without doubt you will be very easily convinced by the quickness of its passage."

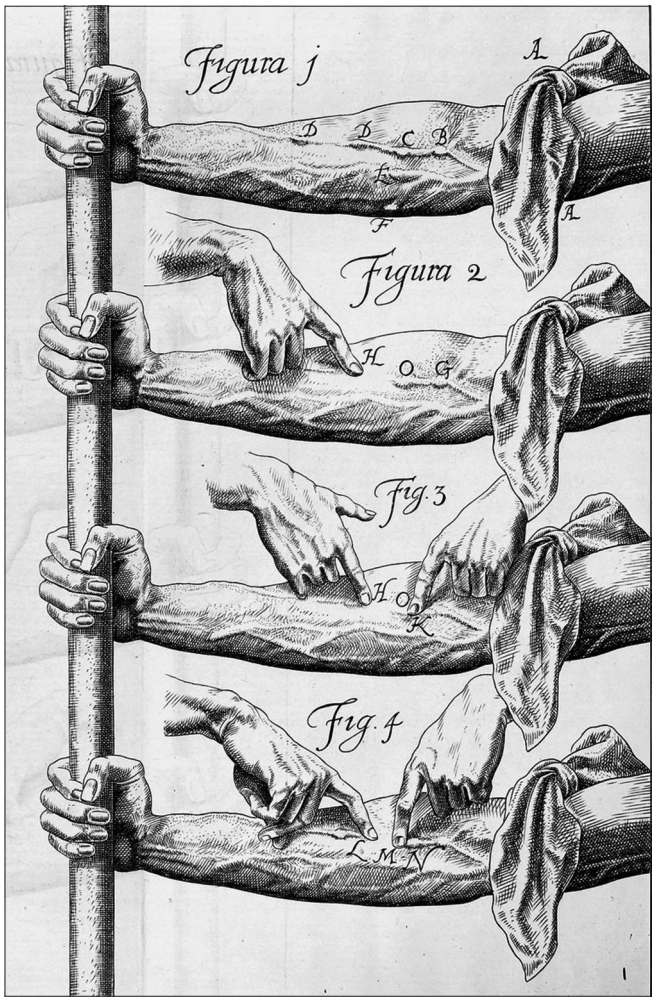

Figure 7: Figures from *De Motu Cordis* (Chapter XIII) showing the direction of venous flow in peripheral veins. Courtesy of the Wellcome Collection

The chemist Robert Boyle met with Harvey shortly before Harvey died, and Boyle recalled that: "…when he took notice that the valves in the veins of so many several parts of the body were so placed that they gave free passage to the blood towards the heart, but opposed the passage of the venal blood the contrary way: he was invited to imagine that so provident a cause as nature had not plac'd so many valves without design: and no design seemed more probable than that since the blood could not well, because of the interposing valves, be sent by the veins to the limbs, it should be sent through the arteries, and return through the veins, whose valves did not oppose its course that way."[39]

De Motu Cordis contains reference to other facets of venous physiology.[37] Harvey understood that a pressure gradient was required to move the large volumes of venous blood to the right atrium and perhaps that venous flow is promoted by: "aspiration of the chest … whereby like bellows they draw in the blood." He clearly understood muscle pumping: "… blood flows from the branches into the larger vessels; this being effected also by the motion and compression of the surrounding parts; for contents are squeezed out of whatever contains them …" The microcirculation was still to be discovered, but he understood *vis a tergo*: "Add also that the impetus of the blood which is urged and driven at every pulsation into all parts … forces the blood contained therein from the porosities into the little veins and from the branches into the larger vessels …"

Opposition

Harvey's views were opposed by many, both in England and on the continent,[29] in spite of his extensive experiments being easily reproduced. Jean Riolan the Younger (1577/1580–1657) was a most influential anatomist and physician and Dean of the Paris Medical Faculty, and he supported Galen's teachings and rejected Harvey's proposals. He postulated that blood ebbed and flowed through the veins returning to the heart just two or three times a day. His criticisms finally goaded Harvey to publish *Exercitationes duae anatomicae de circulatione*

sanguinis (two anatomical exercises concerning the circulation of blood)[43] in 1648 to defend his work with politeness though cutting rebuttals: "I think it a thing unworthy of a philosopher and a searcher of the truth, to return bad words for bad words; and I think I shall do better and more advised, if with the light of true and evident observations I shall wipe away those symptoms of incivility."

The First Venous Physiology Test

A clinical test, best referred to as the Brodie–Trendelenburg test, demonstrates venous reflux secondary to valvular incompetence with varicose veins. It is no longer used simply because it has been replaced by the ultrasound examination employed to identify venous reflux in contemporary practice.

Benjamin Brodie (1783–1862) spent his entire career at St George's Hospital, London. He became the President of the Royal Society in 1858; was a surgeon to King George IV, King William IV, and Queen Victoria; and was made a baronet in 1834. Practicing in the early 1800s before the advent of antisepsis and asepsis, he strongly advised against saphenous interruption for well-founded fear of infection with septic thrombophlebitis.[44]

Friedrich Trendelenburg (1844–1924) completed his medical training in Berlin and was then the Professor of Surgery in Rostock for 7 years, Bonn for 13 years, and Leipzig for 16 years until retirement. He worked in the late 1800s at a time when anesthesia had been introduced and antisepsis was accepted as the best practice, and he safely introduced the operation of saphenous ligation in the mid-thigh.[45]

Both Brodie and Trendelenburg independently described their test, and Trendelenburg indeed attributed the idea to a surgeon, Wilhelm Fabricius Hildanus (1560–1634), working in Cologne and Switzerland 300 years before. In assessing a patient with an ulcer, Hildanus noted that as he: "… lifted the tibia up the blood immediately receded. When the tibia was placed upon the ground the blood again descended, indeed almost immediately.… as if it had been thrown now in this direction, now in that, in a tube."

Brodie's description[44] was that on bringing the leg down from the elevated position: "… the blood rushed downwards of its own weight … and filled the varicose cluster below almost instantaneously.… If I put on a bandage and squeezed out the blood below, and then put my thumb on the *vena saphena* above so as to stop the circulation through it, I found on taking off the bandage, the patient being in the erect position, that the cluster of veins filled very slowly, and only from the capillary vessels. But if, the patient being in the erect position, I removed the pressure from the vein, the valves being of no use, the blood rushed downwards by its own weight, contrary to the course of the circulation, and filled the varicose cluster below almost instantaneously."

Trendelenburg's description[45] was that: "One lays the patient flat again, raises the leg to the perpendicular, lets all the blood flow out of the saphenous field, and compresses the trunk of the saphenous with a finger.… Now one lets the patient down … without removing the compressing finger from the saphenous. We see the whole saphenous vein now remains empty at first on standing.… Only when one removes the compressing finger does a larger amount of blood flow down from above into the saphenous … and the tensely distended varicosities return."

No effective treatment was used for varicose disease beyond simple phlebectomy until the understanding of venous reflux led to the introduction of treatment by sclerotherapy in the 1850s,[46] then saphenous ligation by Trendelenburg in the late 1800s,[45] and venous stripping by American surgeons in the early 1900s.[30]

Conclusion

William Harvey's concept of the circulation may now seem so obvious as to be unremarkable. However, he had to reject 2000 years of teachings that were universally accepted as being unassailable. Even when presented in all its detail, he was opposed for many years in no small part due to the ingrained egos of his opponents. It was more than 200 years before changes in the understanding of venous physiology allowed clinical tests for reflux in varicose disease and operations to stop the reflux. All modern managements have evolved from these discoveries.

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Conflicts of interest

There are no conflicts of interest.

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