Blood Circulation 400 Years after its Discovery

La circulación de la sangre a 400 años de su descubrimiento

ALFREDO E. BUZZI1

ABSTRACT

The English doctor William Harvey discovered that the heart pumps blood to the whole body and that this returns entirely to the heart in a closed circuit, a process that takes place all the time and with all the blood. He published his discovery in 1628 ("Exercitatio anatomica de motu cordis et sanguinis in animalibus") in Frankfurt, although the handwritten notes where he expresses this idea for the first time are dated as early as 1616, that is, 400 hundred years ago. The discovery of blood circulation was the first adequate explanation of an organic process and the starting point of the pathway towards experimental physiology.

RESUMEN

El médico inglés William Harvey fue quien descubrió que el corazón envía la sangre hacia todo el cuerpo y que esta regresa en su totalidad al corazón en un circuito cerrado, proceso que tiene lugar todo el tiempo y con toda la sangre. Publicó su descubrimiento en 1628 ("Exercitatio anatomica de motu cordis et sanguinis in animalibus") en Frankfurt, si bien las notas manuscritas en las que afirma esa idea por primera vez datan de 1616, es decir, hace 400 años. El descubrimiento de la circulación sanguínea fue la primera explicación adecuada de un proceso orgánico y el punto de partida del camino hacia la fisiología experimental.

INTRODUCTION

Modern medical science was born in the Post-Renaissance or counter-reformation era and began to consolidate in the mid-seventeenth century thanks to the work of physicists, physiologists and biologists who were direct or indirect disciples of Galileo. At that time there was a tendency for scientific studies to move away from conservative and traditionalist universities to concentrate in groups of private researchers. Thus the first scientific academies were created, the "Lincean" (Lincei) Academy in Rome (1603), to which Galileo belonged since 1610, and later the Royal Society in London. In turn, authors began to publish their scientific writings in their national languages.

We owe cardiovascular physiology to the studies of the English doctor William Harvey, who was able to combine some previous anatomical observations with the first quantitative medical experiments he performed. His great discovery was to show that the heart sends the blood to the whole body and that it returns in its entirety to the heart in a closed circuit, a process that takes place continually and with all the blood. This discovery is considered as the only advance in physiology of the early seventeenth century. But in addition to the importance of this discovery, Harvey pioneered another aspect: he was the initiator of the scientific method. He referred to genuine, unimagined experiments, which he furnished with irrefutable quantitative demonstrations. It has been fairly asserted that his discovery of blood circulation was the first adequate explanation of an organic process and the starting point of the path to experimental physiology.

However, in his monograph on the generation of animals entitled "De generatione animalium", published in 1651, along with some paragraphs where he shows his scientific reasoning, there are others with confusing, vague and capricious statements, remnants of the pre-scientific era of which the author had not completely departed. It can be affirmed, therefore, that modern medical science did not arise suddenly and globally, but was gradually structured from the middle of the seventeenth century following the path traced by William Harvey in the light of Galileo's thought.

PHYSIOLOGY IN THE 17TH CENTURY

The term "physiology" was introduced in medical texts by the French physician Jean Fernel in 1544, who grasped an Aristotelian concept that described both the structure and the function of the body. But it only reached current significance when it was defined by the Englishman John Quincy in 1722.

The function of organic systems in man was known as a result of isolated observations of the cardiovascular, respiratory and digestive systems, reproduction and other processes, whose analysis was confined to

Rev Argent Cardiol 2016;84:570-574. http://dx.doi.org/10.7775/rac.v84.i6.10117

Address for reprints: Prof. Dr. Alfredo E. Buzzi - Benjamín Matienzo 1849 - 2° B - (1426) Ciudad de Buenos Aires - email: aebuzzi@gmail.com

an empiricism only regulated by induction. But the characteristic of the seventeenth century was that quantitative research methods were progressively applied, the best example being Galileo's Discorsi e dimostrazioni matematiche, intorno a due nuove scienze attenenti alla meccanica & i movimenti locali) ("Discourse and Mathematical Demonstrations concerning Two New Sciences"), published in Leiden in 1638, where he called upon anyone who wanted to study nature to measure everything measurable. His experimental work is considered complementary to the writings of Francis Bacon in the establishment of the modern scientific method.

At the same time, to explain the organic processes of man, a rationalism that used deduction was applied to integrate all physiology in a single doctrine. This is seen in the studies of psychology and biological experiences of the French René Descartes, whose Discours de la méthode ("Discourse on the method"), published in Leiden in 1637, started from the objective knowledge of some phenomena to try to deduce the causes and laws of nature. On the other hand, the application of a rudimentary knowledge of physics to explain the organic functions in health and disease gave shape to a doctrinal school called "iatromechanism", opposed to another one called "iatrochemistry" that, based on alchemy, sought to find chemical explanations for the pathological and physiological processes of the human body. Both doctrines dominated the medical texts of that time.

HARVEY' LIFE

William Harvey (Figure 1) was born on April 1, 1578 in Folkestone, Kent County (south-east of London).

In 1593 he began his studies in Humanities at Caius College in Cambridge, and in 1599 he began his medical studies at the University of Padua, which was the most important center for studying medicine since the days of Vesalius. Despite being English, he could well pass as an Italian: he was of medium-low height, black hair, olive complexion, dark eyes and possessed a choleric temperament. In Padua he was a pupil of the anatomists Fabrizio and Casserio and the philosopher Cremonini. He graduated in 1602.

In 1607 he returned to London and entered the Royal College of Physicians, to which he would donate his library in 1651. Since 1609 he was a doctor at St. Bartholomew's hospital and in 1615 he was appointed Professor of Anatomy and Surgery. As early as 1616, he referred in his classes the idea of blood circulation. But only twelve years later he would decide to publish his discovery in the famous work Exercitatio anatomica de motu cordis et sanguinis in animalibus ("An anatomical study on the movements of the heart and the blood of animals") published in Frankfurt in 1628 (Figure 2).

He later became Extraordinary Physician to King James I and in 1625 was appointed physician to King Charles I, with whom he maintained a growing friend-



Fig 1. William Harvey (1578-1657).



Fig 2. Cover of "Exercitatio anatomica de motu cordis et sanguinis in animalibus" (www.rarebookroom.org).



Fig 3. "William Harvey explains his theory of blood circulation before Charles I", by Ernest Board (Wellcome Library).

ship (Figure 3). He attended the king during the siege of Oxford in 1642 and accompanied him until his execution by Oliver Cromwell's parliamentarians in 1649.

Harvey was a man of lively genius and independent character, interested in the arts and literature, as well as in biology and medicine, and due to his travels he combined the acquisition of paintings and books with anatomical demonstrations. His house in London was plundered during the Civil War, and he lost his books and notes, a misfortune that was aggravated by age, gout and renal lithiasis.

In 1649, his health worsened and he began to suffer multiple gout attacks. However, he continued his research and in 1651 published his monograph on the generation of animals, putting an end to his scientific life by dedicating himself to embryology, just as he had begun.

On June 3, 1657, at the age 79, Harvey suddenly lost his vision and then his speech, succumbing to a massive stroke at home. His last act was to personally pass his ring, watch and other personal belongings to his nephews. He was buried in the family mausoleum in Hempstead, Essex.

BLOOD CIRCULATION BEFORE HARVEY

From the time of Hippocrates and Galen it was considered that blood was synthesized from the food ingested. The useful parts of the meal were transported as a humor to the liver through the portal vein. In the liver, the humor became dark venous blood which then traveled to the ventricles of the heart, where it mixed with the vital properties that gave life, the "vital spirits." The blood was then distributed through all tissues through a centrifugal flow, where it was consumed. Therefore, the liver permanently formed blood from the food, which was constantly consumed in the tissues. Galen only worked with corpses (mainly of animals), in which blood is only found in the veins and not in the arteries. Consequently, he concluded that only veins carried blood, while the arteries carried the "vivifying air." Since there was no obvious direct connection between the two sides of the heart (he never observed the capillaries), Galen suggested that the heart ventricles were connected through invisible pores whose purpose was to allow the blood to move freely between both parts. In his scheme of blood circulation, he sustained that a small part of the venous blood passes from the right to the left ventricle through these "pores" to form the scarce arterial blood while air passed from the lungs through the pulmonary artery to the left side of the heart. It was argued that the left ventricle and the arteries formed an independent, bloodless system that served to ventilate and cool the "natural heat." The defects in this conception are surprising, and we can only wonder how it remained as a true dogma during fifteen centuries.

Later on, the description of pulmonary blood circulation by the Spaniard Miguel Servet (1553) and then by his compatriot Juan Valverde de Amusco (1556) and the Italian Mateo Realdo Colombo (1559), forced to accept the presence of blood flowing from the pulmonary vein into the left ventricle and into the aorta. Already in the thirteenth century, the pulmonary circulation had been described by the Arab physician Ibn-al-Nafis (1210-1288), who in 1260, in his Commentary on Anatomy in Avicenna's Canon, hypothesized a blood flow through the lung and denied the presence of "pores" (this conclusion is based on reasoning on the subject and not on anatomical dissections that were prohibited in the Arab world). But his work was not known in Western societies until the year 1900.

The discovery of venous valves by the Italian Girolamo Fabrizio d'Acquapendente (1603) was interpreted as a mechanism that only avoided the accumulation of blood in the lower parts of the body.

BLOOD CIRULATION WITH HARVEY

From his writings we know that Harvey was interested in heart movement, breathing, brain and spleen functions, locomotion, reproduction, and various issues of comparative anatomy and pathology. Without falling into the philosophical disquisitions of his contemporaries, Harvey discarded many traditional doctrines of classical medicine through observations and experiments, although he still retained in his work several beliefs and errors of his predecessors.

To understand how blood moves in the body, Harvey dissected, observed, and experimented. From the reading of his works it follows that the idea that blood flows emerged in him at the same time as a real sudden illumination and as a working hypothesis. The latter defines him as a true man of science.

The text of the handwritten notes in which he first establishes this idea (1616) indicates that his experiments on the ligature of the arm (constat per ligaturam, he says literally) were the first to convince him of the truth of that idea.

To prove his discovery, he first used a simple reasoning: the amount of blood that passes from the vena cava to the heart and from this to the arteries is overwhelmingly greater than the amount of food ingested. The left ventricle, whose minimum capacity is one and a half ounces of blood (about 47 grams), sends at each contraction to the aorta no less than one-eighth of the blood it contains (about 6 grams); Therefore, every half hour more than 3.000 drachmas of blood (about 12 kilograms) go out of the heart, an amount infinitely greater than that which could have been formed from the food in the liver (as the Galenic theory claimed). Therefore, it is necessary for that blood to return to the heart through the venous system. A whole series of consecutive arguments based on experimentation embodies this previous reasoning.

As a first proof he used the result of what happens in the arm when it is methodically tied above the elbow flexion: the radial pulse is not perceptible and the hand is cold. If it is slightly loosened, the radial pulse is felt again, the veins of the forearm bulge and the hand swells, warms and becomes red. If the ligature is completely untied, the venous swelling disappears rapidly and the subject feels a slight cold in the armpit. From these facts Harvey drew a conclusion: that the blood returned to the heart. This hypothesis was confirmed by an argument similar to the previous one: the calculation of the blood that flows into the limb through the arteries and flows back from the limb through its veins.

The truth is that it had been known for centuries, thanks to the practice of bleeding, that when the arm is tied above the elbow the veins of the forearm swell. But the explanation of Galenic physiology for this phenomenon was very different from that of Harvey: this was because the "vis attractiva" of the vein was excited by the ligature and, secondly, because once the vessel had been incised, the "horror vacui" ("horror of vacuum") would draw to the venous network a plus of arterial blood, all through the arteriovenous anastomoses described by Erasistratus and accepted by Galen.

The second test used by Harvey was based on the function of venous valves: if a medium ligature is performed on a thin individual with thick veins, these will be engorged and will allow seeing every few inches small bumps, corresponding to each of the group of valves of the venous wall. If a finger is pressed between two of these bumps and slid in a distal direction, the blood engorges even more the lower bump and cannot flow beyond it. If the finger is slid proximally, the blood flows easily upwards. Therefore, and contrary to the doctrine of his master Fabrizio (according to which the venous valves would be small gates to regulate the venous flow towards the peripheral parts), these valves are "subtle resources of nature so that blood may flow without difficulty to the heart" (Figure 4). Harvey confirmed in his old age to a great contemporary of his, the English chemist Robert Boyle, that the base of his discovery was established by the studies and observations of the venous valves.

Thus, for Harvey, the passage of blood from the

heart to the arteries, from these to the veins and from the veins to the heart is a fact as true as it is evident. Moreover, this was also confirmed by the estimation of the amount of blood displaced by several slides of the pressing finger in the proximal direction.

This was a typical modern, resolute experiment in Galileo's sense: in the face of reality, an explanatory hypothesis, reinforced by a strong arithmetic argument, and then two conclusive experimental tests regarding the truth of that hypothesis. The transcendental importance of Harvey's discovery is heightened by the exemplarity of the rigorous scientific method imposing its truth. Compared with the ancient Galenic view of the experiment as an epiphany of nature to confirm what the wise man had said about it, there appears before us the meticulous caution with which the modern experimenter multiplies the evidence, as a sagacious and suspicious detective, so that the hidden truth of that nature becomes evident to all.

But Harvey cannot only be considered "modern" by his approach, but also by the extent of his views on animal experimentation ("comparative physiology" as a method for confirming the universal truth of his finding) and also by his comprehension of the reality of the physiological movement. Let's see what Har-



Fig 4. Experiments to prove the direction of blood flow in the veins that illustrate the book "Exercitatio anatomica de motu cordis et sanguinis in animalibus"

vey says about the arterial pulse. Galenicals explained that the arterial wall dilated coincidentally with the pulse because the heart sent the vital spirits along the arterial wall inciting their "vis pulsifica" by increasing the diameter of the vessel's lumen. Harvey denied this explanation, and asserted that it is the "vis afronte" of the bloodstream that the heart ejects into the artery which passively dilates the vessel in question: "The arteries are not filled because they distend, like the bellows, but they distend because they are filled, like the wineskins." Due to his research method and his way of understanding the movement of the artery in the arterial pulse, Harvey reasoned as a rigorously "modern" physiologist.

Harvey explained his discovery in his famous work Exercitatio anatomica de motu cordis et sanguinis in animalibus, published in Frankfurt in 1628. This small book of 72 pages is considered one of the great texts of the history of medicine, despite its poor typographic presentation. In the epilogue, the editor makes excuses for the many misprints, apologizing partly due to the author's absence, partly to the handwriting (difficult to read) and finally to the subject, which was an absolute novelty.

The notes he wrote for his classes (published in 1886 in London as Praelectiones anatomiae universalis) constitute the first part of his book. In the second part he discusses the stages that led him to the discoverv of blood circulation. In his initial chapter (i), Harvey explains the reasons that motivated his studies on the heart, then he presents (ii, iii, iv) his conclusions on the function of the ventricles, the arteries and the atria. he indicates (v) that the main action of the heart is the continuous transfusion of blood from the veins into the arteries and confirms (vi, vii) the mechanism of the pulmonary circulation. With this analysis Harvey refuted Galen's doctrine that the pulse was due to the contraction of the arteries, proving that it was the result of the mechanical impulse of the blood against the arterial walls, when it was ejected with each contraction of the heart. It then deals with the general circulation and discusses the amount and origin of blood that passes from the veins to the arteries through the contraction of the heart. He starts (viii) by reflecting on the analogy between the pulmonary circulation and the general circulation, and calculates (ix) the amount of blood the heart sends to the aorta per unit of time. He recalculates (x) the return of venous blood with the ligature of veins in fish and snakes, so that the heart becomes drained, whereas it becomes congested if the arteries are ligated; he uses (xi) the ligature of the limbs with different intensity, as described above. He distinguishes (xii) the amount of blood drawn in a phlebotomy, discusses (xiii) the role of venous valves in avoiding blood reflux and concludes (xiv) with the need to accept the circular movement of blood, to explain these phenomena. In the final chapters (xv, xvi, xvii) he sustains that blood transports the natural heat and serves for the nutrition of the body.

The doctrine of blood circulation had a profound influence on the medicine of those years and was discussed everywhere, including America, especially the comments of Charles Morton in Boston (1690), Federico Bottoni in Lima (1723) and Marcos Jose Salgado in Mexico (1727).

The discovery was generally accepted, although there was no lack of defenders of the Galenic tradition who published objections to blood circulation, such as Emilio Parigiano (1623), James Primrose (1630), Caspar Hofmann (1636), Jean Riolan (1639) and still after Harvey's death, Matías Garcia (1677). Therefore, Harvey offered a more complete experimental demonstration of circulation in the Exercitationes de circulation e sanguinis (which he published in Rotterdam in 1649) where he particularly responded to Riolan.

CONCLUSION

The discovery of blood circulation was the great breakthrough of the seventeenth century. Harvey's demonstrations gave a fatal blow to Galenic physiology by bringing the solution to this age-old problem. But although Harvey verified blood circulation he could not explain all stages of the process (he did not see the capillaries).

Even though in his anatomical descriptions, comparative anatomy and experimental considerations Harvey reveals himself as a great observer and a skillful experimenter, his theoretical speculations retain a residue of the pre-scientific era from which the author had not fully departed. But Harvey's work is not invalid at all for this reason, since he knew how to harmonize the knowledge of his predecessors, shape them and demonstrate the truth through experimentation.

Conflicts of interest

None declared. (See authors' conflicts of interest forms in the website/Supplementary material).

REFERENCES

- Aird WC. Discovery of the cardiovascular system: from Galen to William Harvey. J Thromb Haemost 2011;9:118-29.
- Androutsos G, Karamanou M, Stefanadis C. William Harvey (1578-1657): discoverer of blood circulation. Hellenic J Cardiol 2012,53:6-9.
- Harvey W. Exercitatio anatomica de motu cordis et sanguinis in animalibus. Traducido al inglés por Chauncey D. Leake. Spring-field, Ill.: Thomas; 1928.
- Harvey LJ. The Scene Of His Last Years And Hours. Med Hist 1960;4:18-31.
- Karamanou M, Stefanadis C, Tsoucalas G, Laios K, Androutsos G. Galen's (130-201 AD) Conceptions of the Heart. Hellenic J Cardiol 2015;56:197-200.
- Micheli A. William Harvey y los inicios de la ciencia médica moderna. Gac Méd Méx 2005;141:233-7.
- O'Rourke Boyle M. William Harvey's Anatomy Book and Literary Culture. Medical History 2008;52:73-91.
- Pasipoularides A. Historical Perspective: Harvey's epochmaking discovery of the Circulation, its historical antecedents, and some initial consequences on medical practice. J Appl Physiol 2013;114:1493-503.
- [No author] A Harvey Anniversary: 1616-1916. JAMA 2016;315:1524.