Historical Perspective: Harvey’s epoch-making discovery of the Circulation, its historical antecedents, and some initial consequences on medical practice

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Pasipoularides A. Historical Perspective: Harvey’s epoch-making discovery of the Circulation, its historical antecedents, and some initial consequences on medical practice. J Appl Physiol 114: 1493–1503, 2013. First published April 4, 2013; doi:10.1152/japplphysiol.00216.2013.—In Harvey’s Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus of 1628, we see the mechanisms of the Circulation worked out more or less in full from the results of experimental demonstration, virtually complete but for the direct visual evidence of a link between the minute final terminations and initial branches of the arterial and venous systems, respectively. This would become available only when the capillaries could be seen under the microscope, by Malpighi. Harvey’s amazingly modern order of magnitude analysis of volumetric circulatory flow and appreciation of the principle of continuity (mass conservation), his adroit investigational uses of ligatures of varying tightness in elegant flow experiments, and his insightful deductions truly explain the movement of the blood in animals. His end was accomplished. So radical was his discovery that early in the 18th century, the illustrious Hermann Boerhaave, professor of medicine at Leyden, declared that nothing that had been written before Harvey was worthy of consideration any more. The conclusions of De Motu Cordis are unassailable and beautiful in their simplicity. Harvey’s genius and tireless determination have served physiology and medicine well.

Aristotle and circular motions; Galen’s De Usu Partium; William Harvey’s De Motu Cordis; William Harvey’s order of magnitude analysis of volumetric circulatory flow; blood circulation

All truths are easy to understand once they are discovered; the point is to discover them—attributed to Galileo Galilei

The Circulation of Blood and the physiologic function of the heart as a pump were established by the English physician-physiologist William Harvey (1578–1657) (44), who is considered to be the father of modern experimental physiology. Harvey studied medicine at Padua (now Padova), near Venice, which at the time had the most prestigious medical university in Europe. It was also one of the most Aristotelian, but Paduan Aristotelianism differed from the genre taught elsewhere: at Padua, they taught Aristotle as a preliminary to medicine, not theology (44). Since the early 15th century, Padua had been ruled by Venice, which fostered freedom of thought. At Padua, Harvey was a pupil of Casserius and, most notably, of the great anatomist Hieronymus Fabricius of Aquapendente who, after Aristotle (60), became known as a father of embryology (28). Besides Harvey, the intellectual climate attracted many of the ablest minds of the time—among them Vesalius, Copernicus, and Galileo (7, 51).

ANCIENT KNOWLEDGE, IN NUCE, ABOUT BLOOD MOTIONS PREDATING HARVEY’S DISCOVERY

That the blood is moved by heart contractions was known since ancient times; specifically since the anatomical and physiological studies of the Greek physician Aelius Galenus, or Claudius Galen of Pergamos (ca.130–ca.200), next to Hippocrates the most celebrated physician the world ever produced (15). He performed extensive dissections and vivisections on animals, as well as human dissections. At Harvey’s time, physicians in Europe had followed Galen’s teachings for 15 centuries. In fact, the enormous influence of Galen’s works, encompassing all aspects of the practice and theory of medicine, extended well into the 19th century, as is demonstrated by the highly abridged English-version epitome of them, prepared by Coxe and published in 1846 as a teaching text (11, 44, 50).

A sizeable number of Galen’s works are lost, and yet at least 122 medical treatises, more or less complete, survive and are in print (33); there is reason to believe that they constitute not more than one-third or one-quarter of his works. Harvey read the Latin, and not the original Greek text of Galen’s works. The eminent scholar Frederick Kilgour of Yale University has concluded that Harvey found Galen’s results useful to him in developing his global concept of the Circulation. He states that Harvey specifically refers to or discusses Galen’s findings and views on 33 occasions (32); of these 33 references, Harvey employs 20 to support his own reasoning and 13 times he disagrees with Galen’s findings or views.

Galen maintained that the ultimate branches of the arteries and veins communicated by fine tubes that he called “anastomoses,” and that anastomoses existed in both the body and the lungs (34, 44). He believed that the two varieties of blood, dark
red flowing in veins and bright red in arteries, originated in different organs—venous blood in the liver, and arterial blood in the heart, as is shown in Fig. 2. Blood was propelled inside the vessels by attraction from peripheral tissues needing nutrition. Carried in an ebb and flow to various parts of the body (consider the apparent ebb and flow in the veins of the hand, as it is raised up and lowered down), blood was constantly consumed by tissues, as nutrient or as matter transformed into flesh, like irrigating water in the fields. Thus intravascular blood was not conserved. Galen believed that the heart contained a distinctive muscle that was capable of exerting a “vis a fronte” (force from the front) capable of spreading the flesh, like irrigating water in the fields. Thus intravascular elements that exhibit a striking resemblance to the urinary system, in Book I of De Motu Cordis, had a foothold on Galen’s shoulder.

SOME NOTABLE SCIENTIFIC FORERUNNERS OF HARVEY

Isaac Newton aptly noted in a letter to his rival Robert Hooke, in 1676: “If I have seen a little further, it is by standing on the shoulders of Giants” (44). Even when interrupted by the remarkable insights of a genius like William Harvey, the advancement of scientific knowledge is a continuum, each step or stride forward always contingent on others that preceded it, as the great philosopher Émile Littré has put it (35). Nonetheless, to Harvey it fell, as the Renaissance drew to an end, through quantitative thinking with quasi-modern order of magnitude analysis and exhaustive experimental work, to conceive, demonstrate, and explain the circulation of the blood. By doing so, he took a decisive stride toward a modern physiology.

Descartes

Descartes was a contemporary of René Descartes (1596–1650), one of the greatest intellects in the history of mankind and the protagonist of the biomedical concept of function, which he related to the conceptual metaphor of living organisms as machines that are assembled from separate parts (44). The functions of the parts could be reduced to mechanical operations, suggesting that organisms were simply automata, akin to the hydraulic-powered mechanical statues (or automatata) that could be found in European royal gardens, which would move, assume different poses, and even sing. Descartes said, “I do not recognize any difference between machines made by craftsmen and the various bodies that nature alone composes” (8). His book De Homine (On Man), published posthumously in 1662, took a thoroughly mechanistic view of the human body, based as it was upon his concept of l’homme machine, the human machine; the representation of the body as a machine still influences modern thought. De Homine is arguably the first modern European book on physiology.

Descartes’ great legacy to medical science was his philosophical skepticism, which drives much scientific experimentation. The great triumph of 17th century physiology came when Harvey applied this skepticism and the Cartesian mechanistic template to the phenomenon of blood circulation and solved what had, since ancient times, been the most fundamental and challenging problem in physiology (44). Descartes read De Motu Cordis, and in his Discours de la Méthode (1637) gave prominence to Harvey’s discovery, stating forthrightly that his own anatomical work had led him too to the conclusion that the blood does indeed circulate around the body. He states (12) that Harvey “has the honour of having broken the ice on this subject, and of having been the first to teach that there are many small passages at the extremities of the arteries, through which the blood received by them from the heart passes into the small branches of the veins, whence it again returns to the heart; so that its course amounts precisely to a perpetual circulation.”

Paradoxically, although Descartes expressed flattering remarks about “Heraueus,” as he Franco-Latinized Harvey’s

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name (13), he also held antagonistic views (48, 64) toward some portions of De Motu Cordis relating to the functioning of the heart, which seem to have emanated from misconceptions that he developed while writing the Discours de la Méthode. In the latter, he erroneously ascribed the motion of the blood, not to the contraction of the walls of the heart, but to the “heat which may be felt with the fingers” (12), and which he infers to be generated there. His view was that the heart was able to circulate blood because it could heat and so expand the blood that entered it; the visible change in the color of the blood is, Descartes assumed, evidence of this expansion.

Aristotle and Jacopo Zabarella

I believe that Harvey’s own approach to the study of the circulation of blood must have been influenced also by the work of Jacopo Zabarella (1533–1589), renowned professor at the University of Padua (54), who had died 10 years prior to Harvey’s entrance to the medical program. Zabarella was a keen student of Aristotle (384–322 BCE) and his methods (37, 49). In his treatise De Methodis (On Method) of 1578, Zabarella distinguishes two different methods of discovery in which a physician can become acquainted with the parts of the human body (38, 41). First, he may learn them through empirical knowledge and anatomical observations, thus assimilating the matter of his discipline without understanding its rationale. This corresponds to the demonstrative method of science, as Aristotle had conceived it. Second, he can also become familiar with the parts of the human body through “philosophy of nature,” where he may understand the reasons that lie behind what he actually observes. This corresponds to the analytic or resolutive method of Aristotle, which proceeds from the whole resolving it into parts or from the end-effect resolving it into the causes producing it.

Zabarella deemed that Aristotle made the same distinction in his books the History of Animals, in which he relies on sense perception to classify the different parts of animals, and the Parts of Animals, in which he offers causal explanations for the observed anatomy. In De Rebus Naturalibus (71), Zabarella points out that medicine adopts its physiological component from the philosophy of nature. If physicians want to know the anatomy of the human body, they must therefore follow Aristotle methodologically. Consequently, they should not study just the History of Animals, but in addition the Parts of Animals, which reveals the functions of different parts of the body by applying analytical methodology. As Zabarella understood further, in medical practice, the resolutive method can proceed from knowledge to cure (38).

Although he is celebrated as a scientific revolutionary, in the genre of Galileo, Harvey was a devoted Aristotelian who saw an underlying unity between various circular motions in the universe—the planets in the heavens, air and rain in the sky, blood inside animal bodies (see Fig. 1). Indeed, he was a life-long theorizer on the purpose and the enigma of circular phenomena: the circulation of the blood (De Motu Cordis) and the cycle of generation (Exercitationes de Generatione Animalium, see later), both forming the microscopic copy of a cosmological pattern. As he put it metaphorically, the heart “deserves to be styled the starting point of life and the sun of our microcosm just as much as the sun deserves to be styled the heart of the world” (26, 44). In some ways, Harvey was not a radical reformer but a traditionalist who maintained many Aristotelian ideas, and he remained till the end of his momentous life a staunch peripatetic. According to the 17th century natural philosopher and diarist-biographer John Aubrey, Harvey “bid me goe to the fountain head and read Aristotle... and did call the neoteriques [upstart (“modern”) philosophers] shitt-breeches” (3, 20, 44).

Erasistratus and Galen

Erasistratus (304–250 BCE) was a Greek anatomist and physician who around the year 300 BCE made a great discovery: the valves of the heart (14, 17). Around the opening by which the venae cavae and right auricle communicate with the right ventricle, he found three membranous folds (tricuspid valve), disposed in such a manner as to allow any fluid coming from the veins to pass into the ventricle, but not to go backward. The opening of the vena arteriosa (pulmonary artery) into the right ventricle is quite different from the tricuspid valve, as Erasistratus observed; it is provided with three pouch-like, Σ-shaped (sigmoidal, or semilunar) valves the arrangement of which is such that a fluid can pass out of the right ventricle into the vena arteriosa, but not back again. He found a similar sigmoidal valve at the origin of the arteria aorta from the left ventricle. The arteria venosa [pulmonary vein(s)] and left auricle had a distinct opening into the left ventricle, and this was provided with triangular membranous...
Thus the 2 ventricles had 4 openings, 2 each; and there were altogether 11 valve leaflets, arranged in such a manner as to permit fluids to only enter the ventricles from the auricles, and to only pass out of the ventricles by the vena arteriosa and the aorta, but not to go the other way. He also concluded that the heart functioned as a pump. Thus, Erasistratus implicitly laid the foundations of the theory of the motion of the blood. Unfortunately, all his works are lost; they were probably destroyed when the Great Library of Alexandria was burned down by the fanatic mob. We have, therefore, only indirect accounts of his work through the fragmentary references to him in the works of his successors, primarily Galen.

Galen’s theory of the motions of the blood in the heart and lungs may be synopsized as follows (see Fig. 2), on the basis of a remarkable passage (27) at the end of the 10th chapter of the 6th book of his ΠΕΡΙ ΧΡΕΙΑΣ ΜΟΡΦΩΝ (De Usu Partium) [Harvey too gives extensive discussion to Galen’s text, in Chapter VII of De Motu Cordis (25)]: On entering the right ventricle, blood must pass by a one-way valve opening inward, so that only an insignificant portion can regress into the vena cava from which it is discharged. Some of the blood passes directly from the right to the left ventricle through “foramina” or “pores” in the interventricular septum. But much, and apparently most, of the blood moves into the vena arteriosa (pulmonary artery) through a one-way semilunar valve that opens outward from the right ventricle. On contraction of the thorax, the blood in the vena arteriosa, having its backflow cut off from behind by the semilunar valve, can only flow forward into the arterial system of the lungs (in modern usage, venous). Whether Galen’s arteria venosa [pulmonary vein(s)] then carries blood to the left ventricle is in question. He almost certainly thought of the arteria venosa as conveying the inspired air, or at least some quality derived from it, from the lungs to the left ventricle. In the opposite direction, smoky wastes were borne from the left ventricle to the lungs via the arteria venosa; this process was made possible by the comparative insufficiency (a remarkable functional attribute) of the mitral valve opening into the left ventricle.

Yet one other essential point about the views of Galen: he was among the first to recognize the heart as a pump. He thought that both the contractions and the dilatations of the heart—what we refer to as systole and diastole—were equally active movements. The heart actively dilated, so that it had a kind of sucking action (the above-mentioned “vis a fronte”) upon the fluids that had access to it, a strikingly modern conception (6, 43–46, 61). The blood in the left ventricle passed into the aorta through an orifice guarded by a one-way semilunar valve opening outward. With respect to the arterial pulse, Galen was of the opinion that the walls of the arteries partook of that which we reasoned to be the nature of the heart walls, and that they had the power of alternately actively contracting and actively dilating (44).
To the vexing question, why the teachings of Galen have come to be misunderstood by scholars of great distinction, no definitive answer can be given. However, substantially correct accounts of Galen’s dogmata have been provided by several authors and essayists, including William Harvey himself (25, 32, 47, 52, 53, 69). He states [p. 51 in Chapter VII in the Keynes Translation (25)]:

“But seeing there are some such persons which admit of nothing, unless there be an authority alleged for it, let them know, that the very same truth may be proved from Galen’s own words, that is to say, not only that the blood may be transfigured out of the vena arteriosa, into the arteria venosa, and thence into the left ventricle of the heart, and afterwards transmitted into the arteries, but also that this is done by a continued pulse of the heart, and motion of the lungs, whilst we breathe. There are in the orifice of the vena arteriosa three shutts, or doors, made like a Σ or half-Moon (sibmoidal or semilunar), which altogether hinder the blood sent into the vena arteriosa to return to the heart, which all know.”

Ibn al-Nafis

Guesses about a pulmonary passageway for blood had been voiced in the Proto-Renaissance by the Arab physician Ibn al-Nafis (1213–1288) of Damascus, who understood that all the blood that reached the left ventricle had passed through the lungs (65). Andrea Alpago, an Italian physician who had lived in the Islamic Orient before moving to Padova, made a Latin translation of Ibn al-Nafis’ work that was published in 1547 (1, 40). Al-Nafis observed that the wall of the interventricular septum is not porous, as was believed by all scholars and physicians adhering to Galen’s works. Blood was channeled from the right heart via the pulmonary artery to the lungs, to be “mixed with air,” and emptied back to the left side of the heart through the pulmonary veins. Whether he had known or not of Galen’s words regarding the passage of blood through the lungs (cf. above) has not been ascertained. He also stated that there must be small communications or pores between the pulmonary artery and vein, an expectation that could be interpreted as a reference to capillary vessels that preceded by about 400 years their discovery by Marcello Malpighi (65, 68) and also followed Galen’s analogous inference by about 11 centuries (34, 44).

Interestingly, Professor Wilson of Yale University concluded (69) that the three different individuals that are generally said to have discovered the pulmonary circuit of the blood, Ibn al-Nafis, Miguel Servetus, and Realdo Colombo, made their discoveries almost certainly independently of one another. However (69), all three seem to have begun their reasoning from the same literary source: the particular passage at the end of the 10th chapter of the 6th book of Galen’s De Usu Partium, where Galen shows (see earlier discussion) that blood that has passed into the pulmonary artery from the right ventricle of the heart must pass through the anastomoses between arteries and veins into the pulmonary vein(s) when the lungs shrink in expiration.

Miguel Servetus and Realdo Colombo

The topic of the pulmonary circulation was tackled again 3 centuries later by the Spanish theologian and physician Miguel Servetus (1511–1553), the guiding life force, though not an actual founder, of the Unitarian Church (22), and the Italian physicians Colombo and Cesalpino. In that time of fanaticism, Servetus’s theological writings were condemned. He published his books either under his own name or under the pseudonyms of “Villanobus” or “Serveto de Revés.” Leibniz, inappropriately in my view (see next, as well as Fig. 1), gave Servetus credit for having been the discoverer (22) of the pulmonary “circulation.” Servetus, in his Christianismi Restitutio (1553) (56), gave a description of the bountiful (vs. restricted, according to Galen) perfusion of blood from the right ventricle through the lungs and from there to the left ventricle and the arteries, and particularly to the brain. However, he did not discuss the motive function of the heart. His stated objective (56) was to indicate the transfer of the Holy Spirit from the inspired air to the brain, the seat of the soul. Being in agreement with Galen that blood is consumed by organs and tissues, Servetus did not mention its return to the heart; accordingly, he should not be considered as a discoverer of the lesser circulation.

Realdo Colombo (1516–1559) (62), who had been Vesalius’s assistant and succeeded him as professor of surgery at the University of Padua, clearly described the pulmonary loop. The process, communicated 6 years earlier in Christianismi Restitutio by Servetus, was perfected and demonstrated more completely in Colombo’s work De Re Anatomica, Libri XV (1559) (30, 39). Colombo clearly outlined the passage of venous blood from the right ventricle, through the pulmonary artery to the lungs, from where it emerges bright red after mixture with some “spirit” in the air, to return to the left ventricle through the pulmonary veins. Harvey read Colombo’s writings at Padua, and he acknowledged him repeatedly in De Motu Cordis (25), as the discoverer of the pulmonary loop. Notable was also Colombo’s description of general cardiac action (67), which correctly stated that blood is collected into the ventricles during diastole, or relaxation of the ventricular muscles, and expelled from them during systole through myocardial contraction; as was mentioned above (6, 43–46, 61), this view is nowadays rendered somewhat controversial by Francisco Torrent-Guasp’s model of the human heart. Colombo determined that the main action of the heart was actually contraction, not expansion, as had been thought until then.

Andrea Cesalpino

In 1571, Andrea Cesalpino (1524–1603) (21), with whose medical works Harvey must have also been acquainted, published Peripateticarum Quaestionum Libri Quinque, a systematic book on the basis of the Aristotelian philosophical framework (9). In it, he described (2, 10) quite accurately the heart valves and the pulmonary vessels connected to the heart, as well as the pulmonary circulation. Although Cesalpino had not attained a thorough knowledge, founded on anatomical research, of the entire course of the blood, he speculated that the heart is the center of the circulatio sanguinis (blood circulation), a term that he coined, and specified that blood flows in a perpetual movement into the heart from the veins and from the heart to the arteries (2, 10). He examined experimentally the difference between the blood flow in veins and that in arteries, and he deduced the presence of vasa in capillamenta resoluta (2), the invisible hair-like “capillaries,” as he was the first to name them, between the two vascular networks; he did, however, acknowledge that these connections were “what the
implies flow toward the periphery; in contrast, when he ligated an artery, it bulged on the cardiac side, implying flow toward the heart (2,9). Moreover, in Quaestio IV of the Peripatetic Problems, the pulmonary circulation is identified unambiguously, although its function is considered to be one of cooling. In paragraph 11, Cesalpino states (9, 10):

“From the contact with cold air or water during its passage (through lungs or gills), nature has provided a cooling process. The lung, then, draws warm blood through the vein-like artery [vena arterialis, i.e., pulmonary artery] from the right ventricle of the heart and returns it through anastomoses to the arteria venosa [pulmonary veins], which enters the left heart. . . . Dissection corroborates this ‘circulatio sanguinis’ [circulation of the blood, see above] from the right ventricle of the heart through the lungs and to the left ventricle of the same. For, there are two vessels which connect into the right ventricle and two into the left. Of these two, one introduces blood only, while the other conducts it out with its valves constituted for that purpose. The vessel which leads in is the great vein on the right which is called the vena cava. The one on the left, leading in from the lung, is small, and has a single coat like other veins. The vessel leading out on the left is the great artery and is called the arteria aorta; the vessel on the right is small, however, and leads to the lungs, and has two coats like other arteries.”

The preceding excerpt bears upon the question of Cesalpino’s place in history and demonstrates that he had probably penetrated into the enigma of the Circulation further than any other physiologist before Harvey—in Italy, he is regarded as the real discoverer (see Fig. 3). However, it is highly unlikely that this is a valid allegation. Consider the following: De Venarum Ostiolis (19), the treatise of the illustrious teacher of Harvey, Fabricius of Aquapendente, was published in 1603, more than 30 years after Cesalpino’s own Peripateticarum Quaestionum Libri Quinque, and a year after Harvey left Padua. It provides undeniable direct evidence of Fabricius’s and indirect consequent evidence of Cesalpino’s total ignorance of the simple hydraulics of blood in the systemic loop.

In it, Fabricius writes that the purpose of the valves in the veins was not to ensure the unidirectional flow to the right heart, but to prevent overdistension of the veins by blood passing through the venous trunks to their tributaries, and also to retard the progress of the venous current so as to afford each part, or organ, time to procure its proper nutriment (in agreement with the Galenic concept). Fabricius also noted that arteries do not need valves because they are not liable to overdistension, given the strength and thickness of their coats. Neither are valves needed to retard the blood stream, because in the arteries there is perpetual flux and reflux of blood (quod sanguinis fluxus reflexusque in arteriis perpetuo fiat). Such, then, was the state of understanding of the systemic loop taught by Harvey’s teacher more than 30 years after the publication of Cesalpino’s Peripateticarum Quaestionum Libri Quinque. The understanding as to the function of the valves was, in nuce, that they were present to sustain the column of venous blood and thus prevent blood from stagnating at the extremities of the limbs with a consequent unequal distribution of nutrient—a view that was the only conceivable one without the complete refutation of the then current and universally accepted Galenic notions on the movements of the blood.

**HARVEY’S EPOCH-MAKING DISCOVERY AND POSTHUMOUS VINDICATION**

Indeed, it was reserved for Harvey, from all the known fragmented anatomical facts to devise a coherent, comprehensive, hydraulically consistent theory of the cyclic, incessant, coupled, and concurrent passages of blood through a greater systemic and a lesser pulmonary loop (see Fig. 1). To this end, he arrived through the application of, paraphrasing Galileo, easy to understand once they had been applied mathematical methods (the point was to apply them!) and exhaustive, meticulous animal studies.

In this context, we need to ask what led Harvey to see mechanisms completely differently than other researchers, thinkers, and experimentalists. It was not simply a matter of his using his eyes better, nor the fact that he used experiment, because his rivals did so too. Indeed, with respect to using one’s eyes, the Circulation is not something that is visible. It is the deduction of a quantitative argument about anatomical pathways, the capacity of the chambers of the heart, its rate of pulsation, and the implicit recognition of the continuity principle of fluid dynamics. The latter was enunciated first by Aristotle (44), whose devoted follower Harvey was throughout his life, and embodies the law of mass conservation, as applied to blood in the Circulation.

**APPLICATION OF THE RESOLUTIVE OR ANALYTIC METHOD OF ARISTOTLE, WITH MASS CONSERVATION CONSIDERATIONS**

Through mass conservation arguments, Harvey rebuked the Galenic view of continual formation of blood by the liver from digested food brought to it via the portal vein, with subsequent passage through the systemic veins to the periphery (Fig. 2), there to be continuously consumed as nutrient or transformed.
into flesh. He started by measuring the quantity of blood in the body of an animal (he took an animal and cut a vein to extract “all” the blood) and saw that its quantity was limited. He also ascertained that by cutting a single artery, “all” the blood may be easily drained from the whole body in half an hour’s time. Therefore, the blood content is not continually formed, in the Galenic notion, but must be preset.

He went on to describe, in Chapter IX of *De Motu Cordis*, how the blood that is put out by the heart in less than half an hour would amount to a multiple of the total weight of a man. It is instructive to consider his reckoning as he presents it [in Chapter IX, in the Keynes translation (25)], albeit somewhat abridged here for brevity. In an approach somewhat reminiscent of a thought experiment, in Ernst Mach’s *Gedankenexperiment* sense, he reasoned that with every successive systolic contraction, the heart pumped, say, 2 fluid ounces of blood out through the aorta, “which by reason of the hindrance of the portals (aortic valve cusps) cannot return to the heart.” He could count the heart beats in a minute—about 72—so he could estimate the heart’s nominal hourly output, 8,640 ounces of blood. Because that much blood would weigh three times as much as an average man (more than 240 kg), Harvey realized that the same blood must be pumped around and around the system: “But grant that it be not done in half an hour, but in a whole hour, or in a day, be it as you will, it is manifest that more blood is continually transmitted through the heart, than either the food which we receive can furnish, or is possible to be contain’d in the veins.” What a neat example of a modern engineering order of magnitude analysis, perfectly suited to the question at hand! Today’s accurate calculations or assessments of cardiac output would not change Harvey’s conclusion that the blood circulates. Indeed, Harvey’s invocation of incontrovertible quantitative reasoning in physiology may be just as important as his momentous discovery of the Circulation!

As a result of the above illuminating quantitative arguments, Harvey came to discuss the concept of a closed-loop circulation (25), as is depicted in Fig. 1. Recapitulating now, through his simple but powerful mathematical calculations of the amount of blood that traverses each side of the heart per unit time and with every systole, Harvey deduced that the amount of blood that passes through the heart even in only one-half hour should be more than the total contained in the body. Bear in mind that all of Harvey’s estimates were intentionally low, so that he could unquestionably indicate the vast amount of blood Galen’s theory required the liver to produce. He states [Keynes translation, from (25)]: “But howsoever, though the blood pass through the heart and lungs in the least quantitie that may be, it is convey’d in far greater abundance into the arteries, and the whole body, than it is possible that it could be supplied by juice of nourishment which we receive, unless there were a regress (return) made by its *circuition*.”

Thus, through his unassailable quantitative reasoning, Harvey argued that the incessant blood motion is readily compatible only with a circulatory system! Quod erat demonstrandum, or ἀπὸ ἡμῶν δεῖξαι, as Euclid, or Archimedes himself would note. This was accomplished through deceptively simple arithmetic considerations. We remember, however, the likewise straightforward and deeply insightful dictum attributed to Galileo: “All truths are easy to understand once they are discovered; the point is to discover them.” The point in Harvey’s case was to conceive the powerfully insightful deduction that emanated, quite naturally, from his order of magnitude analysis.

**APPLICATION OF THE DEMONSTRATIVE METHOD OF ARISTOTLE, WITH FUNCTIONAL ANATOMICAL OBSERVATIONS**

Starting in his first Lumleian lecture to the (later to become “Royal”) College of Physicians in London, in April 1616 (58), Harvey presented in homilies the broad outlines of his ideas about the blood circulation. He proceeded with their publication, however, only in 1628; after more than another decade of further comprehensive animal research to perfect an assiduous experimental validation of his grand idea of the *Circulation*. Clearly, he followed determinedly the Horatian admonition: *Nonumque prematur in annum* (Horace, *Ars Poetica* 388)—“...Then put your manuscript, Away till the ninth year: you can always destroy, what you haven’t published: once out, there’s no recall.”

In studying the cardiovascular system, Harvey became a pioneer also in the study of embryology, having examined the development of the chick in the egg and having performed many dissections of mammalian embryos at various stages. In the course of his tireless functional anatomic cardiovascular studies of scores of species and many embryonic preparations (see below) he formulated his understanding of comparative anatomy and embryology, which formed a leg of his edifice of the Circulation of the Blood. From these experiments, he was also able to formulate his theory of animal generation, which he published in 1651 in *Exercitationes de Generatione Animalium* (24). In this work he propositioned that, rather than existing preformed as a homunculus in the ovum, as believed by his contemporaries, the embryo is formed gradually from its parts, as Aristotle had demonstrated many centuries earlier in formulating his theory of epigenesis.

Harvey labored incessantly; alongside his medical practice, he examined thoroughly more than 80 species in various animal classes, including mammals, birds, reptiles, amphibians, fishes, crustaceans, and insects! Of the essence is that he not only compared their cardiovascular organs, but he also manipulated them in dead and living animals. In all of these endeavors, he followed the paradigm set by Galen (25). He isolated various parts of the heart; he ligated and divided arteries; he famously compressed veins on either side of interposed valves. His observations showed that the cardiac valves allowed only unidirectional blood flow. He thus arrived at the conclusion that the heart valves subserve essentially the same function as the venous valves (i.e., they guard against refluxes of blood), and identified the systolic contraction as the active *working* phase of the heart muscles.

Harvey arrived at the global kinematics conclusion that the blood from the right ventricle flows through the lungs to the left side of the heart, from there to be distributed to the whole body by the arterial vasculature. Subsequently, blood flows centripetally through the systemic veins to return back into the right heart, completing the circle (25). Only the during-his-time-still-unknown pulmonary and systemic capillaries and adjoining microvasculatures formed unidentified gaps in Harvey’s overall circulatory system paradigm (see Fig. 1). Without a microscope, Harvey could not see what connected the arteries and veins, but he perceived that a connection had to exist.
between the arteries and the veins. Accordingly he conjectured, following Galen, the discovery of small arteriovenous insculations or anastomoses, and pores or porosities of the flesh through which the blood seeped from arteries to veins (25).

Furthermore, from his meticulous measurements of blood vessel sizes and the timing of the pulse and the contractions in the heart’s big ventricles and smaller auricles, Harvey correctly advocated that the heart beat originates in the auricles and that the powerful contraction ensues in the ventricles only after they have been filled up with blood from the chambers above them. He likewise deduced that the pulse beat in the arteries was a delayed consequence of the left ventricular contraction.

At this juncture, the question arises: from where did Harvey get the idea of the experimental method? He had two primary foundations: one was the codified work of Galen, who was perhaps the greatest experimentalist in biology and medicine; the other was the new tradition of experimental science that was blossoming in the 17th century in Padua. Galileo was teaching at the University of Padua during Harvey’s student years there, and it seems highly unlikely that Harvey could have avoided at least some acquaintance with his measurement principles and methods. In turn, Harvey’s experimental paradigm influenced many figures rising to influence in British “natural philosophy,” such as Robert Hooke, Robert Boyle, John Wallis, and especially Christopher Wren (see below).

Members of this group worked toward founding the Royal Society of London for the Improving of Natural Knowledge. Its motto, shown in its Coat of Arms in Fig. 4, seems to be inspired by or, at least, in harmony with the paradigm of Harvey and declares “Nullius in verba,” (take no one’s word for it). It is an expression of the resolve of Fellows to withstand any sort of domination by any authority and to verify all statements by an appeal only to facts determined by experiment.

Fig. 4. Nullius in verba: take no-one’s word for it; the motto of the Royal Society of London for the Improving of Natural Knowledge is proclaimed on its coat of arms. It seems to have been inspired by or, at least, in harmony with the paradigm of William Harvey, and affirms a resolve to withstand dominance by any authority and to verify all statements by appealing only to facts determined by experiment. The two keen-scented white hounds symbolize the capacity to pursue and sniff out true knowledge.

MICROSCOPIC DEMONSTRATION OF THE “MISSING LINK” AND HARVEY’S POSTHUMOUS VINDICATION BY MARCELLO MALPIGHI

The capstone of Harvey’s splendid physiologic construct was contributed by Galileo’s student Marcello Malpighi (1628–1694), who provided microscopic evidence of the “missing link,” represented by the capillaries, in 1661, 4 years after Harvey’s death (44, 66). That was also 15 centuries after Galen surmised that the veins communicate with the arteries by fine tubular anastomoses. Malpighi is arguably the father of microscopic anatomy, or histology, because of his many important discoveries, including the red corpuscles, to which he correctly attributed the color of blood, and fibrin, today’s fibrin (44).

Cold-blooded amphibians, including the frog, have capillaries and red corpuscles that are 3–4 times the size of those of warm-blooded animals (44). Conveniently, Malpighi saw the capillaries first in the lungs and the mesentery of a frog, and the discovery was announced in the second of two letters, Epistola duae de Pulmonibus, addressed to his good friend the iatrophysicist Borelli, and dated 1661 (44). “I could clearly see that the blood is divided and flows through tortuous vessels,” wrote Malpighi, “and that it is not poured into spaces, but is always driven through tubules and distributed by the manifold headings of the vessels . . .” In extrapolating his findings to humans, Marcello Malpighi vindicated Harvey, if only posthumously.

EARLY MEDICAL SQUABBLING AROUND HARVEY’S DISCOVERY

As Claude Bernard (1813–1878), the great French physiologist-physician, has remarked, according to an epigraph to Chapter 15 of Flesch R, The art of clear thinking, New York, 1951: “In science the important thing is to modify and change one’s ideas as science advances.” De Motu Cordis, Harvey’s monumental treatise presenting the greatest generalization in the history of physiology, the Circulation of the blood, received heavy criticism from his contemporaries, and because of public criticism he even lost many patients from his private practice. Some questions were, admittedly, legitimate; the ultimate purpose of the circulation of the blood, and the difference in color between arterial and venous blood, remained as two vexing unresolved questions in Harvey’s scheme. His discovery attained wide acceptance only gradually and stingily by the medical establishment, which was accustomed to and comfortable with the ostensibly sensible Galenic texts and doctrines, and found it hard to modify and change their ideas. Some even ridiculed the patently foolish concept of grounding scientific understanding on observation, given that the real world was filled with distortions and exceptions.

Indicative of his difficulties in this regard is that he passionately continued his experiments for decades after the publication of De Motu Cordis. A well-designed experiment on the pulmonary circulation is described, quite vehemently, in a letter written to his friend, Paul Slegel of Hamburg in 1651 (23):

“In a strangled human body, the pulmonary artery and aorta are ligated, the left ventricle opened, and a cannula placed in the vena cava, and water forced in. What happens? [Quid fit?] The right ventricle is greatly swollen [vehementer intumuit]. Through the opening in the left ventricle, however, not a drop of water or blood escapes. So now (the solution having been
predicted), the syringe is introduced into the pulmonary artery, with a ligature around it lest water regurgitate into the right ventricle. We force the water in the syringe against the lungs and immediately water with copious amounts of blood [cum copioso sanguine] leaps out of the cleft in the left ventricle, so that, as much water as is expressed into the lungs, so much flows out of the hiatus mentioned. You can experiment as often as you like, and know for certain that this is so. By this one experiment, I have easily butchered all the arguments of Riolan on this question [Hoc uno experimento, facile omnes Riolani circa hanc rem altercationes jugulaveris]."

The above excerpt from Harvey’s letter to his friend is illuminating in at least two respects: It attests to his utter impatience with his adversaries, some of whom are obviously still going strong in opposing his message, nearly a quarter of a century after its publication; and it gives, in nuce, a self-contained, first-hand account of his incredibly modern approach to physiological investigation, for us to admire! It also emphasizes that the experimental demonstration of the Circulation rested not only on the calculation of the volumetric flow rate of blood passing through the heart with every beat but also on Harvey’s deep understanding of the uses of ligatures of varying tightness in investigating circulatory flows.

Happily, our brains are not physiologically static organs, and they and our convictions can change throughout life and with the passage of time (42). Increasingly, Harvey’s momentous discovery diffused through the ranks of the scientific community and the medical profession, and of other curious minds. Increasingly in the 1630s, Harvey’s system gained ground as the general public began to see it as a paradigm for a new approach to the human body and to medicine. Exploring the human anatomy became fashionable and engendered fascination matching the exploration of the skies. In Amsterdam, the physician Nicolaes Tulp gave public anatomy demonstrations, using cadavers of executed criminals. He was immortalized in Rembrandt’s painting The anatomy lesson of Dr. Tulp, in which, using a forceps, he lifts up a muscle of the left forearm of a cadaver using his right hand. According to an orthopedic surgeon who has studied the painting exhaustively (36), Dr. Tulp is holding his left hand in such a way as to reproduce the movement brought about by this particular muscle—the flexor digitorum superficialis—with his own left hand.

**INITIAL RICOCHET EFFECTS OF HARVEY’S GRAND “BILLIARD BALL STRIKE” AND EARLY MEDICAL APPLICATIONS**

Before too long, Harvey’s discovery of the Circulation became the source of enduring repercussions on medical prac-tice that were natural, rather than imposed by the medical establishment, because the medical profession organizes itself to support and further develop a medical scientific advance and new understanding, once it has been accepted. A solid under-standing of the circulation of blood acted as a “billiard ball,” producing a series of ricochet effects on medical practice. Elaborated in De Motu Cordis in 1628, it marked the birth of modern circulatory physiology and had far-reaching repercussions on the practice of medicine. It led to the first attempts at blood volume replenishment by transfusions after heavy hemor-rhage, and to the administration of solutions of medicinal substances as intravenous injections or infusions.

By 1657, the year that Harvey died, the first direct animal transfusions were conducted by the English anatomist and physiologist Richard Lower (1631–1691). Collaborating with Robert Hooke, he also followed the movement of blood as it passes across the lungs and observed that it changes color when exposed to air. Lower refined and supplemented Harvey’s circulatory concept in his work *De Corde*, which he published in 1669 (18); he attributed arterialization to air actually entering the blood in the lungs—Antoine Lavoisier (1743–1794) eventually showed that arterialization involves O₂ uptake and CO₂ release in the passage of blood through the pulmonary capillaries (29).

Following the publication of *De Motu Cordis*, several individuals in different European countries would start thinking along similar lines; this resulted in conflicting priority claims as to the first human blood transfusion. The first fully authen-ticated human blood transfusion was probably accomplished by Jean-Baptiste Denis (1625–1704), eminent physician to King Louis XIV of France, on June 15, 1667 (63). He transfused the blood of a sheep into a 15-year-old boy, who actually recovered. Denis was, of course, totally unaware of the serological and immunological conditions that impinge on such technically simple undertakings. Having been recognized not to be generally successful, such endeavors were soon outlawed. Conversely, the practice of bloodletting, which had been common since ancient times, seemed to take an upswing in the aftermath of Harvey’s momentous discovery.

One of the earliest attempts at intravenous injection was made in 1656 by (later to become “Sir,” and President of the Royal Society) Christopher Wren (1632–1723), one of the most accomplished individuals of the Scientific Revolution period and a keen experimentalist in the natural sciences, who was strongly influenced by Harvey’s discovery. He is recorded in the historical archives of the Royal Society of London as “...the first author of the noble anatomical experiment of injecting liquor [liquid] into the veins of animals...Hence arose many new experiments and chiefly that of transfusing blood, which the Society has prosecuted in many instances, that will probably end in extraordinary success” (59). His technique did not find immediate therapeutic application, although he succeeded in injecting drugs directly into a dog’s veins, with the help of a hollow, slender quill (from a bird’s feather), to which was attached a small animal bladder.

Among the physicians who ventured intravenous injections and infusions of drug solutions was Johann Sigismund Elsholtz (1623–1688), a German naturalist and court physician to the Elector of Brandenburg and Duke of Prussia. He performed early research on blood transfusions and “infusion therapy.” In his 1667 work *Clysmatica Nova* (16), he investigated the possibilities of intravenous injection. Johann Daniel Major (1634–1693) was a professor of theological medicine and of botany and chemistry at the Christian-Albrechts-Universität in Kiel, Germany (55). Major thought that illnesses might arise from degraded blood; in such cases, cures could be provoked by either injecting a healing medicament straight into the blood stream, or by transfusing intravenously the blood of a healthy individual directly into the patient. To perform his injections, he used tiny silver pipes (needles) rather than the more common feather quills.
CONCLUSION

In Harvey’s opus majus, his Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus (An Anatomical Disquisition on the Motion of the Heart and Blood in Animals), we see the mechanisms of the Circulation worked out more or less in full from the results of experimental demonstration, virtually complete but for the direct visual evidence of a link in the periphery between the minute final terminations and initial branches of the arterial and venous systems, respectively. This would only become available when the capillaries could be seen under the microscope. Harvey’s amazingly modern order of magnitude analysis of volumetric circulatory flow and appreciation of the principle of continuity (mass conservation), his adroit investigational uses of ligatures of varying tightness and in various combinations in elegant flow experiments, and his insightful deductions truly explain the movement of the blood in animals. His end was accomplished. So radical was his discovery, that early in the 18th century the illustrious Hermann Boerhaave, professor of medicine at Leyden, declared that nothing that had been written before Harvey was worthy of consideration any more (4). The conclusions of De Motu Cordis are unassailable and beautiful in their simplicity. Harvey’s genius and determination have served physiology and medicine well!

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Author contributions: A.P. conception and design of research; A.P. performed experiments; A.P. analyzed data; A.P. interpreted results of experiments; A.P. prepared figures; A.P. drafted manuscript; A.P. edited and revised manuscript; A.P. approved final version of manuscript.

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