William Harvey and the Circulation of the Blood: The Birth of a Scientific Revolution and Modern Physiology

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William Harvey was born to a reasonably well-to-do family during a period of unparalled intellectual fervor. The year was 1578, and the period has come to be known as the period of the "scientific revolution." And indeed, it was a revolution, not because of the frequency of scientific discoveries — that prize goes to the present — but because it witnessed a revolution in epistemological thinking, an upheaval in the approach to acquiring the truth about the natural world.

But more about that later.

Because of his family status, Harvey had no problem obtaining a privileged education. He studied at the elite King's School in Canterbury (1588–1594) and later at Gonville and Caius College of Cambridge University, where he received a B.A. He obtained a Doctor of Physic diploma from the University of Padua in 1602. That institution, the alma mater of the same Dr. Caius who helped found Harvey's alma mater at Cambridge, was one of the great centers of medical education at the time, the home of Galileo and the great anatomist Versalius. There Harvey studied under a student of Versalius, Fabricius, who had written a treatise on the valves in veins but hadn't the vaguest idea about what they did other than that they might slow blood flow (6, 13, 14, 17).

Years later, when Harvey was close to death, he was asked by Robert Boyle what had induced him to think that the blood circulated (13, 17). Harvey replied

> ...that when he took notice the Valves in the Veins of so many several parts of the body, were so plac'd that they gave free passage to the Blood Towards the Heart, but oppos'd the passage of the Venal blood the Contrary way: He was invited to imagine that so Provident a Cause as Nature had not so Plac'd so many Valves without Design: and no Design seem'd 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 though the Veins, whose Valves did not oppose its course that way. (4)

After returning to London, Harvey obtained his M.D. degree from Cambridge (1602); he became a Fellow of the Royal College of Physicians in 1607 and the physician to St. Bartholomew's Hospital in London in 1609. Later, at the age of 37, he was appointed to the distinguished position of Lumleian Lecturer in anatomy at the College of Physicians. It was in the latter capacity that he undertook the experiments that were to lead to one of the greatest scientific revolutions of the century — one that was to abolish, without a trace, a dogma that had persisted for almost 1,500 years (11, 12, 14).

The origin of Galenism

To fully appreciate the magnitude of Harvey's revolution, we have to dip back in time to the golden age of Greece, around 400 B.C. By that time, the Hellenist civilization had rejected the mythological notions of earlier civilizations that placed everyday events in the hands of spirits in favor of the conviction that events such as rain or disease have natural rather than supernatural causes and that these causes are subject to critical and rational analysis: a transition from "mythos" to "logos," from mythology to logic or reason (14).

Accordingly, humans were believed to be made up of the same fundamental elements (Fig. 1) that comprise all of the cosmos — fire, water, air, and earth. Furthermore, these elements could have the qualities of being hot, cold, dry, and/or moist. The food and drink that animals consumed consisted of these elements, and in the course of digestion they were converted into the bodily juices or humors, namely the blood, phlegm, yellow bile, and black bile, respectively. From these came the descriptors sanguine, phlegmatic, choleric, and melancholic (11, 14).

Hippocrates (1, 14), considered the founder of Western medicine, maintained that health required the proper balance of these elements; imbalance resulted in disease. Thus, in a sense, Hippocrates and the school of medicine that followed him can be considered the originators of the notion of "homeostasis." Almost two millennia later, this notion was reinvented by Claude Bernard to describe the constancy or *fixité* of the internal environment or *milieu interior* necessary for a free and independent life (2), and the term "homeostasis" was formally introduced into the scientific literature by Walter Cannon in 1939 in his great book entitled *The Wisdom of the Body* (5).

When one reads the treatises that bear Hippocrates' name, for many of these treatises are believed to have been written not by him but by his followers (1), one is impressed by the

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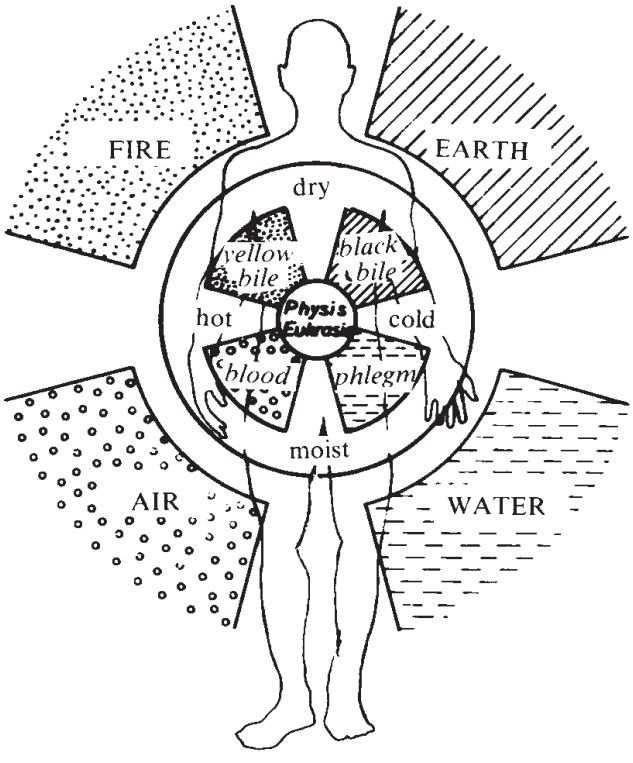

FIGURE 1. The relations among the elements that comprise the universe, their qualities, and the humors present in the human according to the ancient model.

clinical acumen in the face of a nearly complete ignorance of the relation of disease to the structure and function of the human body. What remains of Hippocrates today is his "oath" (1); the physicians' "Sermon on the Mount," intended to initiate them into one of man's noblest professions.

The Hippocratic school dominated Western medicine for the next 500 years, until another Greek came onto the scene, namely Galen, who was born in what is now Turkey but spent most of his adult life and rose to medical fame in Rome (14, 15). Galen built on the earlier Hippocratic concept that human health required an equilibrium between the four main bodily fluids or humors but regarded anatomy as the foundation of medical knowledge and did many dissections on lower animals (15); he also served for a short time as the physician to a school of gladiators and so must have seen the human body in various forms of gory disarray (15). In contrast with Hippocrates, he felt that health depended on the proper balance of humors in specific organs, not only the body as a whole.

Galen viewed the body as consisting of three connected systems (Fig. 2): the brain and nerves, which were responsible for sensation and thought; the heart and arteries, which were responsible for life-giving energy or "vital spirit"; and the liver and veins, which were responsible for nutrition and growth. According to Galen, blood was formed in the liver from food carried to that organ from the stomach and intestines via the portal vein. This "natural" blood then entered the systemic veins and was carried to all parts of the body, by an ebb and flow, where it was consumed as nutrient or was transformed into flesh. Thus blood was not conserved; it was constantly being consumed in the periphery and replenished by ingested nutrients, and this was all carried out by the right ventricle and great veins.

The main task of the left ventricle was to generate a pulsatile force to blood in the arteries, which absorbed "pneuma" or spirit from the lungs. Much of the blood in the left ventricle came directly from the right ventricle through pores in the interventricular septum and some through "leaks" in the pulmonary circulation; the latter were needed to explain the fact that the pulmonary veins contained blood and were not filled with air alone. The main purpose of the "vital" arterial blood, as distinguished from the "natural" venous blood, was to deliver pneuma or "spiritus vitalus" to the peripheral tissues. According to Galen, there was little mingling between arterial and venous blood; each stream had its distinct and essential purpose.

In this sense, Galen was a true post-Aristotelian who blended a touch of empiricism, in this case anatomic findings, with a large dose of causal or teleological speculation; everything had to serve a purpose or final cause.

> All parts of the human body are formed in the optimal manner to serve their intended human purposes. Nature is provident, just, and all knowing and does nothing in vain. (15)

In the case of the functions of the heart and great vessels, Galen's model was biased by the heavy emphasis the Greeks placed on the role of a wholesome diet and fresh air in preserving health. Thus the function of the right side of the vasculature was to deliver the products of a healthy diet to the tissues of the body and that of the left side was to deliver fresh air and cool the body.

This model was to survive, essentially unquestioned, for the next 1,400 years despite the fact that some had denied, and no one had been able to confirm, the presence of holes in the interventricular septum (see below). In the absence of such communications there should be little blood in the arteries, and that was contrary to innumerable observations. But why let dirty facts blemish what appeared to be a nice theory? The fact that the model provided an explanation for the existence of certain anatomic structures that was consistent with "Nature's" purported intent was enough; experimentation was unnecessary!

The demise of Galenism and the birth of a new paradigm

As pointed out above, Harvey was well trained in anatomy, and he, like his idols Versalius and Fabricius, was convinced that the interventricular septum was not leaky to blood. In addition, he was born into an era in which experimentation (the use of the hands) and computation, in addition to simple observation, became recognized as essential tools of the "scientific method." He was well aware of the work of Copernicus and Kepler, who preceded him, and of his contemporary

Galileo, for whom the combination of careful observation and computation resulted in nothing less than a switch between the earth and the sun as the center of our universe; Galileo's dictum "Measure all that is measurable, and make those things measurable which have hitherto not been measured" (13) was deeply impressed upon him. He was also familiar with the somewhat earlier writings of Santorio Santoro, who, sitting on an exquisitely sensitive balance, compared his body weight and the difference between the ingested food and his excreta and was capable of observing that the body lost a certain amount of weight continuously in the form of "insensible perspiration" (14).

But Harvey himself was a pioneer who had no footsteps to follow (11). Unlike the great Kepler, who improved upon Copernicus' observations, and Galileo, whose telescope unequivocally established the Copernican revolution, Harvey did not build on anything, revise anything, or improve on anything. Instead, he eradicated an existing dogma without a trace and replaced it with a paradigm whose essential features are immutable.

It remains today the greatest "single-handed" discovery in physiology and medicine, if not science in general.

This revolution was set forth in an exquisitely written 70-page monograph entitled "Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus" or "Anatomical Essay on the Motion of the Heart and Blood in Animals" (7, 8), commonly referred to as "De Motu Cordis" or simply "De Motu." It was published in 1628 when Harvey was already 50 years old.

Knowing that he was challenging a "big fish," albeit at first unintentionally, he opened the monograph with a letter to the King, Prince Charles, with the statement

> The heart of animals is the foundation of their life, the sovereign of everything within them...from which all power proceeds. The King, in like manner, is the foundation of his kingdom, the sun of the world around him, the heart of the republic, the foundation whence all power, all grace doth flow. (8)

His dedication to the President of the Royal College of Physicians reads like: "Hey, I'm really not out to get anyone, all I want to do is tell the truth!" For example, in this "dedication" he states

> ...the studious and good and true do not esteem it discreditable to desert error, though sanctioned by the highest antiquity, for they know full well that to err, to be deceived, is human....I would not charge with willful falsehood any one who was sincerely anxious for truth, nor lay it at any one's door as a crime that he had fallen into error. I avow myself the partisan of truth alone.... (8)

He closes: "Farewell, most worthy Doctors, and think kindly of your Anatomist" (8), suggesting that he feared the worst.

Harvey's revolutionary conclusion that blood is conserved and circulates was based on only a few observations. The major ones were as follows.

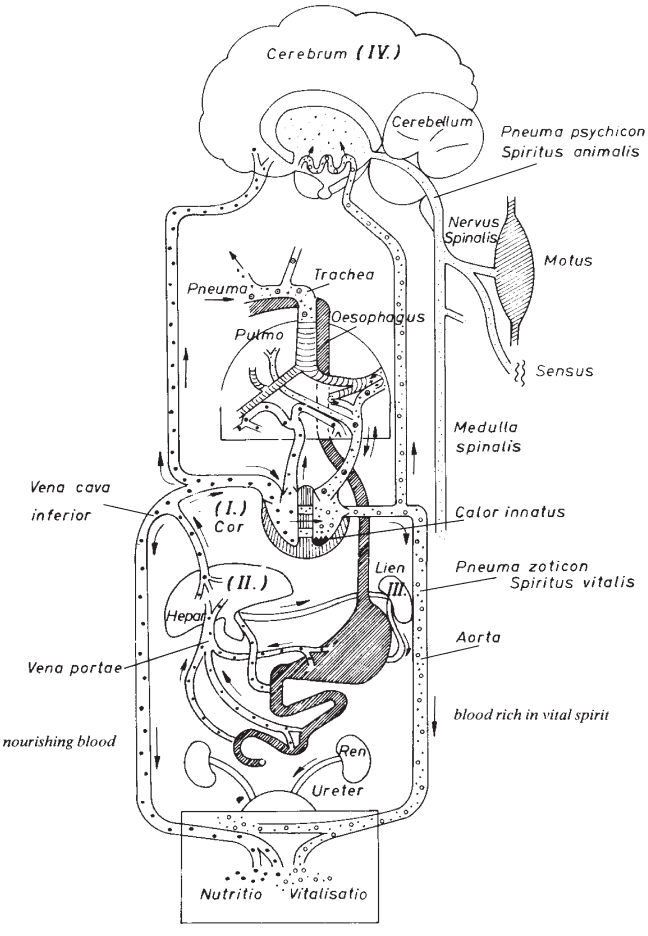

FIGURE 2. Galen's view of physiological systems, particularly the heart and great vessels. Note the communication between the right and left ventricles and the independent flows taking place in the venous and arterial vessels.

First, he measured the total amount of blood that could be drained from sheep, pigs, and some other subprimate mammals. He then measured the volume of the left ventricles of these animals and calculated that, if the left ventricle were to empty with each beat, in one hour the total volume of blood pumped would be much greater that in the ingesta or even that contained in the entire animal. Indeed, this would be true even if one-tenth of the blood contained by the ventricle were ejected per beat. Therefore, he concluded, "...it is a matter of necessity that the blood perform a circuit, that it returns to whence it set out."

He then demonstrated, publicly, that when a live snake is "laid open," compression of the vein entering the heart leads to a small heart that is devoid of blood upon opening it.

> If on the contrary, the artery instead of the vein be compressed or tied you will observe the part between the obstacle and the heart, and the heart itself to become inordinately distended and, at end, to become so oppressed with blood that you will believe it about to be choked.... (8)

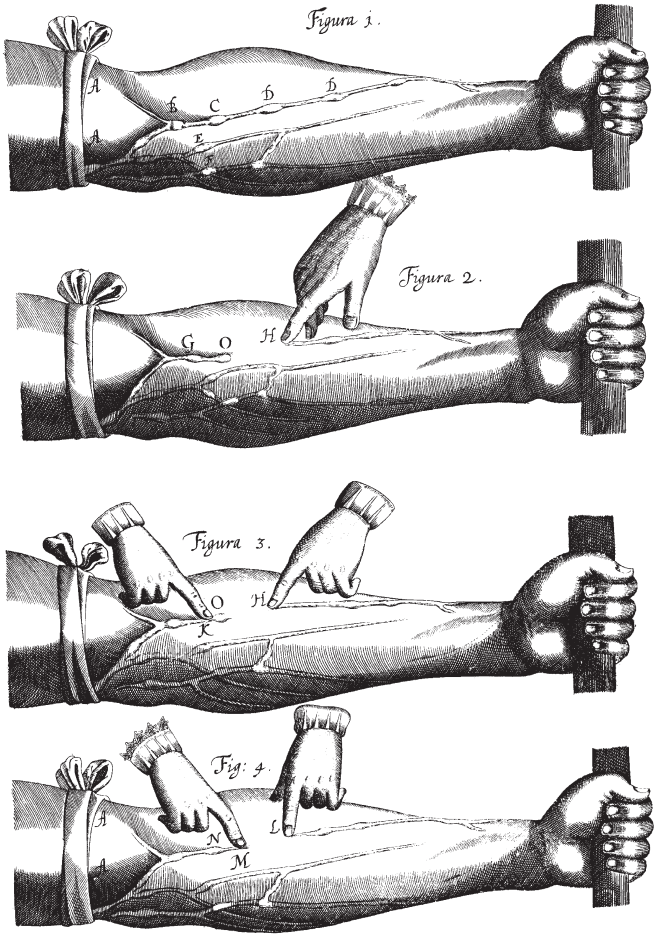

FIGURE 3. Harvey's experiment illustrating the venous valves (nodes or portals) and the unidirectional nature of emptying and filling. He also states: "Now if you reckon the business, how much by one compression moves upwards by suppression of the portal, and multiplying that by thousands, you shall find so much blood pass'd by this means through a little part of a vein, that you will find your self perfectly perswaded concerning the circulation of the blood, and of its swift motion" (8).

He also showed that, following light application of a tourniquet to the arm (Fig. 3), the veins become engorged and that blood can only be milked from an engorged vein in the oral direction — toward the heart — but when the vein is thus emptied it only fills from the periphery. Furthermore, knowing the diameter and length of the cylinder of vein, one can calculate the volume of blood that flows through the vein during rapid emptying and refilling. Harvey showed that in a day more blood flows through that segment alone than the quantity of food ingested.

If the tourniquet is rapidly applied very tightly, as was the practice in preparation for amputation, the arm blanches and veins do not become engorged. Thus veins are filled by arteries. Just how they were filled puzzled Harvey, but not enough for him to question the truth of his conclusion. He postulated the existence of small capillary anastomoses between arteries and veins, but these were not discovered until 1661, a few years after Harvey died, by Marcello Malpighi while studying the lungs of frogs (11).

Why did Galen's model dominate for 1,400 years?

An examination of the transition between the Galenic model of the circulation of the blood and the Harveian model sheds some light on the nature of the progress of science or, more exactly, on scientific revolutions.

Why in heaven's name did the Galenic model last almost 1,400 years? It was obviously baseless. Many anatomists, including the great Leonardo da Vinci, Versalius, and Harvey's mentor Fabricius had failed to find holes in the intraventricular septum for well over 200 years before Harvey, and it seems certain that these were never even found by Galen (11, 15, 17); these "anomolies," however, did not seem to trouble the faithful! While Realdus Columbus discovered communication between the pulmonary arteries and veins and the pulmonary circulation, thus obviating the requirement for interventricular septal pores to provide blood for the left ventricle and explaining the presence of blood in the pulmonary veins, there is no evidence that he questioned Galen's model with respect to the "ebb and flow" of blood in the systemic arteries delivering "spirit" to the periphery. Columbus' findings appeared posthumously in a publication entitled "De re anatomica" in 1560; the anatomist died in 1559 (17). The presence of valves in the heart and veins certainly suggested directional flows. The failure to eat obviously did not lead to a depletion of blood volume. This theory was patently groundless to any thinking, critical mind.

Furthermore, unlike the issue of geocentricity, that is, an earth-centered universe, vs. heliocentricity, or a sun-centered universe, Galen's model was not invested with much theological significance. The difficulties and, indeed, dangers that confronted Copernicus and Galileo in rejecting Ptolemy's geocentric model of the universe (note, Kepler was Danish, so he could work freely outside of the Vatican's reach) had little bearing on the issue of the circulation of the blood.

One important reason for the longevity of the Galen model is that it was not until the early part of the second millennium that the experimentation was once again trusted to shed light on the natural world in which we live. In his Harveian Oration for 1906, Sir William Osler said

> To the age of the hearer, in which men had heard and heard only, had succeeded the age of the eye in which men had seen and been content only to see. But at last came the age of the hand — the thinking, devising, planning hand, the hand as an instrument of the mind, now reintroduced into the world in a modest little monograph from which we may date the beginning of experimental medicine. (12)

Is it possible to express that notion more beautifully?

Another reason can be found, equally beautifully stated, in "De Motu." These are Harvey's words as he opens Chapter VIII ("Of the abundance of blood passing through the heart out of the veins into the arteries, and of the circular motion of the

blood"), in which he demolishes the core of the Galen model

> Thus far I have spoken of the passage of the blood from the veins into the arteries....But what remains to be said upon the quantity and source of the blood which thus passes, is of a character so novel and unheard-of that I not only fear injury to myself from the envy of a few, but I tremble lest I have mankind at large for my enemies, so much has wont and custom become second nature. Doctrine once sown strikes deep its root, and respect for antiquity influences all men. Still, the die is cast, and my trust is in my love of truth and the candor of cultivated minds. (8)

That could have been written by Shakespeare!

The fact is that Galen had been elevated to the status of a demigod, in a class with Socrates, Plato, and Aristotle. He was revered, not simply respected. His writings became viewed as scripture rather than scientific treatise. His views, along with those of other antiquities, though unintended, took on a "quasi-theological" status. These views became the "final words" — closed chapters! Although this was by no means his desire, Galenism became a theology of its own, virtually immune from reasoned challenge. Thus, when findings were uncovered that did not coincide with Galenist theory, they were marginalized instead of being viewed as true, challenging anomalies.

Harvey, in his brilliant monograph, beautifully addresses this issue and leaves a message that is as true today as it was 500 years ago.

> True philosophers, who are only eager for truth and knowledge, never regard themselves as already so thoroughly informed, [so that they do not] welcome information from whomsoever and from wheresoever it may come; nor are they so narrow-minded as to imagine any of the arts or sciences transmitted to us by the ancients, in such a state of forwardness or completeness that nothing is left for the ingenuity or industry of others. On the contrary, very many maintain that all we know is still infinitely less than all that remains unknown. [Nor] do philosophers pin their faith to others' precepts in such [ways] as they lose their liberty, and cease to give credence to the conclusions of their proper senses. Neither do they swear such fealty to their mistress Antiquity, that they openly, and in sight of all, deny and desert their friend, Truth. (8)

Harvey's warnings on the power of dogma and authority are as pertinent today as they were 500 years ago.

But another, perhaps most compelling reason for the longevity of the Galenic model in spite of its obvious, lethal flaws can be found in Thomas Kuhn's work, *The Structure of Scientific Revolutions* (9), which many, including this author, consider a most illuminating work on the nature of scientific progress. According to Kuhn, during any given period every "subspecialty" (e.g., cosmology, mechanics, epitheliology, etc.) is dominated by a near-universally accepted model or paradigm that is the "normal science," found in the standard textbooks, taught in the classroom. Kuhn argues

> In the absence of a paradigm or some candidate for a paradigm, all the facts that could possibly pertain to a given science are likely to seem equally relevant. As a result, early fact-gathering is a far more nearly random activity than the one that subsequent scientific development makes familiar. (9)

In other words, the paradigm provides the logical framework for the design and interpretation of experiments in that subspecialty; it promotes systematic research and discourages

"...in the absence of a paradigm "there is no science'...."

"fishing expeditions." Perhaps the most vivid description of the consequences of the absence of a logical framework or model was written by Copernicus in the forward to his great book, *De Revolutionibus*, addressed to Pope Paul III.

> ...it is as though an artist were to gather the hands, feet, head and other members for his images from diverse models, each part excellently drawn, but not related to a single body, and since they in no way match each other, the result would be monster rather than man. (10)

Kuhn more simply, and less colorfully, said that in the absence of a paradigm "there is no science" (9). As a result, scientific revolutions involve the replacement of one paradigm with another.

> The decision to reject one paradigm is always simultaneously the decision to accept another, and the judgment leading to that decision involves the comparison of both paradigms with nature and with each other. (9)

In light of these considerations, it is fair to say that Galen's model survived, in spite of the fact that it was confronted with many anomalies, because there was no comprehensive model to replace it until 1616 when Harvey started developing the notion of the circulation of the blood in his Lumleian lectures delivered at the College of Physicians, which were open to the public. For the next 12 years, Harvey continued to elaborate on this model, so by the time it was finally published, in 1628, when he was already 50 years old, he had already grown indifferent to the attack and abuse lavished upon it. It was published in Frankfurt in Latin, but the first English translation did not appear until two decades later, so that for a number of years its readership was limited to the educated population. Nonetheless, in spite of its clear-cut and compelling arguments that were above dispute, the monograph did not bring him immediate fame or prosperity. It was attacked by distinguished members of the academic community, often on the

sole grounds that it dared to question Galen and the normal science, so strong was the grip of the authority of antiquity on men's minds. It took half a century before it was accepted by as distinguished a center of learning as the University of Paris. Indeed, many years had to pass before this immortal work became widely recognized as one of the milestones in human accomplishment (6, 11, 12, 13).

In a recent essay (16), Stephen Weinberg, who received the Nobel Prize in Physics in 1979 for his contributions to elementary particle physics in general and the "Standard Model" in particular, took issue with Kuhn's view of the nature or structure of scientific progress as moving from one period of normal science to another or one paradigm completely replacing another. In particular, he points out that, although the Einsteinian revolution changed the context in which we view Newtonian mechanics (i.e., the Einsteinian paradigm replaced the Newtonian paradigm), Newtonian mechanics is still taught in undergraduate physics courses and, indeed, is a limit to which Einstein's equations can be reduced; not so, however, for the notion of the "ether," which was eradicated in Einstein's 1905 work. The Copernican-Kepler-Galilean revolution certainly eliminated the Ptolemaic model of the universe from the textbooks [but see Born (3)]. Galen's model of the role of the heart was abolished by the Harveian revolution, and the great Greek's work has been relegated to the dustbin of history. Also, I doubt whether most students of biology or medicine recognize phlogistin, the miasmic theory of disease, or many other concepts that have fallen victim to scientific revolutions in the Kuhnian sense.

William Harvey is rightly considered the father of modern physiology and medicine. His work not only established a seminal property of the cardiovascular system but also demonstrated the power of computation and the scientific method that has energized the long way we have come since his days and will continue to serve us well on the long road left to be traveled.

Please note, the Ref. 8 translation from the Latin was done by Dr. Robert Willis (1799–1878) for the Sydenham Society's 1847 edition of the Works of William Harvey. The language is more modern than that of the Keynes translation. This translation can be found on the internet at www.fordham.edu/halsall/mod/1628harvey-blood.html.

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