GIANTS IN NEPHROLOGY

Stephen Hales: the contributions of an Enlightenment physiologist to the study of the kidney in health and disease

Garabed Eknoyan

From the Selzman Institute of Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas

Address correspondence to: G. Eknoyan, M.D.; Department of Medicine (523-D) Baylor College of Medicine One Baylor Plaza Houston, TX 77030; Tel:713 798 4748 Fax:713 790 0681 e-mail: geknoyan@bcm.edu

Abstract

Stephen Hales (1677-1761) was an English clergyman who made major contributions to a wide range of scientific topics such as botany, chemistry, pneumatics, and physiology. Early in his career he developed a keen interest in medicine through his association with his younger physician friend at Cambridge, William Stukeley (1687-1765), with whom he dissected animals and attended experiments in the laboratory of Isaac Newton. His fame as a scientist grew and by the end of his life he had achieved an international reputation as a major scientist of the Enlightenment. He is best known for his 1733 Statical Essays, in the second part of which he describes his studies in animal physiology. Most famous amongst those are his assessments of the "force of the blood", which he measured in horses and dogs. Less well known and often unrecognized are his studies on the kidney in health and disease, which are the focus of this review. Amongst others Hales described the effects of hemorrhagic shock which he observed as he bled his animals while measuring their blood pressure; he then studied the effect of increasing saline perfusion pressures on the renal "secretion" of urine; and delved into biochemistry in exploring the composition of and solutions to dissolve bladder stones. His 1733 statement in the introduction to his hemodynamic studies that "the healthy State of the Animal principally consists, in the maintaining of a due Equilibrium between the body solids and fluids" literally predicts the 'milieu intérieur' that would ultimately be formulated in 1854 by Claude Bernard (1813-1878).

Key words: blood pressure, experimental physiology, homeostasis, renal perfusion, Stephen Hales

Introduction

The cultural movement that launched the Scientific Revolution of the 17th century matured in the following century into what has been dubbed the Enlightenment or Age of Reason, a period of major achievements that for practical purposes can be divided into two stages. The first stage during which the new concepts and methodologies of the Scientific Revolution were developed and disseminated; and the second stage when they were tested, studied, refined, expanded and applied. The dominant figures of the first stage were born just before the end or during the 17th century and were the founders who introduced measurement, mathematics and physics into scientific methodology (Galileo, Descartes, Newton, Harvey); whilst the second stage was led by a new generation which fueled by increased literacy, easier access to knowledge and facilitated exchange of ideas (journals, pamphlets, books, salons and academies) generated the intellectual forces of the 18th century that would set in motion the power of enlightened reasoning applied to scientific methodology, which in turn would herald the coming of the Early Modern Age of the 19th century (Figure 1). Whereas the transformative changes of the Enlightenment affected every level of society (social, financial, political, industrial, etc) it was in the sciences that its major impact was most evident. As a result, science became established as a branch of learning, with an exerted effort by universities to establish and expand their departments of the new and emerging scientific disciplines (astronomy, physics, mathematics, chemistry, etc). The three areas of medicine impacted by these transformative changes were in the development of physiology and pathology and the nascent attempts at launching chemistry [1] [2] [3].

The principal progress in Enlightenment physiology was in the rise of experimental physiology and reliance on mechanical explanations to interpret the generated data. The work of René Descartes (1596-1650) and Isaac Newton (1642-1687) were the basis of an increasingly convoluted mechanical philosophy that evolved from its simpler beginnings in the previous century laid by Giovanni Borelli (1608-1679), his colleague Marcello Malpighi (1628-1694), and his student Lorenzo Bellini (1643-1704) [1] [2]. A Scottish physician, Archibald Pitcairne (1652-1713) played a central role in the integration and elaboration of these new concepts into medicine that has been dubbed "Newtonian medicine" [2] [4] [5]. During a stay at Cambridge in 1692, Pitcairne was exposed to Newton who gave him a copy of his "*De natura acidorum*" in which he discusses the short range attractive forces of particles in solution, which Pitcairne went on to elaborate on how they applied to normal and abnormal physiology [4] [6]. Having established that the greater part of the body was fluid this new school of physiologists (Archibald Pitcairne, Robert Boyle, George Cheyne) reasoned that the normal and abnormal functions of the body could be explained by changes in the quantity, texture, flow and velocity of various bodily fluids, especially that of blood and glandular secretions [6]. The principles that emerged reached their apogee in the 1708 publication of "*Account of Animal Secretion*" by another Scotsman James Keill

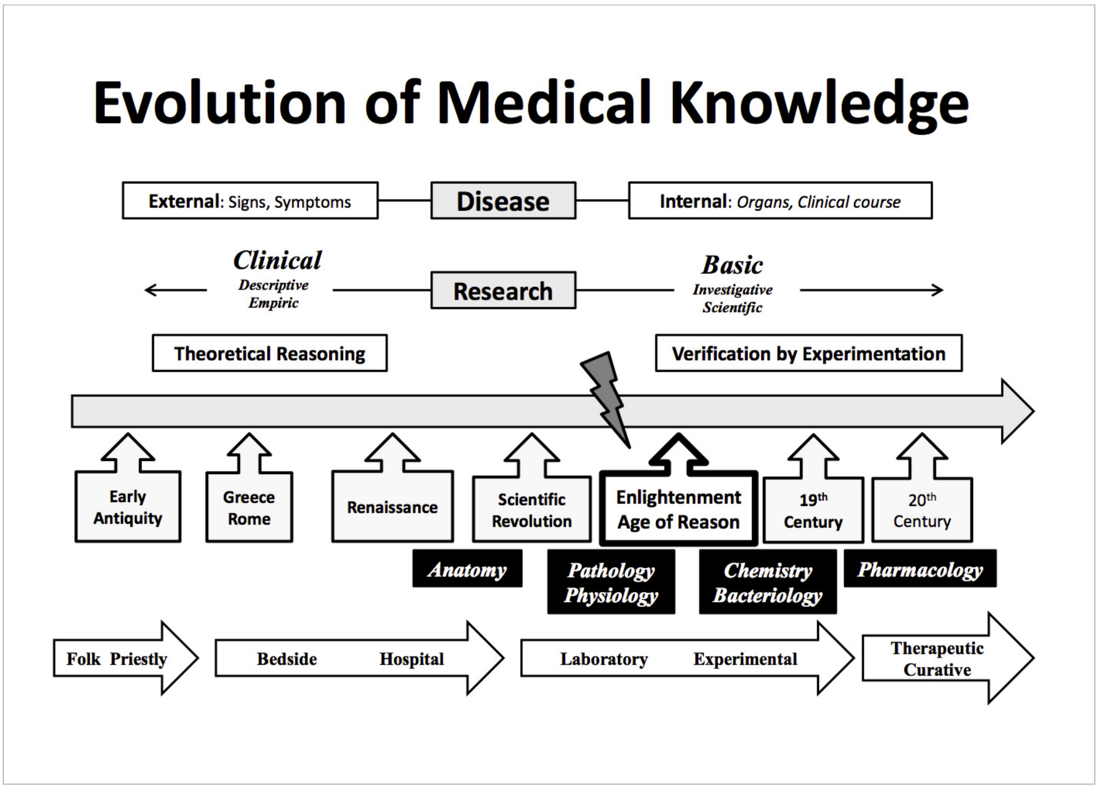

Figure 1.
A timeline of the evolution of medical knowledge. The upper part of the figure shows the conceptual evolution of diseases from a descriptive clinical phase of external findings (signs, symptoms) to that of an investigative basic research phase of internal organ involvement and pathophysiology. The long grey arrow in the center of the figure represents a time line of the classical historical periods shown in the light grey boxed arrows immediately below this arrow. The bottom smaller grey arrows of the figure represent the corresponding stages in the evolution of medicine from its origins as folk and priestly medicine in antiquity to its present therapeutic curative stage. The progress of medical knowledge by the various basic science disciplines during each stage is shown in the black boxes with white italic lettering just below their respective historical period. The lightening symbol at the center of the figure is to highlight the Enlightenment period covered in this article when anatomy transitioned into physiology and chemistry was just begun.

(1673-1719), who considered blood "a simple fluid in which a series of compounds of various shapes and magnitudes are endowed with different degrees of attractive forces" [7] [8] [9]. Familiar with the works of iatromathematicians as well as the metabolic balance studies of Santorio Sanctorius (1561-1636) that he translated into English, Keill was one of the first to work out the ratio of fluid to solid parts of the body through studies of tissue desiccation. He then delved into their broader implications in the context of the Harveian circulation of the blood by estimating the force of the heart, the pressure of the blood and the velocity of blood flow [7] [8] [9] [10]. In the absence of measured data, the efforts of Keill and others at determining the physical forces that defined the circulation were inaccurate and overestimated them rather grossly [11] [12]. The further study, quantification and elucidation of fluid mechanics and the actual strength of the physical forces governing them owes much to a handful of unique individuals who shaped the events that laid the groundwork for subsequent scholars and scientists to explore hemodynamics. One of the most celebrated figures to achieve that end was Stephen Hales (1677-1761).

Stephen Hales - the man

A clergyman by profession Hales was very much a scientific minded man of his times (Figure 2). His studies in the physiology of the circulation and the vascular system have been considered to be secondary in importance only to those made by William Harvey (1578-1657) [11] [13]. It has been said that Harvey demonstrated the logical necessity of the circulation, but it was Hales who provided its rigorous demonstration through his analysis of the hydrodynamics of the vascular system [14]. It has been said also that in animal physiology Hales took "the most important step after Harvey and Malpighi in elucidating the theory of circulation". His contributions to physiology have been acknowledged by Michael Foster (1836-1907) and by John Fulton (1889-1960) who characterized him as "the most able physiologist of the eighteenth century" [2] [15]. In addition, Hales made significant contributions to respiratory chemistry that would stimulate the discoveries of Joseph Priestley (1733-1804) and Antoine Lavoisier (1743-1794), both of whom acknowledge his contributions in their publications, as does Daniel Bernoulli (1700-1782), who actually recommended to his students the reading and study of Hales' *Haemastaticks* [12]. That such scientific work would be performed by a country parson deserves explanation. Although by no means on the level of the great clinical physiologists of the time who interpreted their studies in the context of body function, Hales was essentially a basic experimental physiologist at a transitional time in medical knowledge evolution when physiology was emerging from descriptive anatomy (Figure 1). As a pure physiologist his concern was not with medicine of which he knew little but that of refining the methods of experimental animal physiology to which he introduced the accuracy of measurement and the precision of mathematics. The calculations and contributions to hemodynamic of his predecessors, Richard Lower (1631-1791) and Lorenzo Bellini, notwithstanding, neither had the vaguest idea about the actual force of the blood pressure that had not been measured until Hales' studies. It was his experiments which provided the data that would be completed by Bernoulli [16] [17] [18] [19].

Born in Bekesbourne, Kent in 1677, Hales was admitted to Benet's College (now Corpus Christi) in Cambridge University in 1696 at the age of 18. He was elected a fellow of his college in 1702 and admitted as a fellow in residence the following year. It is there that he studied religion and delved into the sciences over the next 6 years until 1709, when he was appointed perpetual curate of Teddington, Middlesex (now part of Greater London), where he moved, worked and lived until his death in 1761. At his own request, he was buried under the tower of the Teddington chapel that he had added from his own personal funds [19] [20] [21]. His damaged tombstone found in the church porch was replaced in 1911 by a tablet reproducing his epitaph now placed on the west porch beneath the tower [13] [21] [22] [23].

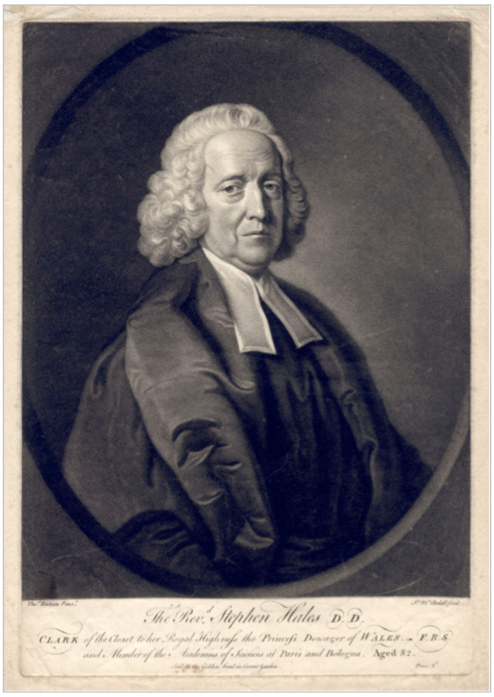

Figure 2.
Stephen Hales (1677-1761) at age 82. Engraved (c. 1810) by James McArdell after an oil painting (c. 1759) by Thomas Hudson. Reproduced with permission from the National Portrait Gallery, London.

Stephen Hales - the scientist

Whereas Hales begun his experimental studies while a resident fellow at Corpus Christi, his interest in science did not end with his departure from Cambridge. Actually he did most of his published scientific work in the fields of Teddington surrounding his curacy. Endowed by an unusually creative and inquisitive mind he occupied himself between his clerical duties with experiments that covered a wide range of the emerging scientific disciplines of the time, including the physiology of plants, the chemical constitution of air, reflex action, and, above all, his celebrated experiments on arterial and venous pressures in warm-blooded animals [20] [24] [25] [26] [27] [28] [29]. He was early recognized as a leading investigator and elected to the Royal Society in 1717, at a time that Isaac Newton was its president. Shortly after his election he read his first paper to the Royal Society on the effect of the sun on the transpiration of plants. For his subsequent contributions he received the Copley Medal of the Royal Society in 1739, and was appointed one of the foreign members of the French Académie Royale des Sciences in 1753. In 1751, he was appointed Clerk of the Closet to the Princess of Wales, the mother of George III, who after his death put up a monument to his memory in Westminster Abbey (Figure 3) [20] [21] [22].

Hale's foundation in the sciences was rooted during his years at Cambridge, in the heady atmosphere left by William Harvey and Isaac Newton. A principal contributor to his scientific interests was William Stukeley (1687-1765), who entered Benet's College in 1703 to study medicine, became a close friend of his senior Hales and stimulated his interest in biology [7] [30]. Another contributor to Hales scientific education was John Vigani (1650-1712), an Italian scientist who became the first professor of chemistry at Cambridge in 1703 [20] [21]. Hales and Stukeley attended his lectures and watched his chemical demonstrations in the laboratory of Isaac Newton. Perhaps a greater intellectual influence on Hales was that of James Keill who by the late 1690s had started lecturing at Cambridge as well as at Oxford [6] [20]. It was around this time (about 1706) that Hales, together with Stuckeley carried out his first circulation experiments on dogs, but it was in Teddington that in or about 1714 he took up his studies in earnest this time on horses, dogs and does that would make him famous [20] [21] [31]. While the university taught him science, Stukeley stimulated his interest in biology, and Keill shaped his physiological thinking it was his own intellectual drive and revived scientific interest after settling in Teddington that formed the basis of Hales' contributions to science.

Hales was slow to publish his studies. It was not until 1727 at the age of 40 that he issued the first volume of his now classic *Statical Essays,* the *Vegetable Staticks,* and six years later that he published the second volume of *Statical Essays*, which he titled

Haemastaticks [20] [21] [31]. Published in 1733, the *Haemastaticks* is not a continuation of his studies in plant physiology published 6 years earlier. In fact, it is a report of his earlier studies of the early 1710s in the pastures of Teddington. Nor is it a book as much as it is a diary or laboratory notebook detailing his experimental studies, appended by his interpretation of their results and the questions raised by each experiment that prompted his subsequent experiment [32]. The published report was considered a model of rigorous research and clear exposition that resembled the work and writings of William Harvey, and their two books (the *De Motu Cordis* of Harvey and the *Haemastaticks* of Hales) were said to be "fitly regarded as a kind of *principia* for the physiology student." [11].

The *Haemastaticks* opens with an account of Hales's most dramatic experiment, a bold and bloody one on a 14 years old mare. Unfortunately, the design of this first recorded study has been miscommunicated as that of measuring the blood pressure in the carotid artery, and the importance of the results of the full experiment publicized as being limited only to that of measuring the blood pressure. Whereas Hales did measure carotid artery and jugular vein pressures that was on another 10-12 years old mare that he records as his third experiment. It is this third experiment that was illustrated as part of an advertising campaign for an industrial company, now out of business, which in the 1960s manufactured transducers, the Statham Medical Instruments, Inc. of Oxnard, California. The original figure clearly labeled as Experiment III (Figure 4) has come to be reproduced without its identifying footnote and often passed on as that of the first measurement of blood pressure. In fact Hale's first classic experiment of measuring blood pressure was performed on an older live mare tied on her back on which after ligating one of her femoral arteries he inserted a brass cannula to which was fixed a glass tube nine feet high (Figure 4). When he untied the femoral artery ligature, the blood rose to a height of more than eight feet. He then detached the glass tube from its brass connection at intervals while measuring the quantity of blood to flow out and recording the resulting serial changes in blood pressure during exsanguination (Figure 5). His third experiment is publicized because he now measured arterial and venous pressure in the carotid artery and jugular vein. Actually, he had already established the "force of the blood" in his first experiment, his choice of the neck vessels was made because he wanted to cannulate the heart of the mare in order to make a wax cast of the intracardiac volume that would allow him to estimate cardiac output. In addition to horses, Hales studied the hemodynamics of the circulation in a number of other animals, including an ox, a sheep, a fallow doe, and several dogs in order to study the comparative physiology of the heart in different sized animals [20] [21] [31] [32].

Hales' direct determination of the systolic pressure for the first time caused widespread interest and

Figure 4.
Measurement of blood pressure by Stephen Hales. On the left: The original figure produced by Statham Medical Instruments, Inc. illustrating Experiment III of Stephen Hales measuring the blood pressure in the carotid artery of a 10-12 years old mare. On the right: The actual first Experiment in which Stephen Hales measured the blood pressure in the femoral artery of a 14 years old mare.

comment. His studies are significant not only because of the pressures which he recorded but because of his secondary observations as in the first experiment that on continuous withdrawal of blood the systolic pressure remained nearly constant until almost a third of the total volume of blood had been removed (Figure 5). He was thus led to postulate the existence of a compensatory mechanism for the constriction of peripheral vessels in order to maintain arterial pressure, which he explored further by perfusing exsanguinated animals with solutions of various temperature and varying composition to determine and record the changes in blood pressure caused by the constriction and relaxation of the peripheral vasculature [17] [19] [31] [32].

Stephen Hales - renal physiologist

In *Haemastaticks* Hales also describes his attempts to study renal perfusion. Essentially, after killing a dog by "washing his blood out" with warm water, and while the animal was kept warm, he placed a brass tube in the aorta above the renal arteries and gradually raised the "pressure of water equal to the force of the arterial blood which had been washed out in killing the dog, yet none of the warm water passed thro' the kidnies into the ureters and bladder" [32]. Not an unexpected finding in the dead kidneys of a deceased animal, which in some ways replicates the earlier studies of Berengario da Carpi (1460-1530) and Marcello Malpighi to perfuse dead kidneys [1].

The *Haemastaticks* includes another renal issue to which Hales turned his attention in the late 1720s, a prevalent problem which had long challenged the resources of the medical profession: the painful affliction of kidney and bladder stones or "distemper of the stone" [20]. Early in 1727, while the *Vegetable Staticks* was still in press, he obtained human calculus specimens from his friend the surgeon John Ranby (1703-1773) and the then president of the Royal Society Hans Sloane (1660-1753). On distilling the stones Hales noted a much greater proportion of "air" than he had obtained from any other substance. Since various chemical agents were known to release this "strongly attracting, inelastic air," he thought it possible to find a solvent to dissolve the calculi and obviate the painful operation of being "cut for the stone." He carried out a number of studies and published their results in 1733 as the second part of his Haemastaticks [32] [33]. His continued attempts to find a useful solvent failed. These studies are noteworthy chiefly for his success in perfusing the bladder of dogs with various solutions and for his invention of a surgical forceps, which Ranby and other surgeons promptly used with success to remove stones from the urethra. In retrospect, where the first part of the *Haemastaticks* is a classic in experimental physiology, the second part on "*Stones in the Kidnies and Bladder*" is relatively naive and literally cluttered with bizarre experiments and simplistic conclusions. Ironically, it was for this largely inferior work on human calculi - not for his remarkable experiments on plants and

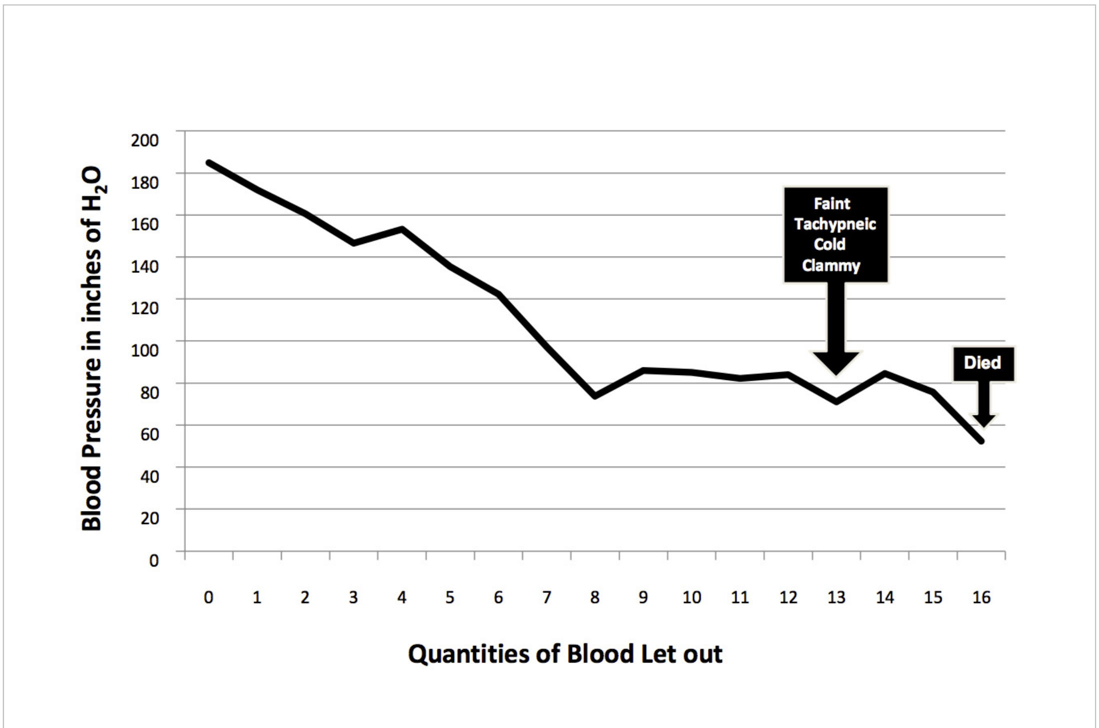

Figure 5.
A graphic plot of the blood pressure changes observed during gradual exsanguinations of a 14 years old mare recorded by Stephen Hales in his first experiment. Note the plateauing of the blood pressure after bleeding the horse 8 quarts of blood, which Hales attributed to reactive peripheral vasoconstriction to maintain perfusion pressure. Shown in the black boxes are his description of the state of the horse.

animals - that Hales was awarded the Royal Society's Copley Medal in 1739 [20] [21] [31].

An interesting sequel of his work on stones was his involvement in the case of Joanna Stepehens' secret recipe for dissolving stones. He was appointed a trustee of the Parliamentary committee appointed to examine the effectiveness of the remedy, upon whose recommendation Joanna Stephens was paid £ 5000.00 in March 1740 to publish her recipe [20] [32] [33] [34].

Stephen Hales - philanthropist, social reformer and public servant

With the publication of *Haemastaticks*, Hales career in experimental animal physiology came to an end. He had been criticized for vivisection of animals amongst others by his neighbor since 1718 Alexander Pope (1688-1744) and a clerical colleague, Thomas Twining (1734-1802) [20] [21]. Pope who became a friend of Hales was horrified by his experiments that he describes as "barbaric" and reports him as "so worthy and good man, only I am sorry he has his hands so much imbued in blood". Twinning in his poem *The Boat*, describing his travel down the Thames, relates his passage through Teddington as,

Green Teddington's serene retreat
For Philosophic studies meet,
Where the good Pastor Stephen Hales
Weighed moisture in a pair of scales,
To lingering death put Mares and Dogs,
And stripped the Skins from living Frogs,
Nature, he loved, her Works intent
To search or sometimes to torment

From 1733 to the end of his life Hales devoted himself to applying his scientific knowledge, technical skills, and creative aptitudes to alleviating human problems, both medical and social [35]. Noteworthy in this regard is his work in the 1740s with ventilators whose use in mines, jails, granaries and ships he vigorously promoted, thereby establishing one of the first principles of preventive medicine [36]. An accomplishment well reflected in the definition of ventilators by Samuel Johnson (1709-1784) in his 1755 *Dictionary of the English Language* as, "an instrument contrived by Dr. Hales to supply closed spaces with fresh air.

At age 70 Hales was chosen by the Royal College of Physicians to preach the annual Croonian Sermon. For his sermon titled "*The Wisdom and Goodness of God in the Formation of Man*" he chose verses 11 and 12 from Job chapter 10: "Thou hast closed me with skin and flesh, and hast fenced me with bones and sinews. Thou hast granted me life and favour, and thy visitation hath preserved my spirit." [37]. Verse 11 he had quoted with some modification in *Haemastaticks* (p. 160) to justify his studies in elucidating God's creation: "*Thou hast* not *only fenced me with Bones and Sinews*, but hast also effectually secured the vital Fluid, in such strongly wrought Channels, as are Proof against its most lively and vigorous Sallies, when either agitated by the different Passions, or by strong or brisk Actions of the Body."

Figure 3.
Memorial to Stephen Hales in the west transept (Poet's Corner) of Westminster Abbey by Joseph Wilton. The figure of Hales is represented in profile on a medallion held on the right by Religion and the left by Botany. A globe in the lower right displays winged wind heads shown blowing air at Botany referring to his contributions to ventilation. Note that his contributions to hemodynamics which entailed vivisection are not represented. Reproduced with permission from Westminster Abbey Library, London.

Conclusion

For his scientific contributions to the to the circulation of blood, the flow of sap in plants and to the chemistry of respiration, Stephen Hales has been considered one of the most creative British scientists of the 18th century. Francis Darwin (1848-1825), son of Charles Darwin, dubbed him "the father of physiology" [13].

Lost among the many contributions of Hales is his statement in the Introduction to *Haemastaticks* that "the healthy State of the Animal principally consists in the maintaining of a due Equilibrium between body solids and fluids". In fact, by his own definition of "staticks", borrowed from the 1614 *De Medicina Statica* of Santorio Sanctorius, Hales meant a state of "functional equilibrium". A concept that he goes on to elaborate in *Haemastaticks* (page 109) [32], "The right healthy State of the Blood must consist in a due Equilibrium between these active Principles, so as not to have them too much depressed and fixed on the one hand, which might tend to an acid Acrimony, nor too much raised and exalted on the other hand, which makes it tend to an alkaline Acrimony." The clearing of these excesses from the blood he ascribes to their clearance in the urine. Clearly insightful and prescient statements on the constancy of the internal environment, which would be promulgated in 1845 by Claude Bernard (1813-1878) as that of the "*milieu intérieur*".

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