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The Scientific Revolution—The Kidney and Nephrology in and about the Seventeenth Century (Part 1)

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ABSTRACT

In the history of the evolution of the medical sciences, it is in the 17th century that the conscious, deliberate, and systematic study of the workings of the human body began. It was a product of the radical changing attitudes of this insurgent century when mathematical reasoning and mechanistic philosophy replaced the teleological outlook of earlier times. It was then that meticulous observation, reproducible quantification, experimental validation, and mathematical exactitude in the quest for truths launched the Scientific Revolution. The effect on medicine was a transformative change from a descriptive to an explanatory body of knowledge during the course of which rigorous anatomical dissections were used for the mechanical explanation of organ function, when morbid changes observed at postmortem began to be related to clinical features of disease, and when the secretive analytical methods of alchemy began to be refined for the study of chemical changes in living matter. Essentially what began with meticulous observations of anatomical features begat physiology and laid the foundations of pathology and chemistry. As a result, studies of organ structure, function, and changes in disease in general, and of the kidney in particular, were clarified and progressed at a rate never achieved theretofore.

The body of empiric knowledge compiled since the dawn of recorded information and promulgated as dogma over the past began to be questioned in the 16th century and underwent a frontal challenge in 17th century Europe (1). The result was a transformative departure from past ways of studying nature that has been termed the Scientific Revolution (2). It occurred within the context of the formidable tensions and major upheavals then occurring in existing systems—social (urbanization), political (nation states), financial (expanding trade), religious (reformation and its counter), artistic (Baroque), warfare (gunpowder), and education (universities)—that were changing the very fabric of life in Europe (3). Central to this pervasive rebellious attitudes and remarkable efflorescence was an expanding public consciousness of the importance of thought (*I think, therefore I am*), reason, and quest for truths (4,5). It was this prevailing critical attitude that in the sciences launched the deliberate systematic investigation of the natural world by rigorous observation, mathematical quantification, and experimental validation. The consequent paradigm shift established the very roots of research methodology that propelled science forward and fostered its unstoppable progress to the present (6–8).

Some of the important factors that contributed to these phenomenal changes were (i) the facilitated transmission of new information by the printing press (books, pamphlets, journals) and a learned public supporting them; (ii) the creation of new and refined instruments (telescope, microscope, thermometer, barometer, hygrometer) that facilitated the quest for exactitude; (iii) the union of mathematics and science (count, measure, weigh) that allowed for the more accurate comparison and verification of reported information; and (iv) the introduction of comparative calculations of probability that gradually evolved into the discipline of statistics and its integration into the language of science (1,2,9,10). In fact, a principal feature of science in the 17th century was the application of mathematical reasoning to explain observed physical phenomena, a movement that began among the astronomers and was soon extended to the study of the human body initiating the revolution that would culminate in the mathematization and scientification of medicine (11–13).

Two crucial components of this new order of original inquiry were (i) increased communication (letters, pamphlets, books) among intellectuals across national borders, thereby creating a virtual

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republic of letters among the new community of citizens concerned with matters cultural and scientific, well exemplified in the preserved trove of the vast correspondence of the luminaries mentioned in this article;(14) and (ii) the exerted training and nurturing of a new generation of investigators, an essential ingredient of scientific progress that had been limited or actually absent in the past (9–15). Thus, where previous medical authorities (Galen, Avicenna) had trained no disciples and left no heritage other than that of their own personal work, they were now replaced by a new generation of scholars who stimulated, nurtured, and encouraged the passion for new learning in their associates and junior colleagues. The driving force of these changes was as follows: (i) the then well-entrenched universities established in the preceding two centuries; (ii) the new universities being founded in Northern Europe; and (iii) often more effectively the emerging learned societies and academies being formed throughout the continent (Table 1).

The predominantly Italian universities which pioneered the introduction of experimental scientific methods in the first part of the century were hampered in its pursuit by their inherent conservative scholastic roots. As a result, it was the more liberal academies and scientific societies that nurtured the continued unfettered growth of science by: (i) establishing in-house laboratories where experiments could be performed; (ii) sponsoring the development and refining of measuring instruments; (iii) maintaining a forum of free exchange and disputation; and (iv) the broader diffusion of their studies by the publication of their proceedings and correspondence (1,2,16). In fact, by their open public debates and experimental demonstrations, they established a method for the critical evaluation of scientific studies, a key model of peer review that has characterized scientific research since then. Yet, another novelty pioneered by these societies was that of national funding of scientific studies, one example of which are the pensions offered by the French minister of finances, Jean-Baptiste Colbert (1619–1683) to members of the Académie Royale (17).

TABLE 1. Scientific Societies and Academies in the 17th century

Society	Year	City	Principal founding members
Accademia dei Segreti	1560	Napoli	Giambattista della Porta
Accademia dei Lincei	1603	Rome	Frederico Cesi; Galileo Galelei; Johannes Eck
Accademia degli Investiganti	1650	Napoli	Tommaso Cornelio
Collegium Naturae Curiosorum	1652	Schweinfurt	Johann Bausch; Johann Fehr; Georg Metzger; Georg Wohlfarth. All four were physicians.
Accademia del Cimento	1657	Florence	Leopoldo Medici; Giovanni Borelli; Marcello Malpighi
Royal Society	1660	London	Henry Oldenburg; Robert Boyle; Robert Hooke; Christopher Wren; Thomas Sydenham; Isaac Newton
Académie des Sciences	1666	Paris	Jean Dominique Cassini; Jean-Baptiste Duhamel; Christiaan Huygens
Accademia Reale degli Arcadi	1675	Rome	Queen Christina of Sweden; Giovanni Borelli; Gian Lorenzo Bernini
Berlin Academy	1700	Berlin	Gottfried Leibniz

The discoverers and shapers of scientific methods

The accrued knowledge during the Scientific Revolution was the work product of many investigators, some unknown, most forgotten, few occasionally remembered, and a small distinct elite who stand out among them all for their inventiveness, ambitious spirit, conceptual imagination, and synthetic aptitude who presented new concepts better than anybody else. These were the talented few who achieved great discoveries and were universally acknowledged for their contributions. As Shakespeare defines these discoverers more poetically but mysteriously, "some are born great, some achieve greatness, and some have greatness thrust upon them."

Among this select group of achievers of greatness who influenced science in the first half of the 17th century are an Italian astronomer, Galileo Galelei (1564–1642), a French philosopher mathematician, René Descartes (1596–1650), and a British physician, William Harvey (1578–1657). The course they followed in advancing scientific knowledge was framed by a patient of Harvey, the British intellectual and statesman Francis Bacon (1561–1626), who in his 1620 book, *Novum organum scientarium* (New scientific instrument), laid down the methods of inquiry and canons of scientific research: empiric observation, rigorous quantification, and experimental validation (18-20).

The individual who launched the process in earnest was Galileo who used mathematical explanation of physical (celestial, mechanical) phenomena and developed the instruments to assess them (17). The one who gave the clearest expression of this new approach and best framed the issues and methods of exploring the workings of nature in general and the human body in particular through mathematical exactitude and reasoned certainty was Descartes (13,21,22). In the introduction to his study of the philosophy and mechanics of the human body, *Traité de l'Homme* (Treatise on Man) Descartes unequivocally proclaims, "I shall try to explain our whole bodily machinery in such a way, that it will be no more necessary for us to suppose that the soul produces such movements as are not voluntary, than it is to think that there is in a clock a soul which causes it to show the hours." Descartes was a solid mathematician, an accomplished physicist, but above all a philosopher. He was not a trained physician and did not make a single physiological discovery but had considerable interest in the mechanical implications of structural and functional correlations, and in his studies ventured into anatomical dissection and vivisection (21–23).

In his thinking, Descartes was influenced by the one person who showed how it all could be applied to the workings of the human body, William Harvey. Harvey's quantification of the movements of the heart and the circulation of the blood, based on extensive experimentation and meticulous calculations, succinctly presented in his 72 page *Exercitatio Anatomica de Motu Cordis et Sanguinis* (Anatomical Studies of the Motion of the Heart and Blood), stands out as the iconic example of the scientific revolution in medicine (23–25). Appropriately, it is considered a turning point in the history of medicine that launched physiology. Harvey is the bright star of the mathematization of medicine, but lost in his glow are the contributions of his older contemporary Santorio Santorio (1561–1636) (27–29). Santorio's lifelong metabolic balance studies published in 1614 as *Ars de statitca* was classified at that time with *De motu cordis* as one of the two foundations of integrating experimentation and quantification into scientific medicine. Aside from the more general applicability and attractive subject of the *De motu cordis* that contributed to its everlasting impact, a major relative drawback of the *Statica* was its use of aphorisms in presenting mainly inferences of the otherwise meticulous studies of Santorio in sharp contrast to the numerical detail, specific calculations, and clarity of Harvey's *De motu cordis*.

Where Galileo, Descartes, and Harvey represent the Scientific Revolution in the first half of the century, their successors in the second half of the century were Isaac Newton (1643–1727) and Robert Boyle (1627–1691), who were a major force in the progress of the Scientific Revolution into the Enlightenment that followed in the 18th century. Newton, arguably the greatest figure of the Scientific Revolution is best known for his theory of matter that recast the physiological mechanisms of his predecessors into that of chemical motion based on the gravitational attractive forces of atoms (corpuscular theory). For that he was dubbed by Voltaire as the destroyer of the Cartesian system. Actually, it was Boyle who actually expounded on the atomic composition of matter in greater detail, and in his 1661 *The Skeptical Chymist* laid the cornerstone of chemical studies that were to come (24,26).

The Maturation and Progress of Scientific Methods

As a consequence of the practical approach to biology nurtured by these discoverers, science came to embrace the search for "mechanisms" using mathematical formulae and equations to provide an explanation of natural phenomenae (13,25,30). These methods applied to medicine have variously been termed iatro-mechanics, iatro-physics, and iatro-mathematics, a classification that at the time only polarized the issues by the dogmatic, often violent, and at times vituperous if not acrimonious, quibbles of their respective adherents and opponents. Actually, the whole process was one of applying the precision of mathematics to medical problems, appropriately termed by some "the mathematical system of medicine." Stated otherwise, ultimately it was achieving mathematical exactitude and reasoned intellectual certainty, and not its labels, that would define scientific medicine (10,31). With the subsequent introduction of the calculus of probability and its evolution to the discipline of medical statistics, the mathematization of medicine was now complete and statistics became an integral component of the language of medicine (10,32).

As most of the then proposed mechanisms were guided by mathematical reasoning that could not be seen by the naked eye, they were illustrated by diagrams that literally visualized the unseen and abound in the works of Galileo, Descartes, Harvey, Newton, Boyle, and their contemporaries. Essentially, much like realistic pictorial illustrations were enhancing the accuracy of anatomy and botany texts published then, diagrams began to be used to illustrate physiological mechanisms and later chemical reactions (33,34). The importance and endurance of these then novel but fundamental additions to the language of science can be appreciated from the fact that one cannot read a scientific article nowadays without encountering the terms "statistical significance" and "mechanism" of some phenomenon or another, and its representation by one or more colorful "diagram." In sum, the descriptive verbiage of past authorities was now clarified by visual renderings of the graphic arts and made precise by mathematical numbers, calculations, and formulae (35).

It was on this background of maturing scientific thought and language that the study of the kidney evolved in the 17th century. The principal contributors to this progress (Tables 1 and 2) will be discussed in the following sections. The list of illustrious investigators, who lived and died between the late 16th and early 18th centuries, shown in these tables is neither inclusive nor intended to exclude important contributions by others. They are merely intended to provide a temporal framework of expanding knowledge limited to the kidney. William Harvey appears on both tables because of his pivotal contribution to the circulation in general and that of renal blood supply in particular.

Table 2 begins by listing two individuals who preceded the Scientific Revolution by almost two millennia. Beginning the story of the Scientific Revolution with Aristotle and Galen is important

TABLE 2. The kidney between structure and function. Anatomy animated

Name Years	Publication Year	The KIDNEY
Aristotle 384–322 BCE	*De partibus animalium* c. 350 BCE	Blood is filtered through the solid substance of the kidney.
Galen c. 129–c. 200	*De usu partium corporis Humani* 2nd century CE	Hepatic blood delivered to the kidney by ebb and flow into the renal vein. The attractive forces of the kidney purify this blood by straining off its watery portion "*as if through a sieve*" and "*secrete*" it as urine.
Mondino 1270–1326	*Anatomia Mundini* 1315	The renal (*emulgent*) vein as it thins down disgorges its blood into the renal parenchyma from whose porosities super-fluidities are filtered (*collatur*) and discharged as urine.
Zerbi 1445–1505	*Liber anathomiae corporis humanis* 1502	Confirmed Mondino. Urine is separated from the blood at the fine openings at the end of the branching emulgent vein where they enter and are assimilated in the renal parenchyma.
Berengario 1460–1530	*Commentaria Mundini* 1521	First experimental study: forced warm water into renal vein, the kidney swelled but no urine produced. Described papilla from which he observed urine coming out like "milk from the nipples."
Vesalius 1514–1564	*De humani corporis fabrica* 1543	Kidney consists of two sinuses separated by a transverse membrane. Blood empties in upper sinus, its thin watery part is strained through the membrane, and drained into lower sinus.
Eustachio c. 1514–1574	*De renum structura* 1564	Detailed copper plate engravings of the kidney showing the branching vasculature, the medulla, and the papillae. Forced fluid from emulgent vein and ureters but failed to show their connection in the parenchyma.
Harvey 1578–1657	*De motu cordis* 1628	Renal blood flow supplied by arterial blood forced by the contractile action of the heart, and drained by the emulgent vein.
Borelli 1608–1679	*De motu animalium* 1680	Injected ink into renal arteries. Postulated a sieve not a filter separating the renal artery from the renal vein at their Y connection with the tubules.
Bellini 1643–1704	*Exercitatio anatomica de structura usu renum* 1662	Fibrillar tubules drain urine at the Y connection formed at their junction with the renal arterioles and veins.
Malpighi 1628–1694	*De viscerum structura exercitation anatomica; De Renibus* 1666	Injected ink into renal artery and observed its appearance under microscope in his eponymous corpuscles (glomerulus) that function as a sieve. No injectate appeared in tubules.
Morgagni 1682–1771	*De sedibus et causis morborum per anatomen indagatis* 1761	End of the animated anatomy of physiology. Foundation of the morbid anatomy of diseased organs.

for several reasons. First, the 'rebellion' of the Scientific Revolution was against the authority of Aristotle (384–322 BCE) in biology and of Galen (129–c. 200 CE) in medicine. Second, they actually founded the science of functional studies and used experimentation, thereby laying down the very foundations of experimental physiology. And third, both, but particularly Galen, defined the classic questions of animal physiology in terms of what differentiates life from death: heat and motion, the two features that defined whether the immortal soul still resided or had parted the mortal body. Their consequent focus on nutrition was a natural step in explaining the source of the "fire" for maintaining animal heat and generating the energy to move. Essentially, the digestion of food and integration of its nutrients into the body (viz, the mystery of "transmutation of bread to flesh") was the important question to explore (30). In this process, the important organs were, according to Galen, the stomach (digestion) and the liver (generation of blood), with the kidney a mere accessory to the nutritive process used to eliminate the super-fluidities of the nutritive blood generated by the liver (24,26). Indeed, Descartes begins his *Treatise on Man* with the ingestion and digestion of food, hastens over the circulation of blood, dwells at length on the nervous system, but never mentions the kidneys!

Anatomy Gets Animated and Begets Physiology

For much of the past history of medicine, physiology was based on the four humors (black bile, yellow bile, phlegm, blood) rather than on organ function. This was to change during the Scientific Revolution to the study of individual organ structure and function with the consequent emergence of physiology (36). Although the term "*physiologia*" had been used by Galen, it was in the context of its original Greek meaning of the study of all natural objects. The first person to use the term "physiology" in its current restricted biological use as the science of normal function of living matter was the French physician Jean Fernel (1497–1558) (37). Fernel's physiology was entirely Galenic but was to change in the Scientific Revolution.

As precision of structural knowledge increased and vivisection was undertaken, questions of organ function began to be explored in the 16th century leading to the emergence of the mechanical physiology of the 17th century. As mentioned earlier, functional studies based on structure can be traced to Aristotle and Galen (Table 2). Unfortunately, their methods of experimental study were never fully adopted by their successors, while their explanations and conceptualizations of function survived, were systematized and dogmatically promulgated over the centuries that followed (24,26). This long-unquestioned edifice began to be challenged in the Renaissance, was frontally attacked and literally purged in the 17th century, but continued to influence medical thinking well into the 19th century (38,39).

In what can be considered a belittling statement that "The kidneys are not present for necessity in animals but have the function of perfecting the animal itself," Aristotle literally condemned the kidneys to a perfunctory role that would haunt their study well into the Early Modern Period (39). He considered the role of the kidneys as that of separating the surplus of fluidities of the blood inside the solid renal substance (parenchyma) and transforming it into urine, to which he refers as "*residuum*" (40). The term 'parenchyma' was actually introduced later by the Alexandrian Greek anatomist Erasistratus (304–250 BCE) as that part of an organ into which the blood vessels seem to disappear, and was initially conceived as a porous tissue jelled from the blood disgorged into it from the veins. Galen was a firm believer in the importance of experimentation and vivisection which he used to study organ function. This is well exemplified in his experimental studies on the kidney that established it as the organ which produces urine, rather than the bladder as it had been assumed (41,42). Unfortunately, he erred in his general concept of physiology wherein he placed the liver at the center of function in generating nutritive blood to which the vital spirits were added in the heart, and defined blood flow as a kind of tidal motion of an ebb and flow of the hepatic and cardiac blood. His notion of the active phase of the heart was to suck blood in diastole, add to it the vital spirits (heat) and push out the vitalized blood in systole.

Galen's notion of kidney function was even more contentious and prejudicial. He does not seem to have examined the structure of the kidneys in any detail and considered them to be composed of an undifferentiated solid mass. In discharging their principal function of removing super-fluidities, Galen considered that the kidneys acted on the hepatic blood from which they attracted and excreted the thin watery part and returned the properly concentrated blood to the liver for delivery to the heart. The "vitalized" blood the kidneys received from the heart was deemed for their own restorative nourishment. What was extracted from the arterial blood (?bile) is not clear. Galen rejected the possibility of filtration alluded to by Aristotle 500 years earlier, and dogmatically concluded that the kidneys "secrete" urine by their inherent "attractive force" (40). Where Aristotle had belittled the kidneys, Galen banned them to negligence.

With the start of anatomical dissection in the 13th century, the structure of the kidney began to be elucidated and its function as a sieve to reemerge (Table 2, Fig. 1). Questioning Galenic anatomy began in Bologna, where the careful dissection and direct observation of cadavers was launched in the 14th century. Relevant to the elucidation of kidney structure and function are the reported observations that (i) the emulgent vein branches into smaller vessels as it enters the renal parenchyma by Mondino de Luzzi (1270–1326); (ii) that urine is filtered at the fine openings of the small vessels in the renal parenchyma by Gabriele Zerbi (1445–1505); and (iii) that the injection of warm water into the emulgent vein results in the swelling of the kidney but produces no urine by Berengario da Carpi (1460–1530) (42–44).

The importance of these early observations notwithstanding, the dominant figure of early

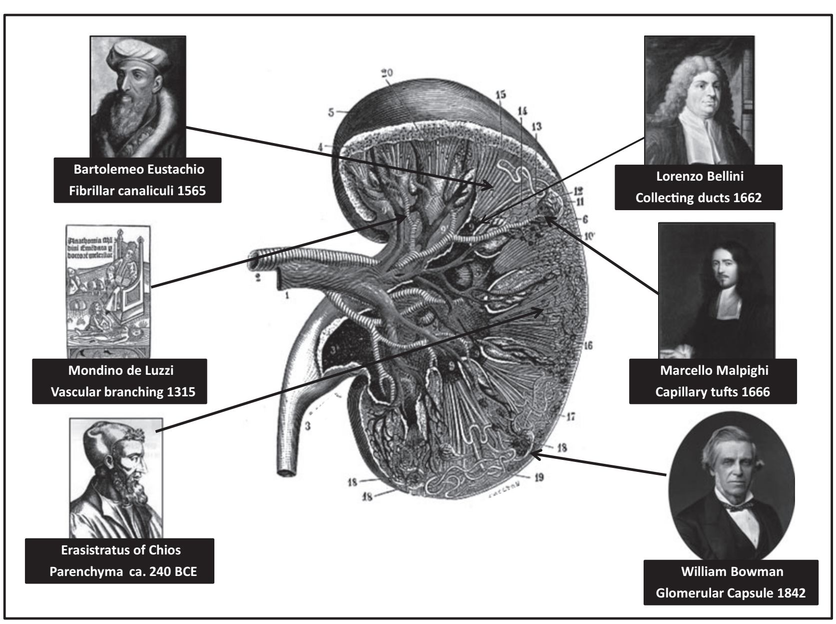

FIG. 1. Principal contributors to the structure and function of the kidney.

anatomical dissections is Andreas Vesalius (1514–1564). Vesalius was a skilful surgeon and a talented anatomist but had little and fleeting interest in function. For all his anatomical fame and criticism of Galen, he continued to place the right kidney above the left one and oblivious to the reports of Mondino, Zerbi, and Berengario reduced renal function to the presence of a transverse membrane between the upper (where blood emptied) and lower (where urine was collected and drained) poles of the kidney. Regrettably, he continued to overshadow the contributions of his contemporary, the Roman anatomist Bartolomeo Eustachio (c. 1514–1574) whose meticulous microdissections of the kidney, lucidly illustrated by copper plates in his *De renum structura* published in 1654 represents the first text dedicated to the accurate study of kidney structure. Eustachio corrected the position of the right kidney as lower than the left, clearly described and illustrated the intrarenal vasculature and the renal calyceal system, and reported the collecting ducts as "small canaliculi" (38,43).

Credit for stimulating functional studies of the kidney in the 17th century belongs to the Neapolitan mathematician and physicist Giovanni Borelli (1608–1679). His fundamental interest in the mechanical physiology of animal life is summed in his 1686 posthumously published two volume text, *De motu animalium* (On the Movement of Animals), in which he proposes to "ornament and enrich (anatomy) by mathematical demonstration" of function (physiology) (45). Although principally focused on the mechanics of muscular motion, in the second volume of *De motu*, Borelli discusses general bodily functions (46). After a detailed exposition of cardiac function, he describes respiration, digestion, and discusses urine secretion in a 30 page chapter titled *De Sanguinis expurgatione in renibus* (On the cleaning of the blood in the kidneys). Perpetuating the heritage of Aristotle, he titles the introductory paragraph of the chapter, "Kidneys do not contribute directly to the life of the animal." The first sentence of the paragraph that follows sums up kidney function better and more succinctly than ever before, "…blood is purified in the kidneys where it is deprived of an excess of serum with excremental elements of salt and tartar" (more on the meaning of salt and tartar in the following section). Importantly, he denies any role of attraction or fermentation in urine production. He compares the kidney to a sieve that filters various blood components trapping those needed for excretion (22). He clearly states that "urine is separated from blood in the kidneys mechanically as a result of the wedging of blood into the very narrow tubes of the arteries which end in the renal lumps" (45).

By the time Borelli wrote his book, he had alienated himself from Malpighi and used 'renal lumps' to avoid referring to them as Malpighi's corpuscles. Essentially, he considered urine formed at the narrow arterioles that end in Malpighi's corpuscles at the Y junction formed where the arterial and venous vessels meet the tubules, which had been identified by his pupil Lorenzo Bellini (1643–1704), and at his invitation reported to the Academia del Cimento in 1642. He concludes with a prescient statement on renal filtration that precedes by 163 years, the 1846 report of the German physiologist Carl Ludwig (1816–1895) on glomerular ultrafiltration:(39) "Therefore, blood does not stay in these glands (of Malpighi) but passes through them rapidly. Even if its course was not continuous (with the veins), it would be carried out at least during one pulsation of the heart" (45).

Especially important in the contributions of Borelli to renal physiology is his sponsorship, stimulation and encouragement of others to pursue it, as in the guiding of his student the Florentine Lorenzo Bellini, and in the collaboration with his academic colleague, the illustrious chair of Theoretical Medicine in Pisa, Marcello Malpighi (1628–1694). Aside from their benefit from Borelli's wisdom and guidance, Bellini and Malpighi had access to magnifying scopes that allowed for their more detailed observation of renal structure and function. Bellini used a handheld magnifying glass (8×) and Malpighi, a two-lensed early microscope (30×). Bellini published his studies on the kidney in 1662 as *Excercitatio anatomica de usu renum* (Anatomical studies of the structure and function of the kidneys). In it, he notes that the fibrillar structures (*canaliculi*) Eustachio had mentioned were tubular tissue that constitutes most of the renal parenchyma, which is reddish in the cortex and paler in the pelvis, and end in his now eponymous perforations at the papillary tip (Fig. 1). He reports that when he compressed the kidney, the papillary pores emitted a fluid that tasted like urine.

Essentially, the renal parenchyma that had theretofore been considered to consist of an undifferentiated, hard, solid fibrinous material was actually made of tubules extending from the cortex to the papillary tips and consisted of an outer cortical and inner medullary zone. Bellini unequivocally rejected the Galenic view of urine formation, which he explained mechanically based on the configuration of the renal vasculature. He argued that the arterial blood delivered to the kidneys is separated into urine at a sieve like arrangement formed at the junction of the renal artery and vein at their smallest subdividing branches where they meet the tubule, where the small components of blood and its excess fluid are collected in the tubules as urine, while the larger components of blood are returned to the renal vein. The connecting point of the Y-shaped anatomical structure (artery, vein, tubule) proposed by Bellini would become the eponymous vascular corpuscles reported by Malpighi in his 1666 *De Viscerum Structura Excertatio Anatomica* (40,41).

Deservedly, by far the better known contributor to renal structure and function was Malpighi, who with his more powerful microscope observed and described the pulmonary capillaries predicted by Harvey, and in the kidney, the glomerular capillary tufts that he described as "*minimae glandulae*" (tiny glands) that form 'corpuscles', an anatomical term applied to the small circumscribed endings of vessels and nerves (40). He states that the glands "drain the urine" that is "excreted"; he does not use the term "secretion" or "filtration." His *De viscerum structura* contains five chapters on the liver, brain, kidneys, spleen, and polyps of the heart.

Malpighi's description of the renal structure in the chapter titled *De renibus* has been extensively reported in the nephrology literature. Rather than repeat them, and as an example of the medical republic of letters mentioned earlier, what follows is reproduced from the account of the book in the *Philosophical Transactions of the Royal Society*: "Concerning the kidneys, he first relates what has been taught of them hitherto; and then delivers his own observations about them, by a long use of the microscope, and his deductions from them. He affirms, that he has always observed the kidneys to be also congeries of small glands, by injecting through the emulgent artery a black liquor, mixed with wine, and by cutting the kidneys longways, and then finding, betwixt the urinous vessels and their interstices, very many such glands which like apples are appendant in the sanguinous vessels, turgid with black liquor. He adds, that, after many trials, he at last found also a connection betwixt thos glands and the vessels of urine. As to the pelvis, he considers that nothing but an expansion of the ureters, as consisting of the same membrane and nervous fibers with the ureters" (47).

Malpighi's relationship with the Royal Society illustrates another aspect of the achievements of the Scientific Revolution. In 1667, he was invited to become a corresponding member of the Royal Society, which published his correspondence in its *Philosophical Transactions* and went on to fund the publication of some of his subsequent works and his purchase of new microscopes. This is a perfect example of the expanding frontiers of the medical republic of letters on its way to the global medicine of today.

Borelli, Bellini, and Malpighi proffered a mechanical explanation for urine formation. Partial support of their view came indirectly from Isaac Newton who had expanded his original concept of attracting particles to that of fluid mechanics inferring laws of fluid pressure, resistance, and attraction of solids moving in a fluid medium (48,49). This was applicable to glandular secretions based on differences in pressure forces between the secreted fluids and the resistance of secretory vessels, a concept relevant to renal function given that the kidneys were then considered glands. The impact of Newton's hydraulic concepts on glandular secretion entered medicine through his interaction with the Scottish physician Archibald Pitcairne (1652–1713), who prior to accepting his professorship at Leiden visited Newton at Cambridge in 1692 (49).

While Pitcairne is not one of the elite discoverers of the Scientific Revolution, he nevertheless had far reaching influence on its progress. An avid believer in the application of mathematics to the mechanisms of bodily functions, Pitcairne extended the hydraulic theory of Newton to that of the 'animal oeconomy' in general and of glandular function in particular (32,50). Essentially, he used probability to argue that it is the differences in size of vascular pores that regulates the passage of some but not other particles dissolved in the liquid (blood) entering them, i.e., the selective separation by sieving of the blood components (depending their size but not shape) through the small (capillary) vessels determined by the size of the vascular passages (pores), "because it is attracted to these passages and has affinity for them" (28). One can almost sense rudiments of what sounds like ultrafiltration, a term that would be introduced in the 19th century. In addition, Pitcairne developed a close relationship with Bellini, with whom he maintained an ongoing correspondence and to whom he dedicated some of his books. He is said to have revived Bellini's interest in urine secretion to which Bellini returned in his "*De urinis et pulsibus*" (On urine and pulsations) published in 1683.

Pitcairne appears also to have influenced the Reverend Stephen Hales (1677–1761), known for his measurement of the blood pressure in a mare, who explored several mechanisms of body function including glandular secretion. In his 1733 *Haemastaticks*, subtitled "*An account of some HYDRAULICK and HYDROSTATICAL experiments made on blood and blood vessels of animals*," Hales also describes his studies of kidney function. 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 and 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" (51). Not an unexpected finding in the dead kidneys of deceased animals and in some ways a replication of the earlier studies of Berengario.

Malpighi's observations were the apogee of renal studies when anatomy became animated and evolved into physiology in the 17th century (24,40). The connection of the corpuscles to the tubules though assumed by Malpighi, Borelli, and Bellini would remain uncertain. Using dye injection studies, the Dutch anatomist Frederik Ruysch (1638–1731) reported in 1729 the appearance of dye in the tubules, while in his 1749 studies, the French anatomist Antoine Ferrein (1693–1769) failed to show the appearance of his injectate in the tubules (52). There would be no further studies of substance until 1842 when William Bowman (1816–1892), using an even more powerful microscope (300×) and meticulous microdissection described the capsule surrounding Malpighi's bodies and established the final connecting link in the postulated Y connection in the

Bellini and Borelli hypothesis of urine formation (Fig. 1) (53).

This recounting of the structural basis of function exemplifies a major accomplishment of the 17th century when structural observations were used in the mechanical explanation of organ function that led to the emergence of physiology as a discipline by the end of the century. It also illustrates the evolution of the applied methodology of Bacon of meticulous observation, experimental manipulation (dye injection) using improved instruments (microscope), validated by repeated observation in various experimental animals, and the use of deductive mathematical reasoning in devising new experiments. The relationship between Borelli, his junior colleague Malpighi, and his student Bellini shows a fundamental contribution of universities and academies in perpetuating the new research spirit by nurturing and training the future generation of investigators. It also heralds the beginnings of specialization, as Eustachio, Bellini, Harvey, and their contemporaries concentrated their studies on specific questions on single organs.

Anatomy Gets Morbid and Begets Pathology

In his death, Malpighi illustrates the next step in the evolution of anatomical observations—that done at postmortem with attempts at correlating morbid anatomy to the clinical manifestations of diseases (Table 3). Malpighi died in Rome in 1694 shortly after what was a stroke that left him paralyzed on the right side. His autopsy was performed by his assistant, the Italian physician of Armenian decent Giorgio Baglivi (1668–1707). The autopsy revealed intracranial hemorrhage and an enlarged right kidney with a large obstructing calculus (54,55). That he had chronic kidney disease (CKD) is definite. He also had left ventricular wall thickening. Whether his CKD and likely hypertension were the cause of his mortal cerebro-vascular accident can be assumed with some certainty, but remains undocumented as instruments to measure blood pressure were yet to come. The postmortem report of Malpighi appears as autopsy number XIII in the first volume of "*Sepulchretum sive anatomia practica ex cadaveribus morbo denatis*" (A repository of anatomy practiced on cadavers) compiled by the Swiss physician Théophile Bonet (1620–1689) during his lifetime and expanded afterward by his students (55,56).

The *Sepulchretum* is a collection of over 2000 autopsy accounts reported by classical authors mostly from the 16th and 17th centuries when autopsies were being performed with some regularity. It is divided into four sections: diseases of the head, the chest, the abdomen, and other conditions. Malpighi's autopsy appears in the section on the head, under the heading *Apoplexy*. The section on the abdomen includes diseases of the kidney classified under the heading of oliguria, polyuria, incontinence, and changes in urine color or consistency, reflecting the urine-based nosology of kidney disease at the time (55,56). Morbid anatomy reached a milestone in 1761 with the publication of "*De Sedibus et Causis Morborum per anatomen indigatis*" (The seats and causes of diseases investigated by anatomy) by Giovanni Morgagni (1682–1771). It is then that organ pathology was launched in earnest. Unlike the urine-based classification of diseases of the kidney used by Bonet in *Sepulchretum* in 1679, Morgagni in his 1761 *De*

TABLE 3. The kidney between functional analysis and disease. Chemistry and pathology.

Name Years	Publication Year	The Kidney
Jean Fernel 1497–1558	*Physiologia* 1542	First use of the term "physiology" in its current meaning as the science of normal function of living matter.
Santorio Santorio 1561–1636	*De statica medicina* 1614	Conducted metabolic balance studies measuring daily weights after food intake calculating the weight and volume of excrements, urine, and perspiration
William Harvey 1578–1657	*De motu cordis* 1628	Renal blood flow supplied by arterial blood and drained by the renal (emulgent) vein.
Jan Baptiste van Helmont 1580–1644	*Ortus medicinae* 1648	Introduced concept of gas as a state of matter launching *pneumatic chemistry*. Compared weight of urine with that of water launching concept of specific gravity.
Theophile Bonet 1620–1689	*Sepulchretum* 1679	Compilation of about 2000 reported autopsies performed during the 16th and 17th centuries. Includes the autopsy of Malpighi.
Thomas Willis 1621–1675	*Five treatises* 1681	Chapter "*On urine*" emphasizing urinalysis as a reflection of changes in the blood. Characterized diabetic urine as "imbued with honey."
Robert Boyle 1627–1691	*The skeptical chymist* 1661	Cornerstone of chemistry. Matter consists of atoms in motion, *corpuscular theory*.
Stephen Hales 1667–1761	*Haemastaticks* 1733	Measured blood pressure in a mare. Perfused a dead dog with warm saline at its own blood pressure and reported no urine production.
Herman Boerhaave 1668–1738	*Institutiones Medicae* 1708	The star clinical educator of the century. Introduced chemistry into medical curriculum at Leiden. Isolated urea from urine.
Giovani Morgagni 1682–1771	*De sedibus et Causis Morborum* 1761	Foundation of morbid anatomy for the study of organ-based diseases.

Sedibus presents diseases of the kidneys based on clinical symptoms and gross anatomy (57,58).

Of further interest to the impact of Malpighi on morbid anatomy is the title of Morgagni's book which may have been inspired by a letter of Malpighi (published posthumously in 1697) in which he expounds on the merit of morbid anatomy, "...anatomy supports the most concrete medicine, showing the origins and seats of diseases, their causes and ways of generation..." In fact, in his papers, Malpighi left a manuscript titled "*Anatomia*" which is an annotated alphabetical listing of the autopsies he had performed or attended between 1666 and 1693. In it he follows the organ-oriented format much like Morgagni did subsequently (54,59).

Physiology Gets Analytical and Begets Chemistry

The mechanical and physical reasoning that begat physiology in the 17th century paved the way for the emergence of chemistry (Table 3). Although the awakening of chemical thought began at about the same time as that of physiology in the works of the embattled, but picturesque Swiss occultist, Paracelsus (1493–1541), progress was slower in chemistry and did not actually mature until the following century (60,61). Nevertheless, it was in the 17th century that rational chemistry freed itself from its roots in the mysterious and secretive ways of alchemy and by the end of the century began to clarify chemical methods and principles. Still, alchemical notions maintained their hold well into the next century. In fact, both Robert Boyle and his contemporary, first professor of chemistry at Oxford Robert Plot (1640–1696), delved into alchemy and had wishful longings for the philosopher's stone. As a result, for much of the 17th century, chemistry was demeaned for its links to alchemy and found little place in universities. Credit for integrating chemistry into the medical curriculum belongs to Dutch innovator of medical education Hermann Boerhaave (1668–1738) in Leiden (62).

To some extent, efforts at the purification of alchemical notions began with the corpuscular theory of Newton on the competing gravitational forces and attractive affinities among different elements, a theoretical concept espoused and pursued by Boyle who dedicated his efforts at elevating the status of chemistry to exploring and explaining the secret workings of nature (63,64). The son of one of the richest men in Britain then, Boyle devoted his life and fortune to experimental studies in laboratories he built in his own living quarters. The importance of his discoveries in chemistry notwithstanding, he did awaken the spirit of experimental systematic chemical analysis that would take another century to mature. Arguably, his principal scientific contribution was in mechanical physics, wherein using the 'Pneumatick Engine," built for him by his friend, the curator of experiments of the Royal Society Robert Hooke (1635–1703), Newton defined the law of inverse relationship between the pressure and the volume occupied by gases (Boyle's law).

Boyle went farther than anyone else in introducing experimentation, new instrumentation, and reproducible demonstration in chemistry. His concept of the elements as composed of different shape, size, weight, and motility found a favorable niche in the Newtonian concept of hydraulics determined by the pore size of the vasculature as the basis of the biomechanical concepts promoted by Pitcairne and Bellini (32,62–64). This notion was extended to the mechanical explanation of disease as due to the obstruction of the vascular pores by circulating fermentation residues of tartar (doctrine of tartar). Its deposition in the kidneys was considered the cause of nephrolithiasis and whose obstruction of the vascular pores of the kidney was considered a contributory cause of dropsy (65).

By mid-century, textbooks for the study of chemical methods were being published such as by Christofle Glaser (d. 1678) "*Traité de la Chymie*" (Treatise on Chemistry) in 1667 and by Christofle Glaser (d. 1678) and "*Cours de Chymie*" (A course of chemistry) in 1675 by Nicolas Lémery (1645–1715) (66). These were methodological manuals rather than explanatory texts. The principal methodological advance of chemistry was that of slow serial distillation and sublimation rather than the scorching heat of the alchemist's furnaces. Large quantities of urine were used in this analytical process that ended in a small, nonvolatile, acidic residue, which when cooled and crystallized had "the taste and shape of regular salt" (66). These would turn out to be mostly chloride salts (sodium, potassium) and urea, whereas the volatile, sulfurous, corrosive residues, the so-called 'volatile alkali', would turn out to be ammonium carbonate (67,68). One of the first books on the chemical analysis of urine for diagnostic purposes was the previously mentioned 1683 "*De urinis et pulsibus*" of Bellini. Using urine distillation studies, he reported that differences in the color, taste, and odor of urine observed clinically were due to variations in its water and solid contents. Another book published 2 year earlier in 1681 was the "*Five Treatises*" of Thomas Willis (121–1675). In the first chapter of the book titled "Of Urines," Willis presents a lucid analysis if the urinary changes observed in various clinical confitions (65,69).

What opened the door to medical chemistry were attempts to explain the digestive process as one of fermentation and separation that entailed the acids and alkali of the digestive juices (70,71). The result was a paradigm shift in explaining how the imperfect food consumed transmuted into the pure components of the body by the heat-based concoction (cooking) of the past to that of a novel chemical process of fermentation akin to that of the fermentation of grapes into wine with its tartaric residues. Essentially, digestion came to be perceived as a stepwise process in which the principal step was fermentation in stomach acid that was subsequently acted upon by intestinal secretions and neutralized by the alkaline bile.

The main proponent of this notion was the Flemish Paracelsian scientist Jan Baptist van Helmont (1577–1644), who went on to attribute the distinctive biting taste of acids to spikes on their small round disk-shaped beads (*rondelets*) whose sharpness was neutralized by alkali mechanically wrapping around its sharp spikes. This concept was espoused and championed by the influential professor of medicine at Leiden, Francis de la Boé Sylvius (1614–1672), who developed it into an all encompassing "acid–base hypothesis." Essentially, all things in nature were divided into "alkali and acid" whose combination resulted in salts; with health being a balance of acids and bases (rather than humors) and disease their imbalance due to abnormal fermentation leading to the generation of excess acids or alkali (67–73). This was a rather simplistic concept based on accepting the classification of acids by their sharp and alkali by their bitter tastes and the effervescence observed when they were mixed. A concept further confounded by the term "salt" used interchangeably as the complex resulting from the combination of acids with alkali and that of the Paracelsian "salt" representing the incombustible ash residue of matter.

Credit for clarifying the issues and defining acids and bases belongs to the skeptical chemist Robert Boyle (62–64). In his 1675 treatise "*Reflection upon the hypothesis of alcali and acidum*," Boyle emphasized that reproducible chemical indicators should be used for the correct identification of acids and bases. The indicator he proposed was a botanical extract of violets (syrup of violets) which turned red with acids, green with alkali and kept it violaceous color with neutral substances and solutions. An observation he had established experimentally earlier in his 1664 "*Experimental History of Colours*." This was a major step forward in clarifying the issues and was adopted by the successor of Sylvius at Leiden, Hermann Boerhave (1668–1738) who went on to isolate urea from the acid residue of urine. It would be in the next century that the French chemist, Guillaume-Francois Rouelle (1703–1770) would clarify the issues further by adding examination of the crystalline structure of salts, the method used by his younger brother Hilaire Rouelle (1718–1779), to identify urea in the urine. It was also in the 18th century that the corpuscular theory would evolve into that of the elements to a great extent by the work of another Frenchman, Antoine Lavoisier (1748–1794) (74).

Conclusion

In the 17th century, mathematics became the language of science, reproducible measurements the test of scientific truths, and the developers and users of measuring instruments the princes of the republic of letters. It was these changing methods for the study of nature that characterized the insurgent attitudes of the Scientific Revolution. It was also then that the rudiments of specialization emerged. The achievements of Harvey, Bellini, and Malpighi were the product of concentrated focused study of specific problems, unlike the broader, often random, usually theoretical studies of their illustrious predecessors. As a result, the understanding of organ structure, function, and changes in disease in general, and of the kidney in particular, were clarified and progressed at a rate never achieved theretofore.

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