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Early debates on urination in ancient Greek medicine

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Abstract. Although considerable effort has been made by scholars to reconstruct the discovery of renal function in modern times, little attention has been paid to clarifying the early steps of ideas about urine production in Antiquity. In the oldest literature, the site of urine formation remained undetermined. Later, the bladder was considered the central uropoietic place. The first documents advocating the role of the kidneys are attested in the *Hippocratic Corpus*. In the IV century, Aristotle provided a theory of kidney activity. The Hellenistic and Greek-Roman physicians were aware of the fundamental role that the kidneys play in urine production. The kidneys filtered the urine and separated it from the blood. Thus, the excreting activity of the kidneys was postulated in ancient Greek medicine. This historical note describes the initial development of theories on uropoiesis and the early emergence of ideas that will provide a basic conceptual framework in modern medicine.

Keywords: mechanisms of urination, ancient Greek medicine, blood vessels, bladder, kidneys, history of science.

EARLY TIMES: BLOOD VESSELS AND THE BLADDER

In the II century CE, the great physician, surgeon and philosopher Galen of Pergamon noted that in his day even butchers knew that the kidneys were responsible for the production of urine (*On Nat. Fac.*, I.13, K.2.30-31). But in the Greek medical environment of the V century BCE, things were different. We find the first ideas on urine formation in the *Hippocratic Corpus,* a collection of some sixty medical books mainly written in the Ionian Greek dialect (Craik, 2015; Fox, 2020; Jouanna, 1999). The debate concerns both the site of urine production and the mechanism of urine formation. In some text of the *Corpus*, possibly the most ancient texts, the kidneys are neglected and it seems that urine is formed by a sort of blood filtration at unspecified anatomical sites located in the genital parts. An example of this view is found in *Diseases II* (*Diseases II,* 1), which belongs to the oldest layer of the book probably dating to the middle of the V century (Littré, 1839-61). Here the author sets forth a theory of urine formation that postulates the role of blood vessels in the direct transport of phlegmatic material from the head

to genital organs, from where it is excreted by urination. Both the kidneys and the bladder are entirely neglected in this account. The site of urine formation is left completely undetermined. Transported by blood vessels, the phlegm is apparently transferred directly into the urine flowing through the genitals. *Diseases IV* probably dates samewhat later than *Diseases II*, namely to the end of the V century or the beginning of the IV. In *Disease IV* (*Diseases II,* 35), a very similar account is reported. The flegm descends from the head through the blood vessels, but here the author states that such humor is sent through the bladder and passes to the outside. The Greek term *diapherō* used in this context implies a movement of fluid across the wall of the bladder. The same mechanism of diuresis is explained in *Regimen in acute diseases* (*Regimen in acute diseases,* 51), a treatise dating back to the end of the V century. Here it is reported that the white wine is helpful in acute diseases because "it enters the bladder more easily than the others, and has a diuretic and purgative effect". Again, the bladder appears as the primary site of urine formation. Only the bladder is mentioned in these passages, not the kidneys. *Ancient medicine* is an important doctrinal text which dates to the end of the V century. In chapter 22, the author includes the bladder among the parts of the body that are hollow. Hence, this structure can expand and contract to attract and release fluids. *Places in Man*, another ancient foundational treatise of the *Hippocratic Corpus*, clearly states in chapter 8 that "the bladder filters the liquid". The Greek term used here to express this function is *diētheō*, whose meaning is 'to filter', 'to strain through', 'to percolate', and also 'to purify'. Thus, as the bladder expands and increases in volume, the cavity attracts fluids that seep into the organ and are filtered by its wall. This concept is clearly stated in an illuminating passage from *Diseases of Woman I* (*Diseases of Woman I,* 2), a treatise whose content may date back to the middle of the V century. When the matrix is filled with blood, it dilates and presses against the bladder. This in turn 'attracts the thinnest part of the blood' contained in the uterus, and the urine becomes red. The effect of attraction is expressed by the verb *eryō*, which means 'to drag', 'to draw', 'to pull', 'to attract', 'to absorb', implying force or violence. The bladder appears to function like a suction apparatus, a sucker that pulls the fluids that seep through its wall along with it. A further remarkable passage is found in the same treatise (*Diseases of Woman I,* 61), where it is said that the excess fluid of a hydropic woman 'seeps through (or enter) the bladder' and is partially excreted by micturition. The verb used to express percolation of the fluid in the bladder is *dierchomai*, which means 'to go through', 'to pass through', 'to arrive'. Thus, in some texts of the *Hippocratic Corpus* the place of urine synthesis is either left undetermined or is identified with the bladder. This viewpoint may represent the oldest one. This assumption is agreed to by the *Anonymus Londinensis*, the anonymous author of a medical papyrus probably from the second half of the I century CE, a short compendium of medical ideas which appears to be taken in part from the *Menoneia*, a collection of medical opinions written by Aristotle's pupil Menon, who asserted that there was a controversy among the 'ancient scientists' (*hoi archaioi tōn philosophōn*)(Manetti, 2011; Ricciardetto, 2016). Some indeed maintained that the bad fluid was 'carried downward and excreted outside by urination'. Others, that the fluid taken in excess was carried 'to the parts around the region of the bladder' whence it was converted into a pungent and salty fluid, the urine, which was absorbed by the bladder. It is possible that both positions reflect an older culture rooted in popular belief and Greek folklore that ignored the role of the kidneys in urine formation. In the *Iliad*, the bladder is cited in two passages. By contrast, the kidneys are never mentioned in Homeric poems. In *Iliad* XXI.204, there is only a marginal reference to the 'fat that lies upon the kidney' (*dēmos epinephridios*). The redaction of the Homeric poetry is in the VIII century BCE, but material goes back to earlier centuries and the Mycenaean age. This may indicate that the 'Homeric culture', as the Egyptian medicine, was unaware of kidney function (Nunn, 1996).

THE KIDNEYS ENTER THE STAGE

Internal Affections is a hippocratic treatise which may be dated to the first decade of the IV century. Here, we find an early indirect allusion to the kidneys as the site of urine production and the clinical picture of kidney stones or nephrolithiasis (*Internal Affections, 14).* In addition to various symptoms, the author mentions the excretion of sandy concretions which, he emphasizes, are formed in the kidneys. Nephrolithiasis originates in the kidneys – the author explains – and should be distinguished from lithiasis of the bladder. The authors of *Nature of Man* and *Aphorisms* write that the finding of small pieces of hair-like, fleshy bodies in the urine is a sign of renal secretion, possibly in connexion with rheumatic fever (*Nature of Man,* 14 and *Aphorisms,* 4.76). The Greek verb attested in *Aphorisms* 4.76 is *ekkrinō*, whose meaning is 'to sort out', 'to separate', 'to expel', 'to secrete'. Thus, the kidney is compared to a gland which secretes urine or other constituents. Furthermore, in *Aphorisms* a connexion is made between the excre-

tion of blood in the urine and the breaking of a small vessel in the kidneys (*Aphorisms,* 4.78). This passage is particularly interesting because it relates blood flow with hematuria. *Nature of Man* and *Aphorisms* are two treatises attributed to the school of Cos. The first is generally dated to the years 410-400; the second, though possibly preserving ancient material, was not written before the IV century. *Glands* is a hippocratic text whose date is disputed (Craik, 2009). Some scholars place this short treatise not before the Hellenistic era. According to others, it belongs to an older period, that is, the end of the V century or the early decades of the IV. In *Glands* (*Glands,* 6), the author states that 'the kidney has glands (*adenes*)' and suggests that the liquid flowing in is not absorbed by the kidneys but flows through them down to the bladder. This appears to be the first passage in the medical literature where the kidney is equated with a gland. The assimilation of the kidney to a glandular structure exerting a role in collecting moisture may well represent a fundamental seminal principle of renal physiology. Moreover, in the hippocratic *Nature of bones* we find an explicit admission of the part which the kidney exercises in urine formation (*Nature of bones,* 4). It is stated that "what is drunk is attracted to the kidneys through the vessels. Then, the water is filtered as also through the kidneys". Remarkably, the function of the kidneys is mediated by blood perfusion through renal vasculature. Again, the verb used to express the filtering activity (*diētheō*) is the same one previously attributed to the bladder. However, the kidney is not the only structure capable of producing urine. Indeed, the sentence goes on to assert that fluids are also filtered through the parts into which the kidneys open, namely the ureters. This is where 'the urine is filtered out and separated from the blood'. The structure of the ureter thus provides both a filtering and a separating function. *Nature of bones* is a hippocratic treatise of difficult dating. It is a compilation of parts containing material from different sources and from different times. The chapter on kidney function shows a marked interest in anatomy and dissection. This does not argue for an early date of composition. Thus, we can temptatively conceive that the concept of kidney involvement in the mechanism of urine production began to circulate in the Greek medical environment towards the end of the V century and coexhisted for a long time with the theory of urine production in the bladder. As late as the first half of the I century BCE, Asclepiades of Bithynia, the founder of the Methodist sect, postulated, according to the testimony of Galen, the existence of narrow, invisible, entirely imperceptible passages in the coats of the bladder. The fluid we drink enters the bladder by first dissolving into vapours and then condensing back into the liquid of urine. According to the theory of Asclepiades and his disciples, still active in the time of Galen in the II century CE, the kidney was created by Nature for no purpose (*On. Nat. Fac.*, I.13, K.2.32). If we now ask the question about the mechanism by which the kidneys are supposed to produce urine according to the Greek medical literature around the turn of the V century, we can conclude that this action is exerted in two ways: i) by filtration (*Nature of Bones,* 4), and ii) by separation and secretion (*Aphorisms,* 4.76).

THE KIDNEY AS A SIEVE-LIKE APPARATUS

We find the first complete and reasonable account of renal physiology in Aristotle (384-322 BCE). According to the Stagirite 'the kidneys excrete the fluid residue' (Marandola et al. 1994). The term used to indicate 'excretion' is *ekkrisis*. He writes that urine is produced in the kidney by the percolation through the body of the organ of the superfluous fluid, which passes from the blood vessel into the kidney. *Diētheō* is the verb used to indicate 'percolation' or 'filtration'. The filtered fluid then collects into the middle of the viscus where a hollow structure is to be found. This structure is the pelvis. Aristotle concludes that from the hollow part of the kidneys two sturdy channels devoid of blood (the ureters) lead into the bladder, one from each, and the fluid is passed off through them from the kidneys into the bladder. This invaluable aristotelian description contains the main points regarding renal function and urine production: the blood vessel supply, the kidney filtration activity, the collection of urine, and its excretion through ureters and bladder. It apprears to be the most precise theory on kidney activity and the anatomy of the urinary system available at the time.

Galen testifies that all the great physicians in Antiquity, including Diocles of Carysus (second half of the IV century BCE), Erasistratus of Ceos (about 330-255/250 BCE) and Praxagoras of Cos (fluorished around 300 BCE), believed that the kidney were 'the organs for the production of urine'(*On. Nat. Fac.*, I.13, K.2.30). This function is well expressed by Galen's formula '*organa diakritika tōn ourōn*', which means that the kidneys are the structures responsible for 'separating out' the urine. *Diakritikos* comes from the verb *diakrinō*, which means 'to distinguish and separate one from the other', 'to divide', 'to part'. We know nothing about the ideas of Diocles and Praxagoras concerning the function of the kidneys. Unfortunately, we are also completely ignorant of the conceptions of Herophilus of Chalcedon (330/320-

260/250 BCE) on this subject. As for the position of the other great Alexandrian, Erasistratus, Galen informs us that he did not comment on the way in which the kidneys function to produce urine, leaving the question (*On. Nat. Fac.*, I.17, K.2.67-69). Moreover, Galen explains that some Erasistrateans near the times of Erasistratus held the view that the kidneys functioned like a sieve in that the renal veins conducted the serous fluid, rather than blood, to the kidneys, a view that, as Galen notes, have flourished for a certain period but was then abandoned. This theory was sharply criticized by Galen himself, who thought it absurd. Why, asks the Pergamene, of the innumerable veins which issue from the vena cava, should blood flow into the others, and the serous fluid be diverted into those leading to the kidneys? Despite Galen's criticisms, the Erasistratean assumption that the kidney could function like a sieve apparatus represents a major intellectual achievement. Even today, the glomerular membrane is viewed as a reticular structure capable of selectively passing or retaining different types of molecules. This idea implies a mechanistic view of animal physiology, the very basic principle on which Erasistratus built his natural philosophy. This idea also entails the complex premise of a certain hydrodynamic pressure which must prevail within the blood vessels in order to force the liquid portion out of the blood. One should consider the possibility that this view of kidney function may have been conceived by Erasistratus himself and disseminated among his students. In the I century CE, Rufus of Ephesus wrote a book *On diseases of the kidneys and the bladder.* Rufus was one of the most influential medical writers of Antiquity. He strongly believes that the kidneys are the sites of urine formation, as diseases of these organs, such as inflammation, suppuration, lithiasis, ulcers, sclerosis, and hemorrages, cause remarkable changes in the quality and quantity of urine. In the chapter on hematuria, Rufus states that "the proper function of the kidneys is to filter the urine from the blood, and to prevent that which is the color of blood, the blood itself, and other thick material from escaping"(Sideras, 1977). The activity of filtering is expressed by the verb *ētheō*, which means 'to sift', 'to strain'. He writes that in hematuria "the kidneys are no longer able to filter the urine, but, being more dilated, they allow some of the blood to pass out of the vessel and other thick material". Here Rufus is very likely referring to the wideness of the pores in the kidney, the presence of which is thus postulated. So, too, for Rufus the kidneys function like sieves. Although Rufus clearly recognizes that urine is produced by the kidneys, the old belief that the bladder is the site of urine formation still persists with him. In describing and discussing the clinical symptoms of diabetes, a disease which he calls 'urinary diarrhea', i.e. the 'strong flow of urine', and which he regards as a joint disease of the liver, kidney, ureters and bladder, Rufus gives the remarkable proposition that the patient suffers from polydypsia, what he drinks is immediately converted into urine, his body becomes thin and emaciated, and 'wastes away toward the bladder'. The reception of the ancient teachings of Erasistratus and Rufus can be seen in the *Anatomia Mundini* of 1316, in which Mondino de' Liucci (c.1270-1326), one of the leading anatomists in the Middle-Ages, equates the kidney with a kind of sieve, a *colatorium*, colander, or drainer, whose porosity (*porositates*) allows urine but not blood to pass through (Mondino de' Liucci, 1531). Thus, the urine seeps, is distilled, collected, and poured from the kidneys into the bladder. Another eminent physician was Aretaeus of Cappadocia, who flourished in the I century AD. His descriptions of diseases, such as epilepsy, syncope and diabetes are among the classics of their kind. Aretaeus provides us with valuable information about kidney function. He states that "the remarkable action of the kidneys is to separate (*diakrisis*) the urines from the blood and to secrete (*apokrisis*)"(Hude, 1958). By contrast, the function of the bladder is to allow 'expulsion' (*exodos*) of urine. Thus, the different function of these two organs can be readibly distinguished. The kidney is like a gland (*adenōdees*), says Aretaeus, in which small, tickling, sieve-like cavities enable the filtration (*diēthēsin*) of urine. The fluid is then directed into fibrous ducts, the ureters, that connect the kidneys to the bladder. Again, Aretaeus reiterates the concept that the kidneys perform a complex function: they filter (*diētheō*), separate (*diakrinō*) and secrete (*apokrinō*). In 1666, the glandular structure of the kidney was recognized by Marcello Malpighi (1628-1694). He discovered 'a number of very small glands' (*glandularum minimarum*), i.e., the Malpighian corpuscles or glomeruli or renal *pomula*, which 'immediately catch the naked eye', when a black fluid mixed with spirit of wine was injected into the renal artery and then the capsule of the organ was removed (Malpighi, 1666).

THE KIDNEYS AS A SELECTIVE ATTRACTION MACHINE

Galen openly asserted that the quantity of urine excreted daily clearly shows that all the fluid drunk becomes urine, except that which is eliminated with the dejections or which flows off as sweat or insensible perspiration. He provided empirical demonstion that urine is produced by the kidneys and passes through the ure-

ters into the bladder. In this perspective, he performed a series of elegant ligature experiments that would probably inspire William Harvey many years later, in the early decades of the XVII century, in his investigative approach to the problem of blood flowing (Wilkie, 1965; Shank, 1985). In vivisection procedures, Galen secured the ureters with ligatures. The bladder did not fill while the ureters on the side next to the kidneys were quite full and distended and almost in danger of bursting. When the ligatures were removed from the ureters, these ducts abruprly emptied and the bladder filled with urine (*On. Nat. Fac.,* I.13, K.2.36-37). Galen also addresses the question on how the kidneys would perform their function of separating urine. He argues that one mechanism could be the driving force of the venous blood, the other the attractive faculty of the kidney itself. Galen's line of thought is logical, consequential, and strongly influenced by the basic principles of his general physiology. He approaches the truth, but fails to grasp it. He argues that if the veins were to force the blood into the kidneys, they would squeeze out not only the urine, but all the blood they contain (*On. Nat. Fac.,* I.15, K.2.57). If the kidneys acted like a sieve, letting through the thinner serous part and retaining the thicker portion of the blood, then all the blood contained in the vena cava would have to pass to them to be filtered. But Galen does not know the circular motion of the blood in the sense formulated by Harvey. According to his physiological theoretical principles, the venous blood is produced by the liver and is slowly carried to the periphery by the contraction of the veins. It reaches all organs and tissues where it is assimilated and consumed. Thus, only a small portion of the total volume of blood would percolate through the kidneys. As much as can be contained in the veins leading to the kidneys. So only that portion is purified. If the kidneys were to function like a sieve, the thin serous part of the blood would flow through the organs, while the thick bloody part remaining in the renal veins would obstruct the blood flowing in from behind. The blood must therefore first run back into the vena cava to empty the veins leading to the kidneys, otherwise there will be no passage left for further blood (*On. Nat. Fac.,* I.16, K.2.65). Such a situation implies a number of complex hemodynamic consequences that are difficult to deal with in a non-Harveyan pattern of blood movement. In a sieve-like perspective, Galen equates the process of urine formation with the process of cheese production (*On. Nat. Fac.,* I.15, K.2.58). For even this, though is thrown into the basket strainers, not all seeps through. The part that is too fine in proportion to the width of the meshes flows downward. The remaining thick part, which is destined to become cheese, cannot get down, because the pores of the strainers will not let it pass. According to Galen's conception, this is the part that obstructs the lumen of the renal veins. Apart from this disadvantage, the kidneys do not have a favourable position to function like a sieve, as they are not situated below the vena cava, but on either side of it. This means that gravity would exert little force on the blood flow directed to these organs. It is therefore impossible for the kidneys to function like sieves. Now, if the movement of urine does not depend on the tendency of a vacuum to be replenished – a general mechanistic hydrodynamic principle advocated by Erasistratus as a general force for the motions of fluids, which was severely criticised by Galen who favoured a vitalistic causation as the attraction of the simile by the simile – then the remaining explanation – as Galen admits – is that the kidneys actually exert a traction force, i.e., a selective movement of fluid. The kidneys possess a specific faculty which draws to themselves the particular quality existing in the urine, as the lodestone attracts the iron. Therefore – Galen concludes – it is impossible to give any other reason for the secretion of urine than the principle of attraction (*On. Nat. Fac.,* II.2, K.2.77-78).

CONCLUSIONS

The early debate about the site of urine production and about the functional model of the kidneys is rich in interesting perspectives. Ancient Greek physicians assumed that urine was formed in the kidney by a process of separation from the blood. Some eminent medical doctors took a mechanistic view and equated the kidneys with sieve-like devices. Moreover, the organ seemed to have an intrinsic secretory capacity. This appears to be a fairly modern view of kidney function. That the hippocratic author of *Glands* and Aretaeus of Cappadocia equate the kidney with a gland seems a fundamental step in understanding the relationship between structure and function of the organ. It is likely that the small, sieve-like cavities mentioned by Aretaeus are the minor calices surrounding the renal papillae. It is noteworthy that, as early as 1521 the Renaissance surgeon and anatomist Jacopo Berengario da Carpi (c.1470-1530) equated the substance of the inner part of the kidney with several female nipples (renal *papillae*), thus equating the kidney with a complex glandular structure that secretes urine in a large cavity situated in the centre of the organ (Berengario da Carpi, 1521). In his seminal 1842 paper, Bowman (1816-1892) himself equates the secretory tubules of the kidney with those of 'all other glands' and refers to 'the nipple-shaped extremi-

ties of the [medullary] cones' to denote the renal papillae (Bowmann, 1842). Given the remarkable structure of the Malpighian bodies and their unique connection with the tubes, Bowmann ventures to speculate that - the tubes and their plexus of capillaries were probably […] the parts concerned in the secretion of that portion of the urine to which its characteristic properties are due (the urea, lithic acid, &c.), the Malpighian bodies might be an apparatus destined to separate from the blood the watery portion – (Bowmann, 1842). Again, secretion and separation appear to be key concepts that come from ancient Greek science. We must wait for the work of Carl Ludwig (1816-1895) to come up with a radically new concept of kidney function. He was famous for his explanation of glomerular filtration in terms of physical cardiovascular hemodynamic forces, but beyond filtration, separation, and secretion, Ludwig introduced the idea of reabsorption of most of the aqueous portion of urine and other substances dissolved in it, a principle unknown to Greek teaching (Ludwig, 1842).

Nevertheless, Galen's legacy was disappointing. Despite his sophisticated experimental approach and fine theoretical reasoning, the Pergamene's notion of a specific faculty of attraction by the kidneys remains nebulous and physically indeterminate. Unfortunately, Galen's doctrine overshadowed previous contributions and the subsequent history of renal physiology will be a progressive emancipation from the attraction principle and the search for a mechanistic explanation of kidney function (Mc Vaugh, 2012). A remarkable point in ancient Greek medicine was the constant linkage between kidney action and blood perfusion. Urine derived either from blood filtration or a selective attraction from the blood. It is perhaps not coincidence that one of the first medical texts in the Western medieval world, the *Anatomia porci ex Cophonis libro* – a document from the XI-XII century belonging to the Salernitan school of medicine – mentions the tiny blood vessels (*capillares venae*) emanating from the renal vein, so thin that they cannot be traced with the naked eye, through which the urine is conducted to the kidney (de Renzi, 1853). We conclude with the words of Malpighi: - For a long time – he wrote in his introduction to *De renibus* – the kidneys have been the subject of varying opinions, some even having regarded them as superfluous and unnecessary, a thought which is certainly not a tribute to Nature. More recently, however, because of their wonderful structure, and because of the very necessary function attributed to them, they have attained a place among important parts of the body – (Malpighi, 1666).

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