The Inception and Formation of the Theory of Hyperfiltration Through the Ages

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With the rising incidence of metabolic syndrome and progressive kidney disease, efforts to halt this progression have become the mainstay of therapies in the era of modern nephrology. The necessity of one versus two kidneys has occupied the minds of leading scientists and philosophers throughout the ages and has laid the foundation for our understanding of progressive kidney disease. This review focuses on the major discoveries of the leading thinkers who with their paradigm shifting ideas and skepticism pushed the boundaries of our knowledge and shaped the theory of hyperfiltration.

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KIDNEYS IN HISTORY

The Biblical Kelayoth

Our belief that the heart is the home of the soul, emotion, and thoughts originates in Mesopotamia and Egypt thousands of years ago. Since the soul needed the heart to enter the afterlife, the heart was left in the mummies. This belief continues in modern times despite our intellectual and scientific views regarding the heart. While, in ancient Egyptian medical literature, there is no definitive word for the kidney,[1] the Hebrews knew about the kidneys through animal sacrifice, the ritual killing through which they were required to exercise dissection of the animals and the separation of various organs. Among which the kidneys "and the fat that is upon them" (Ex 29:13; Lev 3:4) were burned upon the altar.[2] The kidney was mentioned 31 times in the Old Testament, always in the plural, *kelayot* (*sing killia*).[3] In contrast to other ancient languages which ambiguously refer to the testes and kidneys, in Hebrew, there is a clear distinction between them. In all Semitic languages, with the exception of Sumerian, the word for kidneys is remarkably similar. In Hebrew, the word for kidney is *killia* (*Pl kelayoth*), in Assyrian, *kallitu*; in Arabic, *kuliatun*; and in Aramaic, *kulian*. Some writers believe that the word comes from *"kol"* or *kll*, all or complete, *keli*, a vessel, *kl*, something round. Fewer trace a relation between the word to *kalah*, to long about, to desire passionately.[4] The attention of Hebrews to kidneys could have been due to the anatomical features of the kidneys; amongst them are noticeable amount of perinephric fat and location of kidneys in the retroperitoneum. In the Old Testament, it has widely been noted that "all fat belong to Yahweh." Fat was burnet upon alter so Yahweh would receive his portion. Furthermore, Hebrews believed the kidneys were associated with a person's innermost being, ranging from representing morality, character, to the deepest agony in the Old Testament.[5] "Examine me, O LORD, and prove me; try my reins (kidneys) and my heart." (Psalm 26) It is plausible that due to the location of the kidneys in the retroperitoneal area, they represented the innermost part of the human body.[3] "My inmost being [kidneys] will rejoice when your lips speak what is right." (Prov 23:16) This probably relates to the sacrifice rituals "when an animal is dismembered, since the kidneys are the last organ to be reached. Hence, kidneys are a symbol of the innermost being and self-consciousness." Through the medium of the bible, the Hebrew conception of the kidneys influenced language and medicine for centuries to come. For example, in medicine, for years the kidneys were regarded as the seat for the soul. The great Persian physicians of the 9th and 10th century, Rhazes (841 AD to 962 AD) and Avicenna (908 AD to 1073 AD), inherited the biblical view of the kidneys and carried forward the belief that the kidneys were the vessels that stored morality and they opposed the idea of kidney removal.[6-8]

Aristotelian Kidney

Aristotle pioneered contributions to the theory of hyperfiltration through his meticulous anatomical examination of animals. Aristotle first reported the anatomical differences between the two kidneys and the relative importance of one versus two kidneys. Based on his observations from exploratory laparatomies, he was the first to report that an animal can continue to live with one kidney. In his book, *The generation of animals* 350 BC, he states that "No animal, indeed, has ever been born without a heart, but they are born without a spleen or with two spleens or with one kidney.[9]" He further examines the anatomy of kidneys:

> *In the centre of the kidney is a cavity of variable size. This is the case in all animals…. The human kidneys are of similar shape; being as it were made up of numerous small kidneys…. For this reason, should the kidneys of a man be once attacked by disease, the malady is not easily expelled. For it is as though many kidneys were diseased and not merely one; which naturally enhances the difficulties of a cure.*[10]

As the dominance of medieval church subsides over time investigators started to examine the functionality of the kidney by conducting nephrectomies. One kidney being compatible with life was supported by observations from Vesalius (1555), Rhodius (1661) and Balsius (1674). Experimental studies performed by Zambeccarius (1670) and Roonhuyzen (1672) showed that unilateral nephrectomy did not have any impact on the survival of subjected animals.[8]

HISTORICAL MILESTONES

Kidney Function

The effort to fully understand the function of the nephron was a necessary prelude to subsequent efforts to preserve kidney function. The earliest well-articulated comprehensive theory of kidney function was by Giovanni Borelli, who in 1680 stated that the kidney acted as a sieve that produced a filtrate of blood; he specifically stated that the sieve size was such that it did not permit the red cell mass to pass through.[11] Borelli, a mathematician, astronomer, and physiologist, is best remembered for his application of mechanistic concepts to such bodily functions as movement, but his interests were wide-ranging and he reflected and wrote about many aspects of physiology.

Marcello Malpighi wrote the first actual description of the structure that performed the sieve function. In 1661, he was the first to describe capillaries, which he observed in the lungs of frogs. His initial report was in the form of letters to his colleague and friend, Giovanni Borelli.[12] Malpighi later described the glomerulus, but viewed it as a gland rather than a capillary-based structure. William Bowman, whose careful microscopic study was enhanced by his elegant drawings, was the first to correctly characterize the true nature of the glomerulus. His landmark paper on the structure and use of the Malpighian bodies of the kidney, published in 1842, led to an award from the Royal Society.[13] His clear and original description of the process of glomerular filtration, supported by his analysis of the structures that made filtration possible, was the foundation for all of renal physiology. Bowman understood that there was more to urine formation than just filtration, and he proposed the simple concept of tubular secretion. He recognized that his model was most likely incomplete and promoted the idea that further investigation would be helpful. In the same year of 1842, the German physiologist Carl Ludwig presented his thesis titled "On the physical forces that promote the secretion of urine," which was published in 1843.[14] He theorized that glomerular filtration was passive, and it was the osmotically driven process of tubular reabsorption that drove the subsequent formation of urine. He was troubled by his later knowledge that some substances were excreted in the urine in quantities exceeding their concentration in the blood. His two-component theory of urine formation was correct as far as it went, but was not the complete story. In 1859, Herman insightfully postulated that an inequality in the simultaneously observed rate of urine secretion by the two kidneys might derive not only from a difference in the rates of urine secretion by each kidney, but also from different parts of the same kidney.[15] Almost a century later, Oliver and Bricker proposed the "heterogeneity of glomerular function" and "intact nephron hypothesis," which are in fact modern versions of Herman's theory. In 1923 EK Marshall and James Vickers studied the excretion of phenol red by the kidney. Even though only 40% is potentially filterable, as much as 70% could be extracted from the blood and end up in the urine.[16] In 1924, Addis and Oliver beautifully described the histologic changes such as tubular hypertrophy after the removal of renal mass. They also demonstrated that the rate of urinary excretion of urea overload in rabbits reached one hundred percent 110 days following nephrectomy.[17,18] Despite the lack of precise knowledge regarding autoregulatory mechanisms, in 1929 Verney hypothesized that "the reduced kidney then responds at constant blood pressure exactly... as though it were being subjected to an increase in perfusion pressure. Since the glomerulus is the receptor of the pressure stimulus... the increase in the urine flow could be explained in terms of the shift of a given quantity of resistance from the vasa afferentia to vasa efferentia." Such a shift would presumably entail an increase in capillary blood pressure or the blood flow through the noninfarcted region.[15] By 1933, Ellis and coworkers had shown that creatinine clearance increases from 65% to 90% of the preoperative value in humans after nephrectomy.[19] By 1930, the three processes of glomerular filtration, tubular reabsorption, and tubular secretion had all been described. However, they were not yet accepted as part of a unified theory, in part because of ongoing concerns about the kidney's ability to elaborate urine of varying concentration. In 1942, Kuhn hypothesized the final missing piece, elaboration of the renal concentrating mechanism involving the countercurrent between the two limbs of the loop of Henle.[20] The early work of Bowman and Ludwig to the final piece of the puzzle as hypothesized by Kuhn spanned 100 years. The theory of kidney function as described by Borelli until the publication of Kuhn and Wirz's experimental verification of the renal concentration mechanism spanned 271 years.

Models of Reduced Renal Mass and Hemodynamic Studies

The first successful human nephrectomy was performed by Gustav Simon in August of 1869, in Heidelberg Germany, on a female patient with urogenital fistula.[8,17] Historically, investigators had failed to produce chronic renal lesions in experimental animals comparable to those found in humans. In his *De Sedibus*, Morgani (Italian pathologist, 1760), was first to state that the largeness of the intact kidney is a measure of the mass diminished in the diseased kidney, an opinion reposing on no experimentation. While Comhair (Liege, France, 1803) shows for the first time that the removal of both kidneys leads to death in dogs, Rayer (Paris, France, 1841) clearly reports that atrophy of one kidney is always associated with the compensatory hypertrophy of opposed kidney. Thodore Tuffier (Paris, France, 1889) was the first to remove one kidney from dog and a portion of the other kidney at a later time.[21,22] He concluded that there were no changes in the elimination of urine or urea despite the loss of the kidney. However, compensatory polyuria following unilateral nephrectomy, first described by Hermann (1862), was confirmed by Bradford (1899), and then again by Pickford and Verney (1929).[15,23,24] In the beginning of 20th century, Carnot (Paris, France, 1904 to 1907) brilliantly highlights the therapeutic role of extracts from organ as "opotherapies." He was first to describe renal hyperplesia as a result of injecting serum from uninephrectomized animals. He also reports the presence of substance which he calls *homopoetin*, resulting in an increase in red blood cells, 80 years before identification of erythropoietin. Over a 40-year period, studies performed by Chanutin, Platt, Peters, Bricker, Shimamura, Morrison, Hayslett, Kaufman, and Azar greatly illuminated the factors influencing the progression of chronic kidney diseases in human.[25-31] Based on the findings generated from rats with surface glomeruli (the Munich-Wistar strain), Brenner and colleagues were able to provide detailed information on the hemodynamics of single nephron in the setting of reduced renal mass and to demonstrate that selectively reducing the efferent arteriole pressure by angiotensin-converting enzyme inhibitors could slow the rate of progression of renal failure.[32-35] These collective studies on the adverse effects of hemodynamic changes on the remaining nephrons and work on modalities to slow down the rate of kidney failure progression have been some of the dominant concepts in modern nephrology.

It seems we are moving from the physiologic filtration phase to the pathologic hyperfiltration era with the emergence of common metabolic hypertensive diseases. In order to protect the kidney, we need to stay in the physiologic filtration phase and not move fully into the hyperfiltration phase.

We end this review with a statement from Aristotle: "And thus even in men, though it is beneficial to them to have fat kidneys, yet should these organs become over-fat and diseased, deadly pains ensue.[10]"

CONFLICT OF INTEREST

None declared.

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