A History of Uremia Research

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The history of uremia research begins with the discovery of urea and the subsequent association of elevated blood urea levels with the kidney disease described by Richard Bright, a well told story that needs no recounting. What this article highlights is how clinical and laboratory studies of urea launched the analysis of body fluids, first of urine and then of blood, that would beget organic chemistry, paved the way for the study of renal function and the use of urea clearance to determine "renal efficiency," provided for the initial classification of kidney disease, and clarified the concepts of diffusion and osmosis that would lead to the development of dialysis. Importantly and in contrast to how the synthesis of urea in the laboratory heralded the death of "vitalism," the clinical use of dialysis restored the "vitality" of comatose unresponsive dying uremic patients. The quest for uremic toxins that followed has made major contributions to what has been facetiously termed "molecular vitalism." In the course of these major achievements derived from the study of urea, the meaning of "what is life" has been gradually liberated from its past attribution to supernatural forces (vital spirit, archaeus, and vital force) thereby establishing the autonomy of biological life in which the kidney is the master chemist of the living body.

THE HISTORY OF uremia research can be traced to the Scientific Revolution when urea was discovered, through the Enlightenment when it was isolated and characterized, the early modern period when it was synthesized in vitro, its generation in the body elucidated, and its level in the blood linked to kidney disease, and the 20th century when after the advent of dialysis it launched the quest for uremic toxins. That story has been told eloquently by several eminent historians of nephrology.[1-8] Less well exposed is how urea paved the way to the study of renal function, established its clearance as a test of latent kidney disease, and facilitated the exploration of what is life. This article proposes to revisit these latter aspects and to weave the story of urea (*viz* uremia) into the broader history of medicine that would ultimately lead to the identification of the kidney as a vital organ, provide for the study of renal function, launch chemical analysis of body fluids, clarify the concepts of diffusion and osmosis that would lead to the development of dialysis, and introduced the terms uremia and azotemia into the parlance of medicine as nephrology was emerging in the past century.[2,9,10] More dramatically, it will recount how in the course of this progress the study of urea provided the evidence for 1 of the major scientific advances in defining life as neither conferred nor controlled by esoteric and mysterious supernatural forces that had been assumed for millennia past, and thereby established the autonomy of biological life in which the kidney is the master chemist of the living body.

To adequately appreciate the recounting of this progress, one has to turn to the beginnings of medicine in prehistory when the difference between life and death was queried and defined as body *heat* and *movement*. Their early appreciation is reflected in the Greek mythological deities of death and sleep, the half-brothers Thanatos and Hypnos conceived to explain the determinants of life (*heat and movement*) from whence they permeated Greek thought and entered biology through the work of Aristotle (384-322 B.C.) and medicine through that of Galen (120-200 A.C.).[11] In Galen's physiology, which dominated medical thought through the 17th century and beyond, *heat* was generated in the heart where the "*vital spirits*" were added and motion activated by the "*animal spirits*" that were added in the brain and both conveyed to the rest of the body in blood, whose loss of fluidity (clotting) accounted for paralysis or death.[10]

The challenge to Galen's doctrines began in the Renaissance with the entrance into medical thought of what has been termed "*iatrochemistry*." The leader of this movement was Paracelsus (1493-1541), who abandoned the 4 humors of Galen replacing them with mercury, sulfur, and salt that constituted inorganic matter and replaced the "*vital spirits*" with his "*Archaeus*."[12] The mysterious terminology of Paracelsus notwithstanding what he actually achieved was launch the change of alchemy into chemistry that he introduced into medicine by his analysis of bodily fluids, principally that of urine which was readily available in abundant quantities necessary for study.[12,13] Clinically, these principles were quickly adopted because the analysis of urine was deemed important in the understanding of the commonest recognized cause of renal disease then, that of bladder and kidney stones. Another reason the

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analysis of urine became important is that throughout this period and well into the 20th century, the kidney was considered a secretory organ subservient to the vital function wherein absorbed nutritional aliments were converted into components of the living body (so-called "*animal oeconomy*"), that is, that of the gastrointestinal tract. Hence, the use of urine analysis to obtain insight into body metabolism from the nonnutritious waste products the body eliminated through the kidneys.[10] Ultimately, it was chemical studies on urine to explore how organic matter was generated in the body that eroded the 4 Hippocratic humors and the 3 Paracelsian components of inorganic matter and introduced the Newtonian physical tenets of measurable elements for the study of metabolism that would launch organic chemistry.[13]

As it turns out, it was the study of urea as an organic metabolite of tissue turnover that was instrumental in the changes in medical knowledge that ensued. It all started with the early relatively simplistic qualitative efforts at deciphering urinary composition beginning with that of 1 of the initial converts to Paracelsian chemistry, the Flemish physiologist Jan Baptist van Helmont (1580-1644) who first alluded to what would be identified as urea as a "urinary salt" in 1662, and subsequently in a relatively more sophisticated manner by the Dutch physician Herman Boerhaave (1668-1738) who referred to it as an "unusual saponaceous salt residue of urine that tasted different from sea salt" in 1732. The subsequent tedious efforts at analyzing and characterizing urea that would culminate in the synthesis of urea by the German chemist Friedrich Wöhler (1800-1882) in 1827 has been well told and is summarized in Table 1.[1-10,13]

While the chemical analysis of urine was still in its budding stages, progress in anatomy was evolving at a faster pace giving rise to organ-based disease concepts that were capitalized on by the French philosopher–mathematician René Descartes (1596-1650) in launching what has been termed "*iatromechanics*."[10] In Cartesian thought, the body was conceived as a mechanical machine composed of organs performing different functions that cumulatively accounted for the heat that defined life, wherein the "*vital spirits*" of Galen and the "*archaeus*" of Paracelsus were dismissed and replaced by the "*soul*."[14] Actually, the soul as another elusive concept was introduced by Aristotle in his treatise on the nature of living things, *De Anima* (On the Soul). It was revived to explain what could not be attributed to iatromechanics–thought, desire, conscience, and so on… *Iatromechanics* did not last long when it became evident that the living body was "an organism and not a mechanism" and that mechanical explanations could not fully elucidate organic functions with the consequent

Table 1. Principal Contributors to the Historical Evolution of Understanding Urea Metabolism

Name	Life	Country	Contribution
Jan Baptist van Helmont	1580-1664	Belgium	1664 A natural salt of the urine.
Herman Boerhaave	1668-1738	Holland	1732 A native salt of urine that tastes different from sea salt. Resembles "sal ammoniac."
Hilaire Rouelle	1718-1779	France	1773 Saponaceous extract of urine; high in nitrogen content, crystallizes into octahedral rather than cubic crystals of sea salt.
William Cruickshank	d. 1810	UK	1798 Urea crystallizes by addition of nitric acid; isolated the crystals in diabetic urine.
Antoine Fourcroy	1755-1809	France	1799-1808 Urea crystallized, nitrogen content determined, termed
Nicolas Vauquelin	1763-1829	France	"*Urée*."
Claude-Louis Berthollet	1748-1822	France	1785 Urea source of ammonia in urine.
John Bostock	1773-1846	UK	Blood urea elevated in patients with granular kidneys of Richard Bright.
William Prout	1785-1850	UK	1814 Analyzed isolated pure urea crystals. Confirmed findings of Bostock.
Joseph Frédéric Bérard	1789-1828	France	1817 Quantified nitrogen content of urea.
Alexandre Marcet	1770-1822	Switzerland	1817 Urea is distinct from uric acid.
Jean Louis Prevost	1790-1850	France	1821 Extra-renal origin of urea. Elevated blood urea after bilateral nephrectomy.
Jean Baptiste Dumas	1800-1884	France	
Friedrich Wöhler	1800-1882	Germany	1827 Synthesized urea in vitro.
Robert Christison	1797-1882	UK	1829 Blood urea increased in kidney disease.
Gabriel Andral	1797-1876	France	1831 Variations of blood urea levels.
George Owen Rees	1813-1889	UK	1833 Elevated blood urea in diabetic patients.
Pierre Adolphe Piorry	1794-1879	France	1847 Coined term "uremie" (uremia).
Thomas Graham	1805-1869	UK	1850 Dialysis of urea across semi-permeable membranes.
Antoine Bechamp	1826-1908	France	1856 Urea product of protein oxidation.
Joseph Picard	1834-1896	France	1856 Differential urea levels between renal artery and vein.
Adolph Fick	1829-1901	Germany	1868 Calculated filtration rate from urea excretion.
Fernand Widal	1862-1929	France	1902 Level of blood urea accounts for symptoms and prognosis of patients with nephritis.
Hans Krebs	1900-1981	USA	1932 Urea (ornithine) cycle.