The Saga of Two Centuries of Urea: Nontoxic Toxin or Vice Versa?

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Summary: In the early 1700s, a substance ultimately identified as urea was reported for the first time in urine. About a century later, in 1828, synthesis of this organic compound was achieved, thus giving rise to modern organic chemistry. In parallel, physicians showed that urine comes from the kidneys and contains large amounts of urea, which is produced outside of the kidneys, establishing the humoral approach of renal physiology. Urea was the first uremic retention solute to be identified and it has been used as a marker of renal disease ever since. However, progress in the knowledge of urea metabolism has shown that it is susceptible to many extrarenal variations and, therefore, it cannot be a reliable marker of renal function. It reflects protein intake in the stable patient and has been used to assess nutrition and dialysis efficacy in renal patients. Although it has been studied for almost 200 years, its toxicity has been largely debated. An indirect toxicity occurring through carbamylation of lysine residues is now well established and some evidence from recent work also supports direct toxicity of urea, offering additional rationale for interventional prevention of uremic complications.
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The discovery of urea is an example of collaboration between chemists and physicians. In the 16th century, Van Helmont (1577-1644) (Fig. 1) observed a "salt of urine that never occurs outside man's body which is bred in the course of digestion from a substance not a salt…It differs from sea-salt, also present in urine, by remaining unchanged in its course through the body and on putrefaction of urine… The sea-salt in its cooling, adheres to a wooden vessel even while it is separated from saltpeter, but the salt of urine grows together in the bottom of the liquor."[1] Thus, from the late 1500s and early 1600s the existence of a salt-like substance in urine, different from NaCl, and specific to living organisms, was known. This substance was isolated by Boerhaave[2] in Leiden, who called it "the native salt of the urine" in 1727, well before Rouelle the younger[3] in Lyon. Its purification was improved by Fourcroy and Vauquelin,[4] who named this substance *urée* because of its origin, and completed by Prout[5] in London, who in 1814 described its chemical composition with remarkable accuracy as compared with that previously reported by Fourcroy and Vauquelin[4] and later by Bérard,[6] in Montpellier. These efforts in urea purification prepared the field for what is considered the starting point of modern organic chemistry: the synthesis of urea, achieved by Wöhler[7] in 1828. He synthesized urea from silver cyanate and ammonium chloride, being the first to obtain it outside the body from inorganic substances. He wrote to Berzelius in Stockholm: "I can make urea without needing a kidney, whether of man or dog. The ammonium salt of cyanic acid is urea" ($HCON + NH_3 \rightarrow H_2N\text{-}CO\text{-}NH_2$).

In parallel to the contribution of chemistry in understanding kidney function, the physicians were making progress guided by their incredible observational capacities. The question of whether urine comes from the kidneys or locally accumulates in the bladder was answered in the doctoral thesis of Comhaire[8] (1778-1860), who observed that bi-nephrectomized dogs had no urine in the bladder. He failed to show urea retention in his model because the available determination method was not yet sensitive enough to detect actual changes. Urea retention was shown by Prevost (1790-1850) and Dumas (1800-1884),[9] who nephrectomized dogs, sampled blood under alcohol extraction, and, after precipitation with nitric acid, obtained the same crystals in blood as the ones that were observed in urine. Therefore, by improving the ability to determine the urea level in blood before clotting and with a proper study design, this approach showed that urea is produced elsewhere than in the kidneys, and that kidneys are responsible for removing the urea accumulated by extrarenal production. This set the basis for the *humoral* view of renal physiology, as opposed to the *morbid anatomy* theory, which was the dominant approach at that time in Europe (early 1800) as supported by Bright among others. This change of paradigm was described nicely by Richet.[10]

The removal capacity of the kidneys was shown by Picard[11] (1834-1896), who adapted a new method of urea measurement (from Liebig's method) and was successful in determining the level of urea in human blood. This also allowed him to determine levels of urea differentially from the renal artery and vein of

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Figure 1. Jean Baptiste van Helmont (1577–1644), alchemist (painting by Mary Beale, c1674). Jean Baptiste van Helmont, a Brussels-born chemist and physician, was the founder of the Iatrochemical School, which looked for chemical explanations of vital phenomena. He was a man of great intellectual curiosity and studied philosophy in Louvain. His description of the salt of urine offered the first evidence of the urinary content of urea (see text).

dogs, leading to the observation that there was a significant decrease in the urea level in renal veins compared with the arteries, showing a clearance capacity by the kidneys, in contrast to the carotid artery and jugular vein, where the gradient was in the opposite direction. Christison[12] and Gregory[13,14] suggested that retention of urea might be deleterious, and Frerichs[15] (1819-1885) introduced the concepts of retention solutes and uremia when commenting on Bright's reports.

In summary, progress in chemistry by the pioneers in renal medicine of the 18th and first half of the 19th centuries established the basis of renal physiology at the same time that urea, a substance of biological origin, was synthesized from inorganic compounds outside a living body. Urea has since then been a chief element in medicine that has helped to identify renal failure, changing the thinking of renal pathology. It is the most studied retention solute: its accumulation in renal failure is used to identify lack of removal from the body and it is used as a marker of metabolic stability and nutrition. Its toxicity, proposed in the 1800s, is still under debate. The present article focuses on the following: (1) the analysis of the chemistry and metabolism of urea by addressing the question: urea, a marker of uremia; (2) its use to guide renal replacement therapy by analyzing its clearance: urea, a marker of dialysis adequacy; and (3) a reassessment of its supposedly harmless characteristics by addressing the question: urea, a uremic toxin?

UREA, A MARKER OF UREMIA?

Amongst all uremic toxins, urea is the one which shows the highest concentrations in the blood of uremic patients.[16] It is a small water-soluble molecule of 60 daltons. It contains two nitrogen atoms and it is the end-product of protein and nitrogen metabolism. In nephrology, urea levels have been measured and interpreted for many purposes, such as estimating uremia severity, glomerular filtration rate (GFR), protein intake, protein catabolic rate, and dialysis adequacy. Initially introduced by Piorry[17] in 1847, the term *uremia*, meaning "urine in the blood," referred to a blood intoxication by urine, characterized by increased blood levels of urea.[15] Uremia, in its present significance, is the disease clinically characterized by manifestations of the uremic syndrome, which is caused by retention of many more solutes than urea. The question to be answered then is whether serum urea levels still are adequate markers of a disease characterized by an increase in serum urea levels, but also of many other compounds that might be pathophysiologically more important than urea itself.

Blood Urea Concentration and Uremia

The serum concentration of urea is easily measurable and is given as a molar or mass concentration in many countries. In others, including the United States and Germany, however, serum urea concentration is referred to indistinctly as blood urea nitrogen (BUN) or serum urea nitrogen (SUN), and is expressed as the mass concentration of nitrogen equivalents. The conversion between different units is shown in formula 1.

$$\begin{aligned} \mathrm{BUN}\ (\mathrm{mg/dL}) &= 0.47 \times [\text{urea in mg/dL}] \\ &= 2.8 \times [\text{urea in mmol/L}] \end{aligned} \quad (1)$$

The normal range of BUN that generally is accepted extends from 5 to 20 mg/dL, which corresponds to urea concentrations of 11 to 43 mg/dL or 1.8 to 7.2 mmol/L. BUN levels can greatly increase in uremic patients, reaching 10 times the upper limit of the normal range in patients with end-stage renal disease before dialysis. If there is at least some parallelism between urea serum concentration and the stage of uremia, the relevance of plasma urea levels as a diagnostic marker of chronic kidney disease (CKD) is much more debatable. As shown in Figure 2, urea levels increase exponentially with reduced estimated GFR (eGFR), but significant increases become observable only when eGFR levels are reduced to about half the normal value. Urea levels follow a similar trend as that of serum creatinine levels, although the latter are a much more reliable marker because they are less subject to modifications unrelated to glomerular filtration. Even at low eGFR rates, BUN levels do not perform well for screening or identifying CKD patients. In addition, blood urea