

The Development of Ideas About the Significance of Urea

Most modern textbooks of biochemistry emphasize that Wöhler's synthesis of an organic substance, urea, from inorganic salts, led to the founding of biological chemistry as we know it today. However, few chemists, and indeed few people in general, know that Wöhler's discovery was merely the final link in a long chain of observations which had been made mainly by physicians.

The study of urine by medieval and Renaissance physicians and alchemists—the two were often combined in a single person—led to the isolation of phosphorus from the urine around 1670. However, the presence of what is now recognized to be urea was noted even earlier. Jean Baptiste van Helmont, the Belgian mystic, Capuchin monk, and finally physician, founded the iatrochemical school in the early 1600's. Although many of his writings are of little or no value, they nevertheless contained one of the earliest references to urea, which he called a "salt of urine . . . which is bred in the course of digestion from a substance not a salt." He noted that its volatility permitted its separation from the "sea-salt," *i.e.*, sodium chloride, in the urine "by fire and flight."

The next important step in the history of urea was its isolation. Although

most authorities state that this was reported by Rouelle in the *Journal Médical de Lyon* in 1773, the isolation had actually been accomplished by another physician, Hermann Boerhaave, before the year 1727—at least a report of one of his lectures delivered in that year said the work had actually been done "in public many years ago." Boerhaave called it the "native salt of urine" and pointed out that it differed from the mineral salts ingested by animals, which passed unchanged through their systems; that it was volatile; and that it resembled but was not identical with sal ammoniac (ammonium chloride). Like some other dedicated clinicians, Boerhaave was somewhat apologetic about his work in chemistry. He wrote "Nothing was formerly further from my mind than that I should trouble the world with anything in chemistry." Modern chemists who have followed his published directions have been able to obtain urea from urine. Rouelle's later work added little except to indicate that urea had a high nitrogen content. However, he did suggest that urea was the end product of nitrogen metabolism. Just before the end of the eighteenth century William Cruickshank, surgeon to His Majesty's Royal Artillery, improved the method of isolating urea when he reported that it was precipitable with nitric acid.

(He made this discovery while studying diabetes mellitus.)

The next few decades saw the publication of many papers on urea, most of them written by chemists. It is ironic that some of these chemists, notably Fourcroy and Vanquelin, felt constrained to admonish physicians repeatedly to pay attention to *chemical* discoveries, because some of the most important of these discoveries continued to be made by physicians. For example Bérard analyzed many animal substances and reported his findings in his thesis presented to the Faculty of Medicine at Montpellier in 1817. Among his conclusions was the statement that "since urea and uric acid are the most nitrogenous of all animal substances, the secretion of urine appears to have for its object the separation of the excess nitrogen from the blood."

The year 1829 is celebrated as the one in which the chemist Wöhler published his epoch-making observations. It was also the year in which Henry, the pharmacist of the Hospital of St. Antoine in Paris, was asked by the clinical staff to prepare a large amount of urea to be tested for possible therapeutic effects. In order to do so Henry had to improve on the then published chemical methods of isolating it. ■