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HISTORICAL ARCHIVES

Early history of uremia

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Richard Bright's clinico-anatomical observation caused a veritable medical earthquake. In contrast the concept of uremia took many years to develop. In fact, widespread acceptance of "uremia" did not occur until some fifty years after the chemical discovery of urea.

The discovery of urea (1797–1827)

The important, but rather vague, observations of Boerhaave (1668–1738) [1] in Holland and the more precise ones of Rouelle le Cadet (1718–1779) [2] in France suggested the presence of large quantities of an unknown "soapy" substance in the urine. Between 1797 and 1808, A. Fourcroy (1755–1809) and N. Vauquelin (1763–1829) isolated and crystallized this substance, called it "urea" and ascertained the weight of its constituent atomic components [3–5]. These individuals introduced the concept that urea represented the end product of nitrogenous metabolism and was a compound present in all "living tissues". Moreover, they suggested that the principal function of the kidney was to "de-nitrogenize" the body by excreting urea in the urine. Finally, they hypothesized that urea was the source of urinary ammonia, a constituent which had been recently discovered by C. Berthollet (1760–1822). Fourcroy and Vauquelin unmistakably anticipated Claude Bernard's synoptic concept of the 'Milieu Interieur' by proposing that the blood "prend et conserve l'équilibre de composition qui lui est nécessaire" (takes and protects its necessary balanced composition). Using other chemical methods, J.E. Bérard [6] and W. Prout [7] reached the same conclusion in 1817.

Turning their attention to pathophysiology, Fourcroy and Vauquelin predicted that if urea is not "separated" from the blood, an excess might lead to specific disorders. The two embarked on an extensive study of the urinary excretion of urea hoping to reveal some hitherto unidentified diseases. Their investigations were performed in a well equiped, designated hospital, specializing only in this research. In 1808, they expanded their investigations to include chemical observations, long term trials, and animal experiments. In effect, they were anticipating such centers as the Institut Pasteur, the National Institutes of Health, the Royal Postgraduate Hospital, the Karolinska and the Behring Institutes. As Peitzman [8] and Coley [9] emphasized, a similar 'task force' was organized in 1842 in Guy's Hospital when Richard Bright's group supervised a two ward unit linked to a specialized laboratory which had an emphasis on the study of diseases of the kidney. John Bostock and G.O. Owen were directly involved as clinical chemists of the group.

Fourcroy was a remarkable individual; he started as a physician and then became a chemist working alongside Lavoisier. His lodestar was plain for all to see when he founded a journal entitled "La Médecine éclairée par les Sciences Physiques", a publication more than sixty years ahead of its time. His dedication was exemplified by his laborious analysis of more than 300 urinary calculi in a quest to discover a means of dissolving these stones. In 1794, he organized a centralized teaching program which was to encompass all forms of education. With respect to medical training, he established three Facultés de Médecine in which two novel ideas were instituted: the "exact sciences" were taught, and the students were required to visit university hospitals every day. A revolution within the Révolution had occurred.

In 1821, in Geneva, J.L. Prévost and J.B. Dumas (1800–1884) reported that following a bilateral nephrectomy in many different animal species, a significant rise in the concentration of blood urea occurred uniformly [10]. Confirmation that the retained product was indeed urea was obtained by demonstrating that the weight of the atomic components of the blood extract was identical to that of urinary urea. Thus, it could be concluded that urea was produced in the body and excreted by the kidney. These findings were confirmed by L. Gmelin (1788–1853) and F. Tiedemann (1781–1861).

The discoveries of F. Wöhler (1800–1882) were next. In 1827 he was able to synthesize urea, the first organic substance belonging to the animal kingdom to be produced in the laboratory [11]. From Berlin, Wöhler wrote to the revered J.J. Berzelius in Stockholm (1776–1848) that "I can make urea without needing a kidney, whether of man or dog. The ammonium salt of cyanic acid is urea." As a result of this advance, the previous mysterious biochemistry of urea became nothing else than ordinary chemistry. In 1856, M. Bechamp [12] forged the last link when he obtained urea in vitro by protein oxidation.

At this time another relevant discovery of immense importance was made by Henri Dutrochet (1776–1847), a country practitioner, who in 1827 described his investigations on the phenomenon of osmosis in vegetables and animals [13]. As a result of these reports, Thomas Graham (1805–1869), in 1850, used a semipermeable membrane in vitro and was able to separate large from small molecules. The concept of "dialysis" was born and the seed idea for the artificial kidney had been sown.

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Urea versus the dogmas of morbid anatomy (1827–1856)

When Fourcroy first proposed the idea that urea might be a toxic substance, the concept was considered totally unacceptable. In Richard Bright's era, "morbid anatomy" was the accepted doctrine and all other explanations for disease processes were deemed fanciful and unworthy of consideration. A form of "intellectual terrorism" prevailed, an attitude that has persisted to this day. One must admit that the concept of morbid anatomy was a successful science, delineating, within no more than a decade, such diseases as cirrhosis of the liver, visceral tuberculosis, general paresis, diphtheria and typhoid. It was strictly within the constraints of this structural philosophy that Bright made his revealing contribution. However, Fourcroy's hypotheses were not forgotten. In France, P.H. Nysten (1774–1817) [14] had already published a book on the subject. In England, Prout [15] was an active participant in chemical pathology, a difficult challenge when the methods of chemical analysis were at best semiquantititive and existed for only a few of the more highly concentrated plasma components. At Guy's Hospital Bright's group [16], J. Bostock [17], G.H. Barlow [18] and O.W. Rees [19], proposed that urea might be a retained product in kidney disease. However, R. Christison [20] and J.C. Gregory [21], both of Edinburgh, in 1829 and 1831 respectively, reported convincing chemical evidence that the blood urea concentration was elevated in certain patients. They suggested that the retention of urea might have deleterious clinical effects. International confirmation of these findings by P. Rayer (1793–1867) [22] and R.F. Marchand [23] soon followed the British observations.

Confusion reigned. A semiquantitative determination of blood urea required more than fifty milliliters of severely uremic blood, and the poor technique did not lead to reproducible results. This lack of reliability explains why Christison reported that only 9 of 31 patients with "Bright's Disease" had a blood urea determination [24]. Blood urea concentration was increased in all nine patients, but there was no correlation between the approximate urea concentration and the presence of edema, the intensity of anemia, the plasma protein concentration, the severity of proteinuria or the urine output. Furthermore, there was no relation between the blood urea concentration and the presence of acute or chronic renal disease. This uncertainty explains the prudent reserve of the then two great men, Bright [16] and Rayer [22]. Both men published their observations but were reluctant to defend them openly. Nevertheless, both made the important observation that major neurological disorders, such as coma and convulsions, did not correlate with any obvious macroscopic finding, including generalized edema of the brain. This finding supported the notion of uremia as a form of "blood poisoning". A. Wilson [25] and T. Addison [26] lent support to this concept in their writings as well. In 1839 Christison [24] shed light on the matter by considering two categories of clinical findings noted in patients with the end stage of "Bright's Disease". He denoted some findings as "primary", or linked directly to the specific disease affecting the kidney. Others findings, notably digestive and neurological abnormalities, were thought to be "secondary" effects related to renal failure and an endogenous intoxication. With these observations, Christison paved the way for the modern concept of the "uremic syndrome."

In the decade between 1840 and 1850, a change in the climate of opinion occurred, despite the absence of any major chemical advance. G. Burrows [27] had the temerity to promote the cause of 'Humoral Pathology' in "Bright's Disease" by writing that "morbid anatomy is the right hand of pathology; animal chemistry is the left." He supported his argument with quotations from Orfila, who brought science into the study of toxicology in France, and from Magendie, the innovator of experimental pharmacology. Andral [29] provocatively joined in by pointing out that all these suggestions implied that the composition of the blood could be altered. For the traditional physicians there was a danger of "falling into the heresy of Humorism." For Andral this was "an unavoidable fate if that was the direction that the facts were taking." This sentiment was repeated verbatim as early as 1840 in Anger's Thesis, defended in Prague, entitled "Conspectum morbi Brighti Historicum," demonstrating just how rapidly new ideas circulated in Europe. It is interesting to follow Andral's intellectual itinerary. As he stated himself, he had studied medicine three times: when he mastered pathological anatomy, when he learned the new methods of physical diagnosis, and when he started his study on hemopathology (quoted from E.H. Ackerknecht [28]).

Although Claude Bernard was investigating the mechanisms of clinical disease in such chemical conditions as diabetes mellitus and carbon monoxide poisoning, there was a continuing reluctance to accept the theory that renal failure might be accompanied by a toxic humoral disorder. Even Andral [29], who was a protagonist of 'Humoral Disorders,' failed to mention what happens to urea when writing about the blood changes that occur in dropsy. Piorry, who in 1840 [30] had discussed among other endogenous poisonings the consequences of "contaminating the blood with urine," did not mention the blood urea concentration in the book in which he actually coined the word "uremia" in 1847 [31]. Becquerel and Rodier [32] did the same in 1854.

The next turning point was E.T. Frerichs' monograph [33] in 1851, which focused more on the 'uramische Intoxikation' and its clinical signs than on what happened to the kidney itself. He described the clinical uremic syndrome and dared to accept a toxic mechanism as its etiology. His treatise is a medical classic, though the chemical data on which it was based were shaky: the rise of blood concentration of urea was unpredictable and he mistakenly considered that ammonium carbonate, which he also found in the blood, was responsible for the toxic effects of uremia.

In 1856 J. Picard in Strasbourg [34] developed a reproducible and sensitive method for the measurement of blood urea. He was able to detect the 40% fall in urea concentration occurring between the renal artery and vein. Though the technique was criticized by experts, such as Recklinghausen [35], it proved itself quickly, and there was a general agreement that renal failure was a condition accompanied uniformly by a rise in blood urea concentration. Actually both Frerichs' monograph and Picard's method combined to make popular the concept and the term "uremia."

Urea, certainly, but how and what else. . . ?

Although the term uremia came into general usage and blood urea concentration was accepted as a valuable practical marker

of renal failure, urea was still not accepted as the toxic substance responsible for the uremic syndrome. It was obvious to Vauquelin and Ségalas [36] that urea itself was not acutely toxic. Frerichs, [33] who studied nephrectomized animals injected with urea, reached a similar conclusion. Several years later, Claude Bernard [37] revived the suggestion that uremic toxicity was due to ammonium carbonate absorbed from the gut. Experimental pathologists and physicians endeavored to study the poisonous end products of protein metabolism and attempted to relate these products to the appearance of clinical abnormalities, particularly those involving the central nervous, gastrointestinal, and cardiovascular systems. A special tribute has been given to Traube [38], whose studies led eventually to the discovery of the role of hypertension in the signs of advanced kidney disease, even when the blood urea was not especially elevated, and of the fluid and electrolyte disturbances in the clinical manifestations of kidney disease. However, to this day, the precise "uremic toxins" have not been identified. Experimental studies still have not excluded a possible role for chronic urea intoxication. One hundred and fifty years after its birth, "uremia" remains a clinico-chemical enigma.

Conclusion

The early history of uremia represents an interesting example of the evolution of important medical concepts. In 1830 the subject was advanced by intelligent, well-educated nosologists trained to think in structural terms. Few of them had the personal strength to turn against their educational backgrounds. Others who dared to pay attention to the concept of humoral disturbances did not master the chemical approach needed to validate their hypotheses. Both groups, however talented, missed the birth of uremia. Those few investigators responsible for extracting the concept of uremia from 'Terra Ingognita' succeeded in widening their knowledge by becoming expert in both nosology and chemical pathology. It is interesting to ponder what sort of comparable open road nephrologists may be missing today.

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