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Edema and uremia from 1827 to 1905: The first faltering steps of renal pathophysiology

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Edema and uremia from 1827 to 1905: The first faltering steps of renal pathophysiology. After Richard Bright's studies, both edema and uremia were thought to be due to a renal retention of urinary substances; but if so why were they so rarely associated with each other? To solve this dilemma, a few clinicians turned to physics and chemistry. In 1897, Korànyi measured the freezing point depression (FPD) of the urine during water restriction. He found that in advanced renal disease it was lower than normal, approaching that of plasma, a phenomenon which he named *isothenuria*. He introduced the concept of renal insufficiency when, whatever the lesions, urinary excretory function does not adapt to the needs of the body. In the same year Achard and Castaigne found that in uremia, the excretion of methylene blue into the urine was delayed. In contrast, the dye was normally excreted in edematous patients with proteinuria. In 1902 Strauss and Widal, using a new steel needle to obtain blood, each studied the chemistry of plasma and performed water, chloride and nitrogen balances. They revealed that in advanced nephritis without edema there was a retention of nitrogen metabolites but not of chloride, whereas in proteinuric edematous patients the blood urea was normal, and there was a retention of chloride and then of water. Physical chemistry and its objective results had been introduced into renal medicine. Modern renal pathophysiology was now launched.

Soon after Richard Bright's (1789–1858) publication in 1827, attempts to understand the frequent dissociation between uremia and edema, two obvious consequences of a renal retention, stimulated much debate. Bright had remained vague whether the nature of the various clinical manifestations of his disease was single or multiple. In 1839, R. Christison (1797–1882) addressed Bright's quandary as follows: "Future pathological research will probably show that there is more than one organic derangement concerned in the question of nomenclature. There seems a decided advantage to consider two diseases, one primary and one idiopathic" [1]. In 1840 P. Rayer (1793–1867) on the basis of urinary biology [2], identified an *albuminous nephritis* acute or chronic, with transitory or persistent edema, which he distinguished from other forms of nephritis. Rayer's *albuminous nephritis* was not generally accepted as an entity and *Bright's disease* with its variable clinical features and pathological findings, continued to be considered as a single entity.

In 1853, a young Guy's physician, S. Wilks[1] (Fig. 1) reported a series of 61 patients with Bright's disease [3], ten of whom with persistent edema had large white kidneys, in contrast to 29 others with clinical uremia who were not edematous and had small red kidneys. Wilks concluded that there were two diseases rather than two forms of the same entity. His view was accepted by G. Johnson [4], W. Dickinson (1832–1913) [5] and Grainger Stewart (1837–1900) [6] in Great Britain, A. Kelsch (1841–1911) [7] and J.M. Charcot (1825–1893) [8] in France, and K. Bartels (1822–1878) [9] in Germany.

F.T. v.Frerichs (1819–1885) was a protagonist of the single disease theory [10], as were H. Reinhardt (1816–1892) and R. Virchow (1821–1902) and, in Paris, E. Lecorché (1830–1904) and C. Talamon (1850–1929) [11]. They considered that, when the kidney was abnormal, the various clinical manifestations and pathological findings were all due to a single entity, that an inflammatory process was responsible, and that the apparent clinical and pathological differences were due to the disease being observed at different stages. This lengthy and futile debate is well described by J. Bleker [12].

Around 1890 the dilemma of what was known as *dissociated renal impermeability*, that is, edema without clinical uremia versus clinical uremia without edema remained unsolved. Contemporary renal physiologists including C. Ludwig (1816–1893) who focused on the glomerulus and R. Heidenhain (1834–1897) who was more interested in the tubule were unhelpful. Badly disappointed, some clinicians dared to tackle the enigma by means other than those of morbid anatomy. With the techniques then available they began to examine the physical chemistry of the urine and the blood.

Their studies covered three areas of investigation. The results from two of these appeared in 1897. One concerned the osmotic pressure of the urine and blood as applied to renal function ("funktionel Nierendiagnostik"), and the other covered the use

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[1] Sir Samuel Wilks (1824–1912), after having been apprenticed to an apothecary, took his M.D. degree from the University of London by thesis in 1850. Appointed full Physician to Guy's in 1856, he remained on the staff of his hospital till his retirement in 1885. Following the tradition of Bright, he was keenly interested in morbid anatomy. Full of honors and reputation he was known as *The Nestor of Guy's* till his death.

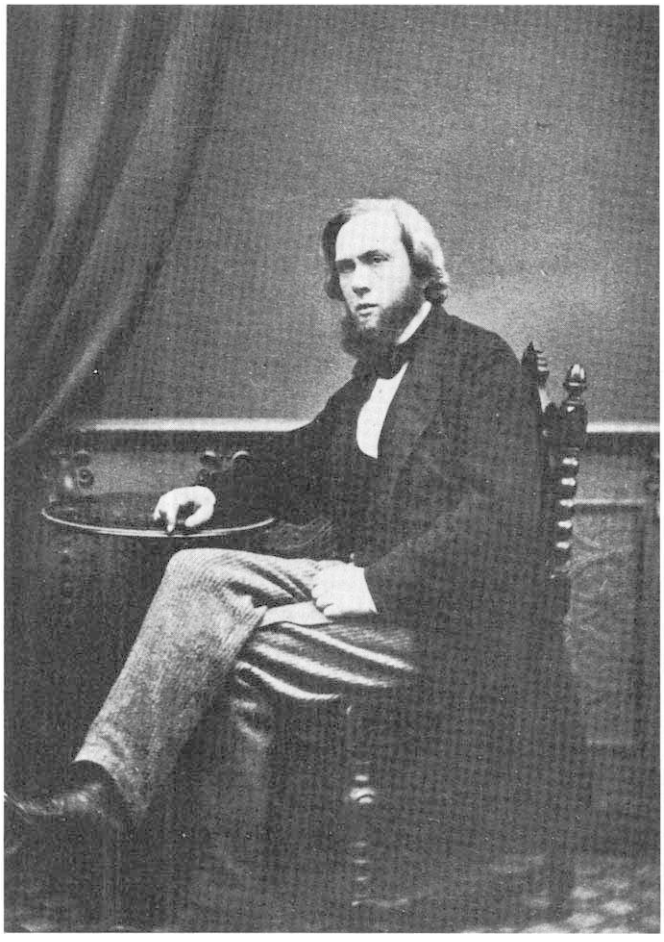

Fig. 1. *Sir Samuel Wilks (1824–1912).* Courtesy of Professor St. J. Cameron and Guys Hospital Medical Photographic Departement.

of the renal excretion of methylene blue in uremic and edematous patients. The third area of study covered blood chemistry measurements and chloride and nitrogen balances, the results of which also emerged simultaneously in Germany and France from 1898 to 1903.

Within ten years the two main syndromes of nephrology had been distinguished physiologically. A new period of clinical nephrology had opened that of the biological nosology of signs. A step which would provide a rational for symptomatic treatment and lay the foundations of modern renal physiology.

Osmosis as applied to renal function

Initially the phenomenon of osmosis was a biological observation. In 1824, Henri Dutrochet (1776–1847) separated the cells of various animal and plant tissues chemically [13]. This enabled him to discover that the cell is a fundamental physiological unit. Using a microscope he noted, in 1826, that a change in the concentration of a solution in which a cell is suspended causes a reciprocal change in the size of the cell. He attributed this phenomenon to a movement of water into or out of the cell and named it osmosis [14]. He then placed pure water on one side of an animal membrane, and a salt solution on the other, and observed a flow of water towards the salt solution. To quantify his findings Dutrochet created an osmometer, a vertical tube with which the height of the water or mercury contained therein at the point of equilibrium provided a measure of the pressure exerted by the water crossing the membrane [15] (Fig. 2). In this way Dutrochet studied a variety of solutions and membranes, biological and otherwise. At first he attributed the movement of water to the density gradient between the two media; later, however, he rejected this idea. He finally coined the term "*exosmosis*," to designate an opposite movement to "*endosmosis*," that is the passage of solutes towards the least concentrated side of a membrane.

Dutrochet applied his theory of osmosis to the circulation of sap and lymph. Indeed, in contrast to the prevailing view, Dutrochet was convinced that ". . il n'y a pas deux physiologies, l'une animale l'autre végétale. . . . La science de la vie est une. ." (There is no difference between the physiology of animals and plants. The science of life is one). Thus, he recognized the unity of physiology and that it was controlled by chemical and physical laws. Since urine is an osmotically active liquid, he proposed that the membranes of the kidney performed *chemical filtration*. As he put it, "un véritable filtre chimique . . . cette activité est analogue a la sécrétion de l'urée par les reins; car on sait par les expériences de MMr Prevost et Dumas, que l'urée existe déjà toute formée dans le sang des animaux" (a genuine chemical filter . . this activity is analogous to the secretion of urea by the kidney since it is known, according to the experiments of Prevost and Dumas, that urea exists preformed in blood) [14, p. 215].

Osmosis rapidly made its mark. In 1829 a review of Dutrochet's research appeared in Edinburgh [16]. There then followed studies on the effects of osmosis on the shape and size of red cells [17], its role in the tubular reabsorption of water [18] and in various metabolic processes [19].

Dutrochet (Fig. 3) started life as a soldier. He then studied medicine and was inspired by the writings of L. Spallanzani (1729–1799) to become a naturalist. For his discovery of osmosis he was elected to the Académie des Sciences in 1831 when he was a relatively inactive country doctor in Touraine in the Loire Valley. There is no doubt that Dutrochet's finding of osmosis diverted attention from his even more fundamental discovery that all tissues are made of individual cells [13]. A century later this fact was pointed out with some vigor by A.R. Rich (1893–1968) [20]. Had Dutrochet not been convinced of the existence of cells, he would not have been able to deduce that the swelling and shrinking of these small membranous sacs was due to an osmotic phenomenon.

Physicochemical studies into osmosis were made by T. Graham (1805–1869), who coined the term dialysis (diffusion through membranes of different permeabilities), by A. Dubrunfaut (1797–1881) who put osmosis to industrial use and M. Traube (1826–1894) who invented artificial membranes. W. Pfeffer (1845–1920) produced a true semipermeable membrane with which he found that osmotic pressure was linked to the concentration of molecules. In 1885, J.H. Van't Hoff (1854–1911), defined the laws which control the expansion of molecules in liquids and gases, establishing the theoretical basis of osmotic pressure.

Osmosis was reintroduced into biology in 1871 by H. De Vries (1848–1935), then a student in Leyden. He called the

NOUVELLES RECHERCHES

SUR L'ENDOSMOSE

ET L'EXOSMOSE,

SUIVIES

DE L'APPLICATION EXPÉRIMENTALE DE CES ACTIONS PHYSIQUES

A LA SOLUTION DU PROBLÈME

DE L'IRRITABILITÉ VÉGÉTALE,

ET A LA DÉTERMINATION DE LA CAUSE DE L'ASCENSION DES TIGES ET DE LA DESCENTE DES RACINES.

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CHEZ J.-B. BAILLIERE,

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LONDRES, MÊME MAISON, 3, BEDFORT STREET, BEDFORT SQUARE;

BRUXELLES, AU DÉPÔT DE LA LIBRAIRIE MÉDICALE.

1828.

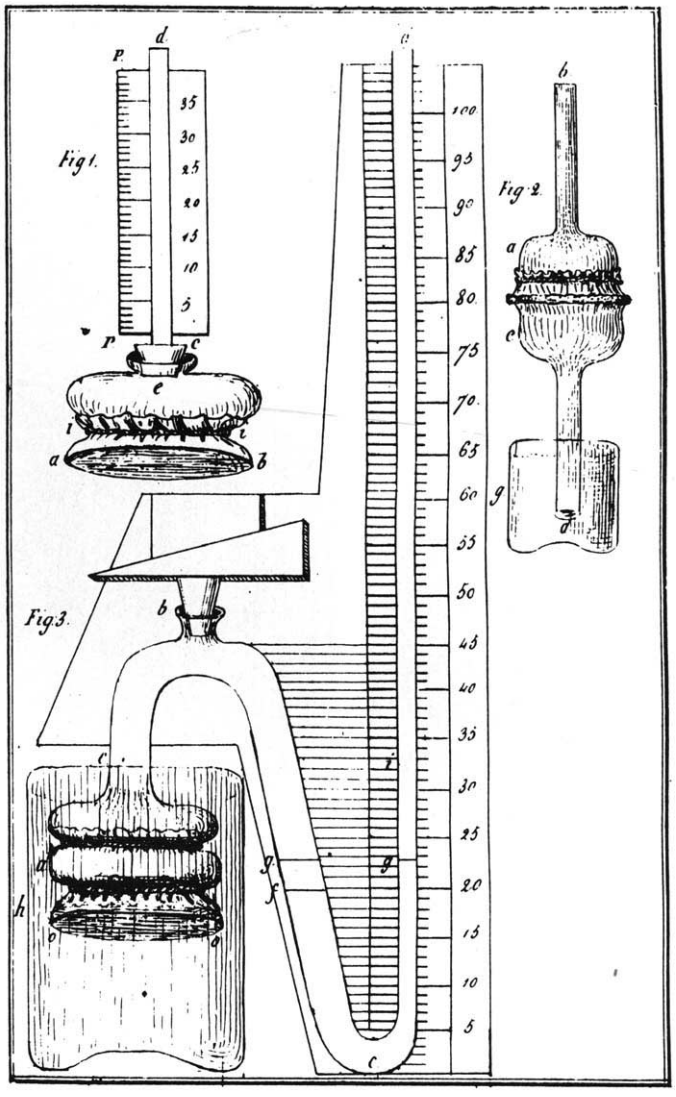

Fig. 2. *Dutrochet's Osmometers.* On the left is the title page of Dutrochet's third book gathering all his principal studies on osmosis [15]. On the right are wood engravings depicting his osmometers. (1) The first and simpler osmometer. The upper reservoir, sealed at its base with a piece of bladder wall *i-i*, is filled with the experimental solution. The osmotic pressure is read on the graduated scale *p* at the highest fluid level reached in column *d*. (2) A more sophisticated device. This osmometer is identical to that of *l*, except that the lower extremity *d* is plunging in a third reservoir *g*, which is filled with colored water. As long as *t* water is transferred from *c* to *a*, the dye ascends from *d* to *e*. (3) Device used by Dutrochet to measure high osmotic pressures. The u tube *c* is partly filled with mercury, and the experimental solution is poured through the opening *b*, which is then securely closed. The reservoir is plunging in pure water *h*. The difference of level of mercury in the two branches of the u tube measures the osmotic pressure.

progressive contraction of the protoplasm of plant cells, immersed in saline solutions of increasing concentrations, *plasmolysis* [21]. His findings led him to conclude that cells are permeable to water but relatively impermeable to mineral salts such as sodium chloride. By measuring the concentration by weight of various salts he was able to identify the concentration at which cells just start to shrink. He noted for example that a 8.2% solution of $MgSO_4$ had an osmotic pressure identical to that of a 4% solution of NaCl, leading him to conclude that "these two solutions must be seen as having (more or less) the same degree of concentration." The adjective *molar* is missing but its inference is perfect. He found that all the cells in a plant preparation immersed in a 27 to 28% solution of cane sugar had an identical plasmolysis threshold. He was thus able to state that all plant cells have the same osmotic pressure [21, 22]. It was the biological work of De Vries which inspired Van't Hoff.

De Vries created the terms iso-, hypo-, and hypertonicity and determined the isotonicity of a large number of saline solutions. Soon after, the finding that, for some salts, identical molar concentrations had a different plasmolytic threshold was explained by Arrhenius's ionic dissociation of salts. These results were confirmed by the red cell hemolysis threshold method of H. Hamburger (1859–1924) [23] and by the freezing point depression method.

Fig. 3. *Henry Dutrochet (1776–1847): bronze medallion casted in 1842 by Pierre Jean David d'Angers (1788–1856).* Courtesy of Professeur E. Aron, Tours, F.37000.

The estimation of the freezing point depression (FPD) as a means for measuring total osmotic pressure of a solution was a methodological advance of great value. In 1876, F.M. Raoult (1830–1901) in Grenoble, took up the work of L. de Coppet (1841–1910) of Geneva and found that the extent of FPD was a measure of the total molecular concentration of a solution. Moreover, he compared the FPD with the rise in boiling point and the decrease in vapor tension, the *colligative* properties of W. Ostwald (1853–1932). As the measurement of FDP required only a small volume of solution this technique was ideally fitted for use on biological specimens. An investigative tool had been found.

From 1890 onwards the measurement of urinary FPD was introduced into the study of the physiology of the normal and abnormal kidney

E. Hoppe Seiler (1825–1892) had put urine and blood from the same healthy individual on either side of a semi permeable membrane and observed the transfer of water into the urine. H. Dreser (1860–1925)[2] noted this unpublished finding, and in 1892 [24] measured the FPD of blood and urine of men and animals subjected to various physiological conditions. Dreser was a physician and a physical chemist. He pointed out that the FPD of blood was 0.56°C and remained constant regardless of the level of hydration. In contrast, the FPD of urine varied with water intake. In humans it ranged from 0.16° to 2° falling to 4°C in the fluid deprived cat. He considered that the thermodynamic work of the kidney stemmed from the difference between the FPD of blood and urine. Shortly afterwards, J. Winter in Paris studied the FPD of serum and serous effusions (which he found to be the same) and of milk, gastric fluid and urine [25]. The FPD of urine ranged from 0.45° to 2.40°C thereby confirming the findings of Dreser.[2]

The measurement of urinary FPD in renal disease

Between 1895 and 1910 A. v. Korànyi studied the FPD urine from normal and abnormal kidneys. In 1907 he summarized his results in a famous textbook on medical physical chemistry [26]. He assumed that the kidney regulates the osmolality of the urine so that the osmolality of the blood should remain constant. Thus, the kidney controls the *milieu intérieur*. He therefore pointed out that (i) a reduced rise in urine FPD to water

[2] Heinrich Dreser was active in renal physiology and pharmacology, having introduced the therapeutic use of heroin (1898) and aspirin (1899). Besides the research mentioned above, he studied glomerular function in frogs according to the Nussbaum technique, the changes in FPD in urine during sugar diuresis, the diuretic action of caffeine and he attributed the excretion of an acid urine to the secretion of H^+ ions by the cells of the tubules. Cushny criticized all his work without exception in the *Secretion of the Urine*, 1917.

restriction should be an early indication of an impaired excretory function, and that (ii) an increase of FDP of the blood should mean a severe renal failure.

Korànyi confirmed that normal urine FPD varied from 2.4 and 0.08°C, according to the intake of water [27]. In addition he noted that, in patients with terminal uremia, the maximal urine osmolality under water restriction was not modified and approached that of plasma (isosthenuria). Thus the FPD of urine had a physiological meaning [26, 28]. He established that the urine FPD was dependent on the state of the kidney and not on a systemic metabolic change. Indeed, in unilateral renal disease with no detectable abnormalities of the blood, the urine from the normal side was normal while the urine from the abnormal side was isosthenuric and little influenced by water intake. This finding was confirmed by Albarran (1860–1912), a Parisian urologist with a passion for investigating renal function [29]. Korànyi was aware that he was promoting the idea that the kidney itself could induce a physiological change and then developed the concept of *renal insufficiency* based upon hyposthenuria [28]. Though he may not have created the term, his work gave it its true meaning, that of an excretory function which fails to meet the needs of the body. He also revealed that a physiological defect of function could be independent of the type of structural lesion, and that the quantitative measurement of urine FPD during water restriction made it possible to detect a *clinically latent* stage of uremia before its full symptomatic development [26].

At this point Korànyi turned his attention to the rapid rise in serum FPD which occurred after bilateral nephrectomy in animals from 0.57 to 0.65°C or more in 24 hours. However, the water content of the serum measured by refractometry remained unchanged, and Bickel in addition noted that its electrical conductivity did not change [30]. Korànyi [26, 28] deduced that the increase in molecular concentration in the serum demonstrated by the rise in FPD must therefore be due to the presence of nitrogen waste products, urea at first. Up to that time there had been relatively few measurements of serum FPD from patients with renal insufficiency. Korànyi collected 170 cases, including 10 of his own, whose serum FPD varied from 0.60 to 0.70°C. It was particularly high in clinically severe cases. His findings in animals thus matched the clinical picture.

Korànyi then tried to link the osmotic pressure of the blood to the presence of edema as well as to uremia. Such a biophysical approach was rare at that time. He considered that the clinical findings and the investigations of Achard and Paisseau [31] suggested that urea played no part in the accumulation of edema, but rather that it was due to the retention of some other dissolved substances. He thought that the possibility it was the retention of sodium chloride in particular had been well demonstrated by Widal in Paris and Strauss in Berlin (see below). Korànyi explained the different behavior of urea and sodium chloride by pointing out that while urea penetrated red cells, as shown by Gryns [32], sodium chloride remained extracellular. There the latter exerted an osmotic pressure which drew water out of cells which caused a compensatory thirst which led to an increased intake of water. If edema occurred he thought it was due to the inability of the kidney to excrete the extra water. Korànyi had another unprescient hypothesis in that he also believed that retention of sodium chloride and water by the kidney was associated with that of other toxic substances which caused either changes in vascular walls or limited the ability of cells to take up sodium salts, etc. Such occasional weaknesses in Korànyi's work in no way detracts from its significance in the progress of medical knowledge. The majority of his studies were reliable trailblazers in both the normal and pathological physiology of the kidney, and the ensuing results fitted neatly into the logic of the milieu intérieur. Indeed his work led to an intense interest into the regulation of one of its most important components, that of osmolality. Moreover he explored, in various clinical situations, the adaptive function of the kidney on the homeostasis of water. He also shed light on the independence with which the different constituents of the urine are excreted.

Fig. 4. *Alexander v. Korànyi (1866–1944).* Courtesy of Bibliothèque Interuniversitaire rue del' Ecole de Médecine, 75006 Paris, France.

Korànyi's work soon brought him fame but gradually fell into neglect. The simpler and older but less physiologically meaningful measurement of the specific gravity of the urine was substituted for the measurement of its osmotic pressure. The concentration test of Volhard [33] and Addis [34] or the dilution test of Vaquez and Cottet [35] became standard references in the clinical evaluation of renal function.[3] Fifty years later, Zak

[3] With the aim of deriving additional information from the urine FPD Korànyi produced a large number of ratios in which the FPD was

[36], working with Homer Smith [37], returned to the study of water excretion focusing on the filtration reabsorption hypothesis, based upon a osmolar u/p ratio and the concept of water clearance.

Alexander v. Korànyi (1866–1944) (Fig. 4) was born in Budapest, the son of a Professor of Medicine who had spent years under house arrest in a village near Debrecen, for having taken part in the Hungarian Revolution of 1848. He graduated in Budapest, then studied with F. Hoppe Seiler in Strasbourg where he devoted himself to the physicochemical study of the physiology of the healthy and diseased kidney [38]. Thereafter he returned to his native city as Professor where his attention became, to some extent, directed away from the kidney. He died in Budapest in 1944.

The renal excretion of methylene blue

Using a similar basic approach to that of Korànyi, C. Achard (1860–1944) and J. Castaigne (1871–1951), between 1897 and 1902, studied what they called the *permeability of the kidney*, by measuring the urinary excretion of methylene blue [39, 40]. They stated that "Le besoin se fait sentir d'ajouter à l'étude des organes lesés, celle des fonctions troublées et de compléter l'investigation anatomique par l'investigation physiologique. Il faut donc inventer des méthodes spéciales, permettant de vérifier non plus simplement le mécanisme des organes à l'état statique mais encore observer ces organes en action, à l'état dynamique. . . . D'observateur, il (le médecin) se fait expérimentateur" (There is a need to study the disturbance of function of organs in order to supplement anatomical data with physiological investigation. It is therefore necessary to invent special techniques that will allow us to evaluate the functions of organs, not only under static conditions but also under dynamic conditions . . . The physician should adjust his position from that of observer to that of experimenter). These studies on the excretion of dyes were prompted by Rayer's two clinical observations that in advanced nephritis, after eating asparagus, the urine does not smell of mercaptan, and that because of their delayed excretion the administration of certain drugs to uremic patients may produce toxic effects.

The elimination of methylene blue was studied following the injection of 0.05 g subcutaneously. In normals 50% or more was excreted in the urine within the next 24 hours. As expected it was found that in impending uremia, *interstitial nephritis* or *advanced Bright's Disease*, the excretion of the dye was delayed so that less than 50% appeared in the first 24 hours. The delay was solely due to the abnormal kidneys for the elimination of the dye continued until the entire dose had been excreted, the time required for this to occur being dependent on the degree of *renal fibrosis*. Moreover, it was noted that in the presence of unilateral disease the diminution in the rate of dye excretion was confined to the diseased kidney [41]. In a manner similar to the measurement of urine FPD during water restriction, the rate of methylene blue excretion also gave a quantitative measure of the decline of renal function in what was then called *the latent stage* of chronic nephritis.

Fig. 5. *Charles Achard (1860–1944).* Courtesy of the Bibliothèque de l'Académie Nationale de Médecine.

Of perhaps even greater interest was the finding that in edematous patients with much proteinuria the excretion of methylene blue was normal, L. Bard and L. Bonnet [42]. This condition thus had to be dissociated from that of impending uremia with little proteinuria and no edema. Having confirmed this difference L. Bernard [43] in 1900 insisted that there were two biological types of nephritis, *parenchymatous* and *interstitial*, as suggested by Wilks 50 years before purely on clinicopathological grounds [3]. The elimination of many other dyes were studied. Rowntree's IV Phenolsulphonaphthalein method [44] replaced all the preceding tests.

In 1902 Ch. Achard (1860–1944) (Fig. 5) published a 435 page book *"Les Nouveaux Procédés d'Exploration"* [45] devoted to the latest methods with which to investigate functional abnormalities of various organs including the kidneys.[4] This book and that of Korànyi and Richter [26], and many others of a similar nature, give an idea of the extent that medicine was permeated, at the beginning of the century, by a scientific approach, the so-called "functional diagnosis." In Europe this fruitful development was much less evident after World War I. Achard was

compared with the concentration of sodium chloride, or the output of water or other urine components over 24 hours. At first, these maneuvers were enthusiastically followed in Germany and France, but they were abandoned as they did not appear to contribute to the understanding of the observed troubles.

[4] The content of this book depicts the shift towards scientific medicine that was taking place. It includes 130 pages devoted to radiology, less than 5 years after the discovery of Röntgen, 120 pages to biohematology, 30 pages to clinical cytology, 50 pages to bacteriological serology, 30 pages to cryoscopy, 20 pages to the regulation of the composition of the blood and 50 pages to methylene blue excretion.

Fig. 6. *Jules Castaigne (1871–1951).* Courtesy of Professor Alain Castaigne, Paris, France.

a leader in biochemical investigation, particularly in the 20's on the nephrotic syndrome, his steadfast commitment being the regulation of the extracellular spaces [46]. Joseph Castaigne (1871–1951) (Fig. 6), a dedicated internist, left Paris after World War I and became the successful Dean of the Medical School of Clermont-Ferrand.

In summary, therefore, at the end of the 19th century the *funktionel Nierendiagnostik* of Korànyi based upon the osmolality of the urine and the methylene blue test of Achard and Castaigne had already given a biological scaffold for the two main clinical syndromes of chronic renal disease: edema and uremia. The two new complementary methodological tools explored different aspects of renal function. They had revealed that the underlying mechanisms responsible for edema and uremia, though still unknown, were different. Although Strauss in 1902 considered that these two techniques had produced an "upheaval" [47], the medical community ignored their far-reaching implications.

However, it was not long before the ability to investigate the chemistry of the blood and to perform balance studies confirmed and extended the suggestions that had been based on the previous investigative methods.

Clinical blood chemistry, and chloride and nitrogen balances

The Strauss needle: The mandatory tool for blood chemistry

There is good circumstantial evidence that the chemical study of the blood did not open up until the introduction of the venesection needle by Strauss between 1898 and 1902. Previously blood chemistry had had a restricted role in clinical medicine. Until 1903 clinical papers by Korànyi [28], Bernard [43], Jaksch [48, 49], and Achard and Paisseau [31] clearly stated that blood was obtained by either cutting a superficial vein or making multiple small skin incisions at the site of

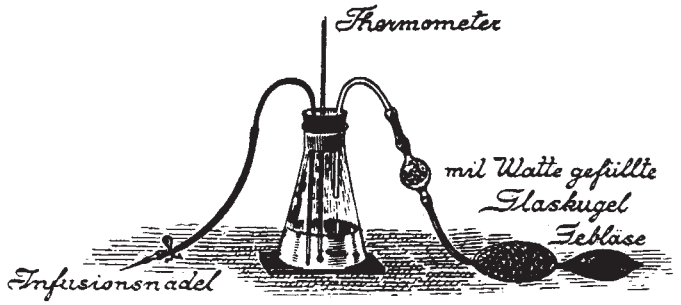

Fig. 7. *H. Strauss's apparatus for rapid i.v. perfusion [50].* At variance with that appearing on Figure 8, there is no device for gripping the needle.

cupping. From 1905 on, however, there is no further mention how blood is obtained, although by then numerous estimations of blood substances were being performed by all medical disciplines. This change must have been due to the use of the Strauss needle. Nevertheless, it has not been possible to obtain confirmation of this assumption either from the authorities of hospitals in Paris or even from some of the original manufacturers of the needle who are still in business.

H. Strauss was a physician at the "Charité" in Berlin. His original steel needle was 6 cm long with an internal diameter of 2 mm. The first illustration of the needle appeared in a paper in 1898 [50], which was mainly concerned with the use of a pneumatic pressure injecting device (Fig. 7). The needle is barely visible. It was not until 1902 that Strauss [47] published a detailed drawing of the needle including a good view of its perpendicular "Handgriff" with which it could be grasped (Fig. 8).

In 1931, F. Volhard [51] underlined Strauss's highly significant work on the retention of non-protein nitrogen and urea in the blood, but he failed to mention Strauss's needle. In the *Biographisches Lexicon* in 1901 [52] the name of Strauss was not associated with nephrology and his needle is ignored. In the 1933 edition, however, it is interesting to note that these omissions are corrected [53].

Strauss and Widal

It was Strauss in Berlin and Widal in Paris, in and around 1900, who overturned the then, almost ritualistic views on renal disease. Breaking free from the confines of anatomy they studied the chemical nature of the metabolic troubles afflicting their patients. The two men differed considerably in their approach and in some of their methods. Strauss (1868–1944) (Fig. 9) opened his chemical net wide by studying all possible humoral abnormalities at all stages of chronic nephritis in a large group of patients. He assumed that the kidney plays a central role in the metabolic balances of all those substances which are excreted in the urine. He then arranged his results according to the accepted clinico-anatomical classification of renal disease, that is, parenchymatous or interstitial nephritis and transitional forms. Ironically, outside France, Widal (1862–1929) (Fig. 10) is principally remembered today for his bacteriological work, typhoid in particular. In his renal work, which he subsequently took up, he totally ignored any consideration of renal pathology. His contribution to nephrology was confined

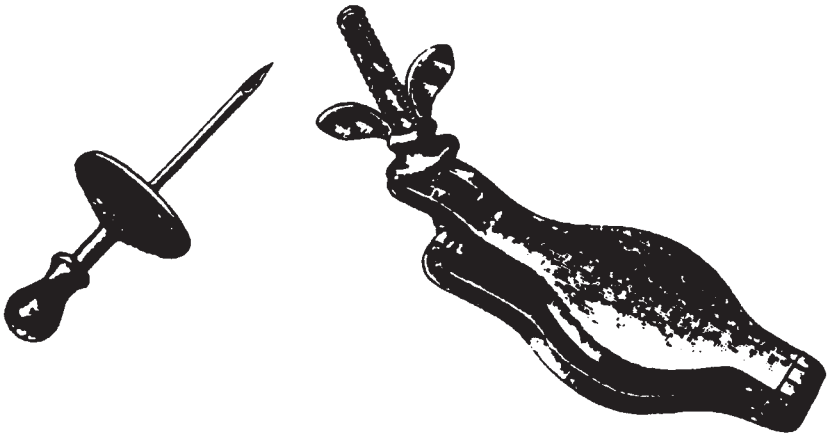

Fig. 8. *Strauss's steel needle used to draw blood under sterile conditions (Straussche's Nadel zur sterilen Blutentnahme) and his tourniquet clamp [45].*

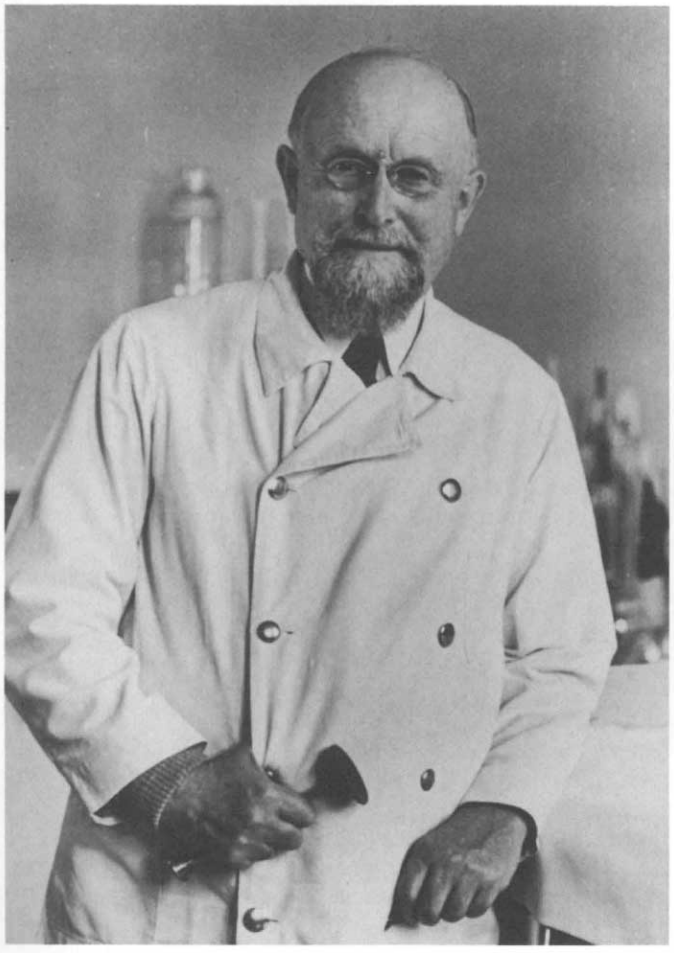

Fig. 9. *Hermann Strauss (1866–1944).* Courtesy of Herbert Sonnenfeld, Archiv, Inv. Num, 268/22, Berlin Museum, Abteilung Judisches Museum.

exclusively to the study of edema and uremia. His method was to thoroughly study a few patients who were on varying intakes of either sodium chloride or protein. Strauss's and Widal's findings and conclusions overlap almost exactly. Their main contributions were on the origin of edema and uremia.

Edema

Strauss noted that in the edema associated with heavy proteinuria and hypoproteinemia, plasma chloride and urea were normal. Nevertheless, though the concentration of chloride in the plasma remained normal, edema was due to renal retention of chloride, for when the edema spontaneously disappeared there was an associated brisk increase in the urinary excretion of chloride and not of sulphates and phosphates. Moreover, Strauss successfully treated edema with a salt free diet [54, 55]. He concluded that edema was due solely to the urinary retention of sodium chloride. Independently, Widal agreed [56–59]. He and Lemierre [56] found that in four patients with renal disease but no edema, large changes in salt intake produced no change in weight, the urinary excretion of chloride changing in line with the intake. But in two of three edematous proteinuric patients a sudden large intake of sodium chloride caused a brisk increase in weight while the extra intake of salt was not excreted in the urine. In another edematous patient [57] who was studied for six months, it was repeatedly possible to induce substantial reversible changes in weight and edema by large changes in the intake of sodium chloride (Fig. 11). During that six months the blood urea remained constant, eliminating any lingering possibility that edema was related to protein intake. An illusion that was nevertheless to persist for another 40 years in both Europe and America.

Strauss and Widal's conclusions on the origin of edema in renal diseases was the culmination of much work and speculation by others. Some had confirmed the constancy of plasma chloride in the face of large changes in salt intake (Langlois and Richet) [60]. Others had put forward the idea that in addition to the retention of sodium chloride edema formation also included a primary disturbance to water balance. They considered that there was some generalized abnormality of the cells which caused them to retain water (Korànyi [26], Achard and Loeper [61], and Georgopoulos [62]). This was opposed by Widal who pointed out that the renal retention of sodium chloride, which did not penetrate the cells, would on the contrary cause water to come out of cells. There is a suggestion that Widal did indeed consider that edema was due to a secondary accumulation of water out of cells following the renal retention of sodium chloride: "La connaissance des lois qui président à l'isotonie des humeurs de l'organisme, la notion du rôle fondamental joué

Fig. 10. *Fernand Widal (1862–1929).* On the right, the reverse side of the medal coined after Widal's death recalling his main contributions to medicine and the diversity of his biomedical interests. Courtesy of the Bibliothèque Interuniversitaire Rue de l'Ecole de Médecine.

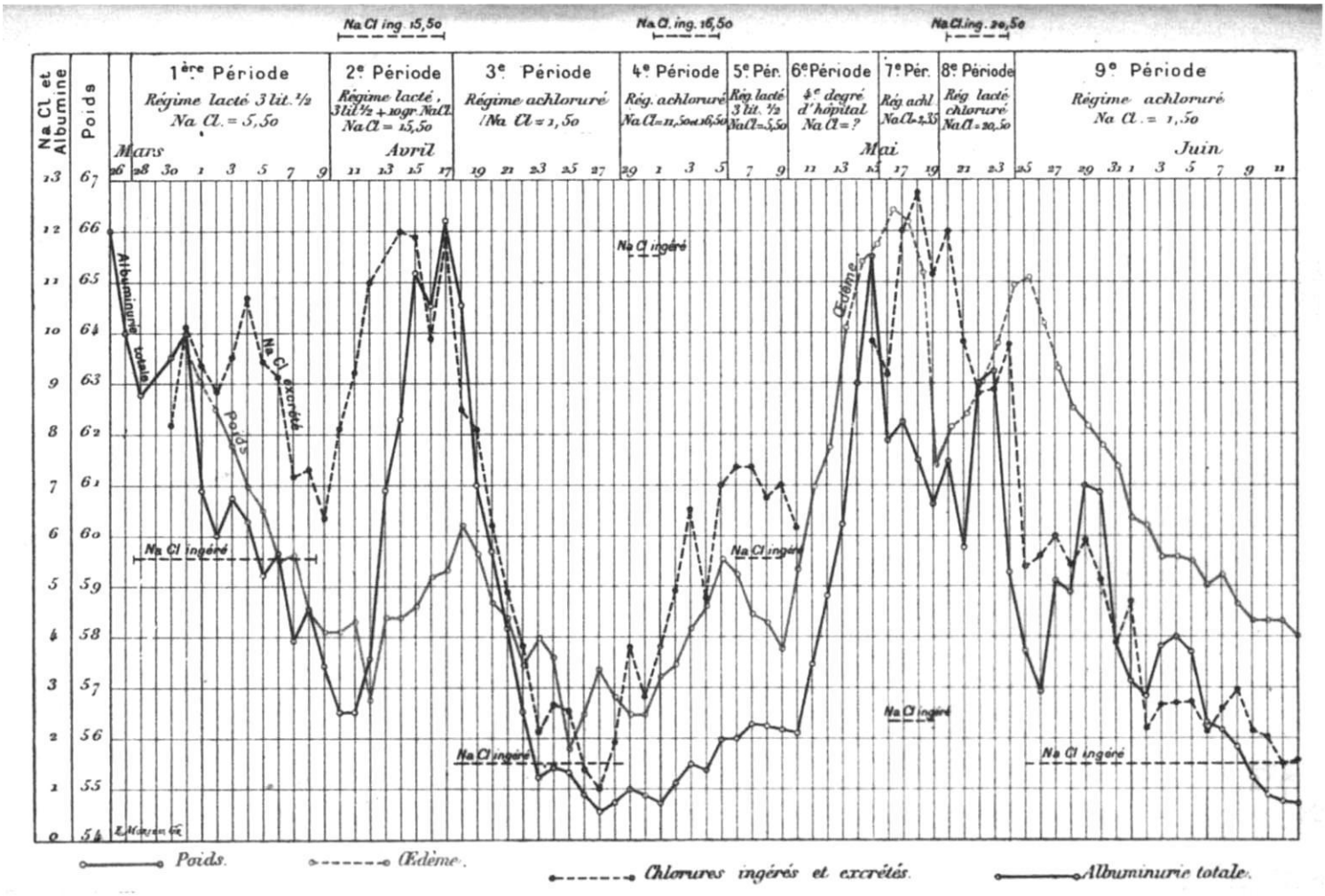

Fig. 11. *Chart of one of Widal's albuminuric and edematous patients who was submitted to various diets.* Sodium chloride-free diet induced loss of weight and dispersing of edema. A sodium chloride-rich diet provoked the reappearance of edema. Protein input did not interfere with edema [57].

par le chlorure de sodium dans le maintien de l'équilibre osmotique de ces humeurs, devait tout naturellement conduire à l'hypothèse que la rétention de ce sel dans certains tissus pouvait y attirer une partie de l'eau de l'organisme et provoquer à leur niveau l'apparition de l'oedème'' (Knowledge of the laws which govern the isotonic nature of the humoral system of the body and the concept of the basic role played by sodium chloride in maintaining the osmotic equilibrium of this humoral system, should quite naturally lead to the hypothesis that the retention of this salt in certain tissues could attract some of the body's water and cause edema at such sites). Chauffard had also observed a patient with hepatitis in whom the extent of

edema was linked exactly to the input of sodium chloride [63]. Other concepts for explaining edema proliferated. In addition to primary water retention and an abnormality of protein metabolism, there was Starling's demonstration [64–66] that the low oncotic pressure of hypoalbuminuria causes a transfer of plasma ultrafiltrate towards the tissue spaces.[5]

Uremia

Strauss's and Widal's contribution to the study of uremia was to extend and make coherent some interesting isolated findings which had appeared in the previous 75 years. There had been Prevost and Dumas [74], Gmelin [75] and Marchand [76], who between 1822 and 1838 had demonstrated that bilateral nephrectomy causes a rapid rise in blood urea. As at that time, however, the amount of blood needed to estimate its urea content was large, it was not often done in humans, and the results from the few that were performed were unconvincing (Christison [1], Bostock [77]). In 1850 J.v. Liebig published a better assay for urea which Picard (1834–1896) adapted for its estimation in the blood of men and dogs [78]. He thus became the first to note that the concentration of urea in renal vein blood was lower than in renal arterial blood, and that the blood urea of patients, before they became symptomatically uremic, rose to what he called *intermediate blood urea levels*. In other words, Picard was the first to show that blood urea might be raised without any clinical evidence of uremia (latent renal insufficiency). His work was praised by Claude Bernard [79], criticized by v. Recklinghausen [80] and then forgotten. His attempts to obtain a university appointment were turned down and he then went into general practice.

In 1880 the hypobromide assay of urea became available, which should have stimulated its wide use in clinical medicine. However, according to Bartels [9], Fleischer [81] and Lecorché and Talamon [11] it was not performed. R.v. Jaksch's paper on the measurement of blood urea in various diseases appeared in 1902. Subsequently Strauss [47], on a larger number of patients, confirmed that the concentration of blood urea in Bright's disease could vary widely over a range of 30 to 500 mg/100 ml. He pointed out that the clinical signs of uremia were found at the highest concentration. Symptomatic uremia occurred, however, at a concentration which varied from patient to patient. In line with Picard, Strauss found that patients with concentrations as high as 200 mg/100 ml could still be free of symptoms.

Characteristically, Widal's primary contribution emerged from an intense study of a few patients over a prolonged period of time. A patient on a constant diet had a blood urea which remained around 120 mg/100 ml over a controlled period of several weeks. The protein intake or the oral intake of urea was then varied. It caused parallel changes in blood urea over a range of 36 mg to 195 mg/100 ml [82]. Each change in diet induced a gradual change in blood urea over a period of five days when a new plateau was reached. At the new point of equilibrium Widal found that the rate of urinary urea excretion had changed in the same direction as the blood urea and the protein intake. From these observations he concluded that the concentration of urea in the blood controlled the rate of excretion of urea in the urine, or in other words, that the level of blood urea was a *regulating factor* in the maintenance of a nitrogen balance.

As a result of Strauss and Widal's work the concentration of blood urea (or non-protein nitrogen) became as important as hyposthenuria and an impaired excretion of methylene blue for the detection and assessment of renal failure, whether or not they were clinical signs of uremia. Strauss and Widal also observed that the blood urea might rise in a variety of diseases but that, in the absence of a renal lesion, levels greater than 100 mg/100 ml were exceptional. However, they differed in their interpretation of the apparent paradox that most uremic patients do not have edema and can excrete a large additional load of sodium chloride normally. Strauss' suggestion, which should warm the heart of some contemporary physiologists, was that the excretion of sodium was normal because the hypertension, which usually accompanies uremia, forced the sodium through the kidney [47]. Widal and Javal were more cautious. They proposed that in renal disease a rise in blood urea was due to one unknown mechanism and retention of sodium chloride was due to another [83].

Widal later worked on the clinical features of anaphylaxis. He became a leading light of the medical scene in Paris. Strauss in 1910 became head of the department of internal medicine at the Jewish Hospital in Berlin. In 1944, at the age of 76, on his way to Auschwitz he became a victim of Hitler's racially besotted tyranny [84].

These are the beginnings of renal pathophysiology. Their integration into clinical medicine was extraordinarily slow. One has the impression that the few clinical pioneers whose investigation shed light on these problems were working in isolation from the main body of their colleagues. On the whole, Strauss and Widal's work on edema was ignored until 1940. Neither did the studies appear to influence their peers in physiology. Cushny, one of the principal pillars of renal physiology at that time, even appears to have considered that at least one discovery made by renal physicians was useless and irrelevant to the proper study of renal function. He denigrated the measurement of urinary FPD: "some years ago the measurement of molecular and ionic concentration of the urine by means of its freezing point was introduced as a clinical method of determining the efficiency of the kidney . . . Clinically the results have proved disappointing and misleading . . . This cryoscopic method was much overvalued and has rightly been abandoned" [85, p. 34]. In Cushny's book Korànyi's name does not appear in the 385 references. The growing acceptance of the *filtration-reabsorption* theory made it difficult for renal physiologists to envisage that a functional lesion of a kidney, such as a leakage of protein, could coexist with an excess of function, such as an increased absorption of sodium chloride. Thus for a relatively long time the early discoveries on the origins of edema and uremia in renal disease which had emerged from the wards were disregarded by the physiologists. There is a suggestion that the concept that an abnormality caused by disease is merely a disturbance of a normal function, had not yet become thoroughly assimilated.

[5] A large number of publications devoted to the metabolism of NaCl in nephritis with or without edema appeared between 1880 and 1906: C.v. Noorden [67], Bohne [68], Reichel [69], Hofman [70], Lindemann [71], Carrion and Hallion [72], and Claude [73]. However, they often used unreliable methods and obtained inconsistent and unreproducible results that failed to elucidate the mechanisms of edema. The accomplishments of Strauss must thus be shared only with Widal.

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