In the early 19th century, although nephrology did not yet exist as a subspecialty of internal medicine, studies of renal physiology and kidney disease were actively underway in many German states, as well as German-speaking universities in neighboring countries (eg, the University of Tartu in today’s Estonia). After the advent of the German Empire in 1870, these efforts continued in the German-speaking world, providing important contributions to the evolution of physiology and clinical medicine in general. Although much of what was written did not contribute to progress in the field, individual key contributions to our specialty were made by several outstanding scientists and clinician/scientists who worked at this time in universities of German-speaking countries.

Although scientific publications in the German language could be considered dominant in Europe at the time, a trend that started to wane only after the First World War (WWI), we emphasize from the outset that in those days medicine was international and much less national and restricted by borders than in subsequent decades. To illustrate this point, it is worth mentioning that, for example, among the 250 collaborators working in the Department of Physiology of Carl Ludwig at the University of Leipzig were Henry P. Bouditch (Boston, MA), Walter H. Gaskell (Cambridge, UK), Ivan P. Pavlov (St. Petersburg, Russia), Adam Politzer (Vienna, Austria), and John J. Abel (Baltimore, MD), as well as scientists from Poland and Estonia. In these happy days before blind nationalism ravaged Europe, scientific exchange across borders was lively, consistent with the motto of the German poet Johann Wolfgang von Goethe (1749-1832): “There is no national art or national science, both belong to the entire mankind” (“Es gibt keine patriotische Kunst und keine patriotische Wissenschaft. Beide gehören, wie alles hohe Gute, der ganzen Welt an”).

Before discussing the major contributions of the scientists...
described here, it also is useful to mention that some of the best investigators in the German-speaking countries performed important work relevant to the understanding of kidney disease, although they did not work directly on the kidney. For example, a fundamental advance in 19th century medicine was the use of the scientific approach; in German-speaking countries, this revolutionary change was epitomized by Rudolf Virchow (1821-1902). Another development significant to the emerging knowledge of the kidney was realized by Hermann von Helmholtz (1821-1894), an all-around genius in physics known for the discovery of the law of conservation of energy. von Helmholtz invented the ophthalmoscope, and this instrument led to the early recognition of the fundus changes in patients with kidney disease. In addition, Adolf Fick (1829-1901), who introduced the law of diffusion, also developed a method to measure cardiac output that ultimately led to the concept of renal clearance by Homer W. Smith.

Of scientists who focused their attention on the kidney itself, the following individuals are those who, among many other pursuits, made key contributions to the understanding of kidney function and kidney disease and were responsible for progress and huge leaps forward:

- The physiologist Carl Ludwig introduced the concept of glomerular filtration
- Jacob Henle described the normal anatomy of the kidney (and provided a description of cellular casts in urine sediment)
- Friedrich Theodor von Freytag investigated the concept of the evolution (today we would say progression) of kidney disease based on histologic analysis of kidneys at autopsy, introduced the concept of glomerular hypertension, and recognized the importance of interstitial fibrosis
- Hermann Senator recognized the presence of albumin in urine in the absence of primary kidney disease (and its reflection of general health, ie, its status as a risk factor, in today’s terminology)

**CARL LUDWIG (1816-1895)**

Carl Friedrich Wilhelm Ludwig (Fig 1) was born in the small town of Witzenhausen, in the state of Hesse. He studied medicine at the University of Marburg, where he was expelled because of his political activities. However, he was allowed to return and obtained his medical degree in 1842 after writing a dissertation on renal filtration. This epochal study started a revolution in biomedical science at a time when “vitalism” was still prevalent. Vitalism was the concept that the functions of a living organism are due to a vital principle distinct from physicochemical reactions, leading to the idea that the processes of life are not explicable by the laws of physics and chemistry alone. The title of Ludwig’s dissertation was still in traditional Latin (De Viribus Physicis Secretionem Urinae Adjunctibus), but (at that time still a revolutionary act) he published a German translation 1 year later with the title Beiträge zur Lehre vom Mechanismus der Harnsekretion (Contributions to the understanding of the mechanisms of urine secretion).

Ludwig was the first to suggest that filtration of fluid driven by a pressure gradient across a membrane, in other words, a purely physical process, underlies the process of urine formation. In his masterpiece, he provided experimental proof that urine formation can be explained by the laws of physics and chemistry, namely ultrafiltration in the glomerulus. His summary is still delightful to read today: “So we see in this arrangement a simplicity of the action of purely physical forces — a harmony the beauty of which is not surpassed by any natural process.” As mentioned, at that time this proposal was a revolutionary departure from the prevailing conceit of vital-
ism, which was defended by no less than the famous anatomist and physiologist Johannes Müller (1801-1858): the kidney was still regarded as a "gland" in his 1834 textbook. The new paradigm that glomerular filtration underlies urine formation therefore had repercussions in biology going far beyond the kidney. Ludwig's new data, new concepts, and new methods provided the catalyst in these crucial years for the transition from romantic natural philosophy to the application of natural sciences in medicine.5,6

Ludwig's experimental approach had a decidedly modern feel. He first had studied the passage of urine through semipermeable membranes. Later, he used in vitro injection of dye from the arterial and ureteral sides of kidney specimens and histologic examination. These dye injection experiments permitted him to elucidate the anatomy of the renal vasculature and identify the 2 capillary beds, the glomerular and peritubular beds, which he found were connected in series. He subsequently constructed an apparatus specifically designed to reproduce the flow pattern within the kidney and imitate the filtration process (Fig 2). Based on the anatomy of the renal vasculature, which he had obtained from the injection experiments, and the effect of pressure on filtration in his custom-made apparatus, Ludwig even speculated that glomerular filtration is regulated by contraction of the muscular walls of the efferent and afferent arterioles, slowing or accelerating blood flow as a result of the attendant pressure changes. As quoted by Davis et al,7 he concluded that the fluid components of blood "penetrate the intact vascular walls," in other words, glomerular capillaries, and that this process is opposed by a further downstream process of "reabsorption." He thought that this "secretion" (ie, filtration) through "thierische Häute" (animal membranes) occurred through minute openings and that the passage of fluid through these openings did not lead to any change in the fluid's composition.7

Ludwig also argued that the compounds found in urine were synthesized within the body, and the idea of pressure on filtration in his custom-made apparatus, Ludwig even speculated that glomerular filtration is regulated by contraction of the muscular walls of the afferent and efferent arterioles, slowing or accelerating blood flow as a result of the attendant pressure changes. As quoted by Davis et al,7 he concluded that the fluid components of blood "penetrate the intact vascular walls," in other words, glomerular capillaries, and that this process is opposed by a further downstream process of "reabsorption." He thought that this "secretion" (ie, filtration) through "thierische Häute" (animal membranes) occurred through minute openings and that the passage of fluid through these openings did not lead to any change in the fluid's composition.7

Figure 2. Renal anatomy drawings by Ludwig. (A) At top, a representation of the renal microvasculature, including (left) glomerular and (right) peritubular networks. Underneath, the relative total cross-sectional areas of different vascular segments are shown. (B) Pressure profiles across the capillary beds. Reproduced from Davis et al7 with permission from the European Renal Association-European Dialysis and Transplant Association.

World Kidney Forum
After this brilliant debut, Ludwig never worked on the kidney again. For political reasons, he, a known political activist, was forced to emigrate from Hesse. He accepted a chair at the University of Zurich in 1848 and in Vienna in 1855. Finally, he was able to come back to Germany in 1865: he accepted the chair at the University of Leipzig, where he earned fame by perfecting instruments and techniques for physiological research, for example, the kymograph, flowmeter (Stromuhr), organ perfusion ex vivo, and the mercury blood pump, as well as by his groundbreaking work on hemodynamics, gas exchange, lymph flow, and saliva production.

JACOB HENLE (1809-1885)

As recounted in various sources,5,10,11 Friedrich Gustav Jacob Henle (Fig 3) was born in 1809 to a Jewish merchant family in Fürth in Southern Germany. He studied medicine at the University of Bonn and University of Heidelberg. In Bonn, he met Müller, with whom he collaborated and whom he followed in 1835 to Berlin, where Müller had accepted the chair of anatomy and physiology. There, Henle was the first to offer a course in microscopy in the German speaking countries, illustrating just how revolutionary microscopy still was in those days.

Henle’s professorial thesis on microscopic analysis of the cuticula (surface layer) of the intestinal tract introduced the then revolutionary concept that all internal and external surfaces of the body were covered by epithelial cells. He was the first to distinguish 3 basic types of epithelium: epithelium squamosum (squamous epithelium), epithelium cylindricum (columnar epithelium), and epithelium cylindricum vibratorium (ciliated columnar epithelium). He recognized that all inner and outer surfaces of the body are lined with epithelial tissue, which has been called “one of the most momentous generalizations of the century.”11

In 1840, he was appointed professor of anatomy and physiology at the University of Zürich. There he published one of his fundamental monographs, Allgemeine Anatomie (Comprehensive Anatomy), the first systematic treatise of histology. This 3-volume handbook of human anatomy (1855-1871) is considered by many authorities to be the greatest of the modern systems of anatomy. This was followed later by the standards Handbuch der rationellen Pathologie (Handbook of Rational Pathology) and Handbuch der systematischen Anatomie des Menschen (Handbook of Systematic Anatomy of Man). These books were remarkable not only for the accuracy and completeness of description, but also for the excellence of his illustrations.

Of particular importance is his early interest in pus and infectious disease, which began while he was at Zürich, but that he also pursued thereafter. In 1840, he wrote a key publication, Von den Miasmen und Contagien (Of Miasmas and Contagious Matter). Using microscopy, he made the key observation of the presence of microorganisms in pus and the excretions of diseased animals. He pursued the concept of “materia animata” (animated matter) as the cause of infectious disease. Notably, later at the University of Göttingen, Robert Koch was his assistant. Although Koch is known for documenting the role of microbes in disease, he and Henle formulated the list of conditions that need to be met to prove the causal role of microbes. These now are known as Koch’s postulates, but in the past, they were also called “ Henle-Koch postulates.”

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In 1844, Henle moved to Heidelberg University, where he was appointed as professor of anatomy and subsequently, from 1852 until the end of his life, he held the chair of anatomy in Göttingen. It was in January 1862 that he ensured himself a place in future nephrology textbooks by the description of what is known today as “Henle’s loop.” He had recognized that 2 types of tubules existed in the medullary
tissue; on the one hand, the ductus papillaris (papillary collecting duct) with a diameter of 50-60 μm and consisting of uniform columnar epithelium, and on the other hand, much smaller tubules with a diameter of 20-30 μm that were lined by small squamous cells. This second type returned in a narrow hairpin loop back into the medullary tissue. He recognized that these loop-like tubules are arranged in a circular fashion around what we know today are the collecting ducts. He immediately communicated this landmark discovery because he had instantly recognized the great potential functional importance of this type of geometrical arrangement. He contacted Carl Ludwig in the hopes of finding a functional interpretation, to which Ludwig replied that it was evident from the morphology of the structure that it had a key functional significance, and suggested that comparative anatomic studies would be an important source of additional information. Unfortunately, for several decades, the pedestrian assumption prevailed in most quarters that the loop was only the consequence of some peculiarity of organogenesis.

Another less frequently cited discovery of some interest to clinical nephrologists was the recognition of cellular cylinders in urine of patients with kidney disease. This was one of the spinoffs of Henle’s effort to go beyond descriptive anatomy and use the microscope for clinical problems.

Beyond medicine, Henle was an interesting and impressive personality. He was a liberal and therefore had great difficulties with Prussian authorities. As a student, he was even imprisoned because of his membership in an outlawed fraternity and released only after the personal intervention of Alexander Humboldt. Henle was a polyglot (speaking French, Italian, and Danish—in those days, apparently not English!) and had broad interests: he was an accomplished painter and enthusiastic violinist (violin, viola, and violoncello); he befriended the composer Mendelssohn-Bartholdy and was regularly invited to his musical matinees. In Zürich, he had a romance with a seamstress, Elise Egloff, of modest background (he saw to it that she was educated in a boarding school to become “suitable” as a professor’s wife), and his exchange of letters with her even entered German literature.

**FRIEDRICH THEODOR VON FERICHES (1819-1885)**

Born in Aurich, Friedrich Theodor von Feriches (Fig 4) studied medicine at the University of Göttingen (1838-1841) and returned to Aurich to practice ophthalmology. He apparently was bored and returned in 1846 to Göttingen, where he obtained a professorship at the age of 27 years. His primary interests were physiologic and chemical studies. Four years later, in 1850, he went to Kiel, and in 1852, he went to the University of Wrocław. Finally, in 1859, he was appointed as director of the Charité in Berlin, II Medical Clinic (where the famous Paul Ehrlich was his assistant in 1878). Later in life, his primary fields of investigation, which made him famous and are more widely known today, were liver disease (he discovered leucine and tyrosine crystals in urine of patients with hepatic coma) and diabetes mellitus, a topic that he covered in a famous textbook.

In Göttingen, he wrote within the short period between 1846-1850 a monumental monograph on glomerulonephritis that has never been translated into English and, as has been argued before, therefore did not gain the recognition that it deserved. This masterpiece on Bright disease and its treatment (Die Bright’sche Nierenkrankheit und deren Behandlung) was written when he was only 32 years old. There, he described the important observation that short-term infusion of urea is not sufficient for producing uremic syndrome, although its long-term infusion leads to considerable morbidity in nephrectomized dogs.
However, the major contribution of von Frerichs was the use of the then-primitive microscopic technique of pluck preparations ("Zupfpriparate"; i.e., microdissection) to investigate at autopsy the kidneys of patients who had died of acute and different stages of chronic kidney disease. The idea that motivated him is reflected by the introduction of his monograph: "... in order to understand disease processes, one has to turn away from the description on the surface, i.e. of symptoms, and focus on causal interrelations" ("innere Zusammenhänge der Erscheinungen"), which he believed could be studied using the new methods available in anatomy and physiology.14 In short, von Frerichs argued that anatomic lesions provide reliable clues indicative of the pathology underlying different stages of glomerulonephritis.

He criticized previous publications that described a diverse array of anatomic presentations, arguing that this was not because of the existence of truly distinct forms of renal inflammation, but rather the observation of consecutive stages in the development of a single progressive disease process. Von Frerichs drew beautifully intricate representations of the glomerulus and peritubular microcirculation (Fig 5), writing (in a surprisingly modern tone): "Within Malpighi’s capsules ... a considerable amount of fluid must leave the vessels and enter the tubules ... The composition of such fluid must be determined by the degree of hydrostatic pressure and the characteristics and the pore diameter of the vascular walls of the glomerulus."14 From this, he deduced that "during pathological processes ... there will first be an increase in transudation subsequently compounds will be filtered, permeation of which is restricted when glomerular pressures are normal, first protein, later fibrin [Faserstoff]. Finally, the capillary walls tear and blood as such will leave the vessels."14 He concluded that "[t]he disturbances of transudation will first and primarily take place in that part of the capillary system of the kidney which even in the healthy state will be exposed to a higher pressure of the blood column, i.e. in the vascular tuft of Malpighi’s bodies. It must be here that circulatory abnormalities cause an increase in pressure to such an extent that the albumin in the blood plasma and fibrin are transudated."14 Strikingly, these words were written more than a century before the measurement of glomerular capillary pressure by Brenner confirmed the existence of glomerular hypertension.15

von Frerichs also provided one of the early hypotheses of a rational mechanism for the formation of casts: "Albumin will directly transit from the capsules of Malpighi into the tubules and will then end up in the final urine. The fibrin will pass by the same route, but it will only rarely reach the bladder urine in a fluid state. Usually it will coagulate within the tubules, particularly in the lower tubules, but also in the contorted tubules of the cortex. Such fibrin coagulates are replicas which reflect the form and shape of the tubules from which they were washed out."14

Figure 5. Schema of the renal microcirculation. Illustration from Friedrich Theodor Frerichs’ Die Bright’sche Nierenkrankheit und deren Behandlung.14 Reproduced from Schwarz and Ritz13 with permission from the European Renal Association-European Dialysis and Transplant Association.
concept that interstitial lesions are a key factor in the progression of renal disease: “If an exudate in the renal interstitium is transformed into interstitial tissue, it acts as a scar and compresses the adjacent parenchyma and promotes its atrophy. One finds . . . newly formed interstitial tissue consisting of elongated spindle cells [Faserzellen] and even completely developed fibrils which can be isolated and definitely distinguished from the remnants of the basal membranes of the tubules.”

It is a fascinating thought that despite the primitive methods available one and a half centuries ago, von Frerichs’ brilliant mind was able to develop concepts such as glomerular hypertension and interstitial fibrosis, among others.

HERMANN SENATOR (1834-1911)

Hermann Senator (Fig 6) was born 1834 in Gnesen (Gniezno) in the Province of Posen, in what today is Poland. He received his medical training at the University of Berlin under the tutelage of the physiologist Georg Müller and the internists Johann L. Schönlein and Ludwig Traube. He obtained his MD with a thesis on liver disease, and in 1868, he obtained a degree in internal medicine and pharmacology at the Charité hospital in Berlin. He was also an expert in forensic medicine and was a widely acknowledged authority in this specialty.

Senator published a total of 200 original articles on clinical and experimental studies. The work of most relevance from a nephrology perspective was his work on albuminuria and his textbook on renal disease. Senator defined “albumen” as the serum component in urine that was coagulated by heat at 55°C-82°C. Applying this technique, he noticed that traces of albumin (<0.05%) could be detected in urine of apparently healthy humans. He performed a number of detailed studies of albumin excretion in individuals without primary kidney disease, which he published under the title Die Albuminurie im gesunden und kranken Zustande (Albuminuria in Health and Disease). This monograph was believed to be so important that the Sydenham Society published it in 1884 (Fig 7), and 7 years later, a French version was published in Paris (Traité de l’albuminurie). There was so much demand for this book that he published a revised and rewritten version 8 years later (Die Albuminurie in physiologischer und klinischer Beziehung und ihre Behandlung). As noted previously, his work has now largely been forgotten.

The work of Senator was important because in those days, there was bitter controversy about the mechanism of albuminuria. Heidenhain was of the opinion that glomerular filtrate was the product of glandular-like secretion in the glomerulus and any protein in urine was of a secretory origin. In contrast, in his albuminuria monograph, Senator concluded that “the disturbance of the circulation in the Malpighian tufts is the cause of albuminuria, but the ill effect of this disturbance are of less serious import upon the walls of the vessels than upon the epithelium which covers the vessels.”

As a result, Senator attributed the retention of albumin under normal conditions to a property of the epithelium, which today we would refer to as podocytes. He continued, “We are therefore forced to assume that (albumin) is filtered through the Malpighian tufts, but in an extremely minute quantity as a result of its small capacity for filtration of albumin because the escape of albumin from the Malpighian tuft is prevented by the epithelial investment of the vessels.” It is of interest that this view differed from the then popular hypothesis based on the work of Ludwig that glomerular filtrate is entirely albumin free. Senator further argued that filtration of albumin across the glomerular membrane was modulated by blood pressure.
He even considered the possibility that albumin was reabsorbed by the tubules and wisely stated that there was evidence neither for nor against this hypothesis.

Senator’s documentation of albuminuria in healthy individuals is of great interest from today’s perspective. Recently, we have become aware of the prognostic significance of urinary albumin in individuals without primary kidney disease. On this issue, he stated, “The question as to whether under normal conditions the urine does or does not contain albumin and that albuminuria is invariably a sign of disease . . . most recent observations show that exceptions exist to the dogma.” He argued that “Improved methods of investigation and the discovery of delicate reactions have resulted in the discovery of albumin in very many instances, but in minute quantities, in the urine of perfectly healthy men and this albumin . . . differed in no respect from the albumin of the ordinary forms of albuminuria.”

The albuminuria prevalence figures that Senator reported were “5% of healthy soldiers at rest and 16% after a march as well as 12% in healthy persons undergoing life insurance investigation.” In passing, he also mentioned that he found albuminuria in a diabetic patient. He assessed the variation of albumin excretion during the day and found that it was most frequently demonstrable in the morning hours and after a meal. In patients with massive albuminuria (presumably kidney disease), he showed that albuminuria increased upon consumption of animal proteins, such as meat or eggs.

Senator even concluded that albuminuric individuals should be followed up to detect potential deterioration in their health status. This notion was taken up in 1893 by the Life Assurance Medical Officers Association. In 1912, a publication appeared that showed that of 396 individuals with albuminuria during an insurance health check, 22 had persistent albuminuria. Against the background of today’s knowledge, it is of interest that 25 had died (compared with the 16 expected from the life insurance tables), an early hint that albuminuria also is an indicator of cardiovascular risk.

**CONCLUSIONS**

Together, Ludwig, Henle, von Frerichs, and Senator laid a solid basis for basic and clinical research on the kidney that continued well into the 20th century. Germany’s role in science and medicine had diminished after WWI, but even so, significant advances took place in the fields of renal physiology and kidney disease. As highlighted previously, one of the contributors to these developments was Franz Volhard (1872-1950), whose monograph Die Bright’sche Nierenkrankheit: Klinik, Pathologie
und Atlas (Berlin, 1914) revolutionized the understanding of the histology of glomerulonephritis and who made the distinction between “benign” and “malignant” hypertension. Another significant contributor to German post-WWI nephrology was Georg Haas, a forgotten pioneer who in 1924 was the first to perform hemodialysis in a human, transiently reversing the coma of a terminally uremic patient.23 After WWII, there was an explosive growth of renal physiology in Germany (Karl J. Ullrich, Klaus Hierholzer, and Klaus Thurau).

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