Whereas kidney disease is old, nephrology is a relatively young discipline. The seeds of the study of kidney disease were sown by Richard Bright (1789-1858) in 1827, but it was only in the second half of the 20th century that the study of the kidney as a specialty finally emerged as a budding discipline after the first International Meeting of Nephrology in Evian, France, in 1960. In the interim, and especially in the first half of the 20th century, important contributions to our knowledge of kidney function in health and disease were made by pathologists, physiologists, and internists who worked in and contributed to several other fields of medicine, none of whom considered themselves nephrologists. The major figures who dominated this period have been duly acknowledged for their seminal contributions to the emergence of nephrology.1,2 The contributions of many others who made it all possible and provided the infrastructure that would spread nephrology worldwide remain unrecognized. One such figure is Erich Frank (1884-1957; Fig 1), better known for his contribution to the understanding of diabetes insipidus.3 His life and many other contributions to the leading causes of chronic kidney disease (diabetes, hypertension, and proteinuria) provide considerable insight into the formative years of nephrology during a period of great social and political turmoil that preceded its emergence as a discipline after World War II.

To quote from the subtitle of Steven Shapin’s book, Never Pure, the life work of Frank represents a historical study in the understanding of kidney disease as it was produced by “people with bodies, situated in time, space, culture, and society, and struggling for credibility and authority” and in his case for survival. His work represents the evolving understanding of kidney disease as much as it does that of the major geopolitical

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changes affecting Europe at the time, as well as that of the emergence of the new Republic of Turkey, which provided him safe haven to continue the work he had started in his native Germany.

ERICH FRANK: LIFE AND TIMES

Frank was born on June 28, 1884, in Berlin to a Jewish mother (Dorothea) and a Christian father (Albert) who was a teacher at a local gymnasium (the upper level of secondary school, which prepared students for admission to university). After his secondary education, Frank began his medical studies in 1902 at the University of Breslau (now the University of Wrocław, Poland). This was a period in which research was venerated and the system of medical education encouraged good students to find their way into research. A written thesis of original research that usually was published was a requirement for obtaining a medical degree in Germany. Thus, it was as a medical student that Frank embarked on the study of albuminuria in Breslau. In 1907, he passed the Staatsexamens (National Medical Examination) and transferred to the University of Strasbourg (then known as the Kaiser Wilhelm Medical Faculty), where he presented his thesis on “orthostatic albuminuria” (Fig 2) and was granted a medical degree in 1908.

From 1908 to 1911, Frank worked as an assistant to Wilhelm Weintraud (1866-1920). Weintraud, a trainee of Felix Hoppe-Seyler (1825-1895), had been recruited by the head of the medical department of the University of Breslau and Oskar Minkowski (1858-1931), famous for his research on diabetes mellitus and the first to show its relationship to the pancreas. In Breslau, Frank studied salvarsan, one of the magic bullets of Paul Ehrlich (1854-1915; another graduate of Breslau and Strasbourg), and wrote his well-known paper on diabetes insipidus.

In 1911, Frank began his academic career as a resident in internal medicine at the University of Strasbourg and worked at Wiesbaden Hospital, which was affiliated with the university. In 1913, he was promoted to associate professor, and in 1919, to professor of internal medicine in Breslau, where he served as the head of internal medicine of the Wenzel-Hancke Municipal Hospital in 1926-1933. In Breslau in 1918, Frank married Erna Führich, who was born in Katowice, Poland, in 1889. From this marriage, they had a daughter, Sabine, born in 1919, and a son, Ernst Frank, born in 1925.

As Germany turned to Nazism, the University of Breslau came under the influence of Nazi ideology, and there followed an aggressive policy for the eviction of university faculty of Jewish heritage. As a result, together with thousands of other citizens and many renowned scientists and schol-
ars, Frank sought asylum away from his country. It is in this context that in September 1933, Albert Einstein (1879-1955) sent a letter to İsmet İnönü (1884-1973), then Prime Minister of Turkey, asking permission “to allow forty professors and physicians from Germany to continue their scientific and medical work in Turkey”, adding that “in accepting this request, your government not only will perform an act of high humanity, but will also bring profit to your own country” (Fig 3). The letter was referred to the Ministry of National Education, where it was considered incompatible with existing laws and initially was rejected.

About this time, the new Turkish Republic founded by Kemal Atatürk (1881-1938) was keen in modernizing its education system. In 1932, Albert Malche (1876-1956) of Switzerland, who was a pedagogy professor, had been invited to prepare a report on reforming the Turkish educational system. Among other suggestions, Malche had proposed a major infusion of academic talent from abroad. A Western style of higher education had long been sought by the Ottomans, leading to the establishment in 1846 of Darül-fünun (House of Sciences) in Istanbul. Despite repeated attempts at reform, Darül-fünun remained a mediocre institution until 1933, when, on the basis of the Malche report, it was transformed to Istanbul University. By the direct personal intervention of Atatürk, the new university became host to a number of Jewish educators fleeing Germany, including the 40 mentioned in Einstein’s letter, most of whom (including Frank) accepted the offer and emigrated to Turkey. As a consequence, more than two-thirds of the faculty of Darül-fünun was relieved of their duties and replaced by new faculty. By the following academic year (1933-1934), all directors of the 12 institutions of Istanbul University were German refugee scholars.

This was an opportunity for Frank to leave behind the threatening environment of his native country to pursue his academic career in a safer place. He was invited to take the position of co-chair of the Department of Internal Medicine of the new Istanbul University. Joining him on the medical faculty were other distinguished scholars, such as Rudolf Nissen (1896-1981) from Charité in Berlin to head surgery; Wilhelm Liepmann (1878-1939) from Berlin University to head obstetrics; Joseph Igersheimer (1879-1965) from Frankfurt University to head ophthalmology; and Friedrich Dessauer (1881-1963), also from Frankfurt University, to head radiology.

Frank was assigned to head the medical services of the Vakıf Güreba Hospital, which

Figure 2. The cover of Frank’s first publication on orthostatic proteinuria, a medical thesis that appeared more than one century ago. Reproduced from Ord. Prof. Dr. Erich Frank’in Dünya Tıbbındaki Yeri ve Türk Tıbbına Katkıları with permission of Nobel Tıp Kitabevi Ltd.
Albert Einstein’s letter addressed to Turkish Prime Minister İsmet İnönü, whose handwritten and signed note referring the letter to the Ministry of Education appears in the upper right under the date of the letter (September 17, 1933). Of note, the original letter was assigned to the Ministry of Health, then cancelled by a strikethrough. Reproduced with permission from the Archives of the Government of the Prime Ministry of the Turkish Republic, Department of the Ottoman Archives.
was a vakıf (foundation) charity hospital that accepted the gureba (poorest) patients from all over Turkey. It was one of the teaching hospitals of Istanbul University located in the Marmara region of the Fatih district of Istanbul. It was built in 1843 during the reign of Sultan Abdülmecid I (1823-1861) by a grant from his mother Bezmiâlem Sultan (1807-1853); hence the full name of the hospital, the Valide Vakıf Gureba Hospital. (A fictionalized version of the sultan and his mother appears in Jason Goodwin’s novels, The Bellini Card and The Janissary Tree.) A modern hospital with the same name now stands on the site of the old hospital.

Frank’s first contract extended from September 1, 1934, until August 31, 1939, at a salary of 600 Turkish liras per month (Fig 4). The contract also allowed for the hiring of a laboratory chief and a dietician, if their need could be documented. Frank petitioned for these positions shortly after his arrival, convincing the authorities to recruit Kurt Steinitz (1907-1966) as laboratory chief and Elisabeth (Elsa) Wolff (1894-?) as dietician.

Steinitz was a medical graduate of Leipzig and Heidelberg Universities with an interest in chemistry, and he had collaborated with Frank in Breslau at the Wenzel-Hancke Municipal Hospital. He moved to Turkey in October 1934, where he took the position of laboratory chief of the Vakıf Gureba Hospital. Steinitz organized the laboratory, taught medical students clinical pathology, and embarked on the investigation of kidney function in humans. In the years that he worked at the hospital, Steinitz conducted studies on the determination of glomerular filtration by endogenous creatinine clearance and on glucose excretion in humans that were published in the Journal of Clinical Investigation in 1940 and are quoted by Homer Smith (1895-1962) in his classic book The Kidney: Structure and Function in Health and Disease. In the first article, Steinitz showed the hyperbolic increase in serum creatinine level with progressive loss of kidney function in humans. In both articles, Steinitz expresses his indebtedness and acknowledges the encouragement of Frank in conducting these basic investigations. Steinitz’s contract expired in 1943, whereupon he left for Palestine, where he became the first physician to develop an artificial kidney and the first to dialyze a patient in Israel.
Elsa Wolff was born in Loslau, now Wodzisław Śląski in southern Poland. Upon graduation in nursing from Breslau in 1922, she worked in Frank’s clinic until 1928. After 2 years of working in Switzerland and Poland, she returned to work for Frank in Breslau until 1933. As one of the few representatives of modern dietetics, on moving to Turkey, she organized the first hospital-based dietary department in the country. She was instrumental in the training of many nurses as dieticians, who later went on to serve in other hospitals as dietary experts. With Frank, she wrote a popular diet book in Turkish on the dietary management of patients.19 The book includes 20 chapters, the 4th of which is on diet in diabetes; the 8th, on diet in kidney diseases; and the 14th, on that of kidney and bladder stones. After 32 years of service in Turkey, Elsa retired in 1965 and returned to Germany.20

Shortly after assuming his position, Frank submitted a petition to the Dean of Istanbul University School of Medicine, Nureddin Ali Berkol (1880-1955), requesting the following:

1. Personnel: 2 additional residents in addition to the 4 assigned to his service; one to work in the outpatient clinic, and the other, in the research laboratory. Two more nurses to allow for continuous 24-hour nursing coverage of hospital wards.

2. Resources: 2,500 Turkish liras to establish a dietary service and obtain new instruments for the diagnosis and treatment of patients.

3. Revision of medical education: Frank considered the quality of medical education inadequate and made several recommendations for improving the training of medical students, suggesting the incorporation of a combination of French and German medical principles to improve education and health care services in Turkey.

In the years that followed, Frank and his team completely reorganized internal medicine services at Istanbul University, treated thousands of patients, educated hundreds of medical students, and trained many house officers as physicians and investigators.21 Frank also collaborated with Turkish academicians and contributed to their careers, acquiring in the process the loyalty and support of colleagues throughout the country. In short, his work was central to the development of modern medicine in Turkey. His efforts were appreciated by not only his students, colleagues, and patients, but also by the Turkish government, which remained favorably responsive to his requests for the support and expansion of medical services.

In 1951, Frank launched a new medical journal titled Istanbul Contribution to Clinical Science, of which he served as Editor-in-Chief until his death in 1957. The inaugural issue of the journal contained 4 articles. The first, written by Frank, was a review titled “An update on the pathogenesis of essential hypertension.”22 The other 3 were prospective clinical trials, one of which was a study of the effect of oral potassium loads in healthy volunteers. Thus, of the 4 inaugural articles, 2 were related to nephrology. After his death, his fellow Orhan Ulutin (b. 1924) became Editor-in-Chief of the journal, which in 1962 was reorganized as the Turkish Journal of Hematology, the official publication of the Turkish Society of Hematology.

After World War II, Frank received several offers for academic positions from various countries, especially the United States and Germany. However, he was content with his job in his adopted homeland and always grateful for the invitation to Istanbul University in his most difficult and insecure days. Unlike most of those who had sought refuge in Turkey with him, Frank refused these attractive offers and elected to continue his work and teaching in the Istanbul University, surrounded by his students, assistants, and patients. He retired from the university in 1953 and died on February 13, 1957, after a fulminant illness, probably hepatic failure.23

ERICH FRANK: THE SCIENTIST

Frank had the hallmarks of a true scientist: a profound analytical ability, a keen intellect, an all-embracing mind, and humility and humanity. As a graduate of the German medical system, he was a clinical scientist. As a trainee of Breslau, he had a special interest in diabetes mellitus. As an informed investigator, he kept abreast of the accumulating new studies of the kidney in health and disease. His
Box 1. Principal Scientific Contributions of Frank to Medicine

Nephrology
- Description of orthostatic proteinuria (1908)
- Concept of essential and renal parenchymal hypertension (1911)
- Concept of hypertensive nephrosclerosis (1911)
- Description of renal glycosuria (1913)
- Textbook of Nephrology (1941)
  (in Turkish)

Other Fields of Medicine
- Micromethod for blood glucose determination (1910)
- Pathogenesis of diabetes insipidus (1912)
- Pathogenesis of aplastic anemia and essential thrombocytopenia (1915)
- Role of thrombocytes in anticoagulation (1915)
- Description of hypersplenism (1915)
- Discovery of an oral antidiabetic: Synthaline B (1925)
- Description of factor VIII and pathogenesis of hemophilia (1927)
- Description of orthostatic proteinuria (1908)
- Concept of essential and renal parenchymal hypertension (1911)
- Concept of hypertensive nephrosclerosis (1911)
- Description of renal glycosuria (1913)
- Textbook of Nephrology (1941)
  (in Turkish)

科学 contributions encompassed several branches of medicine, including diabetes, nephrology, hematology, and neurology (Box 1). What follows is a review of his contributions to nephrology and a brief summary of his contribution to other fields in medicine.

Contributions to Nephrology

Frank’s interest in the kidney can be traced to his student years in Breslau. His medical thesis, prepared under the supervision of Weintraud, was on orthostatic proteinuria and was published in 1908 as Über den genuinen orthostatischen Typus (Genuine Orthostatische Albuminurie) (Fig 2). After Richard Bright’s landmark report of the kidney in dropsical patients and its differentiation from other causes of dropsy by the presence of albuminous urine, albuminuria came to be considered the manifestation of a serious inflammatory lesion of the kidneys termed “nephritis.” Debate during the ensuing decades centered on whether nephritis could exist in the absence of dropsy and whether albuminuria could be present without progressive loss of kidney function.

To address this latter issue, Frank undertook his thesis work in an attempt to differentiate benign from serious kidney disease, with its focus on orthostatic albuminuria as a benign disorder that required no treatment and might improve with exercise. In his report, Frank emphasized that the pathogenesis of this type of albuminuria was not orthostatism per se, but rather the lordotic position of the patient, and thus he measured urinary albumin excretion in 2 positions. First, he placed a pillow under the lumbar region of supine volunteers in bed to create a lordotic position, noting that albuminuria appeared after 1 hour and disappeared several hours later when the volunteer returned to the normal flat position at rest. Next, he asked a standing patient to bend forward, assuming a kyphotic position, and noted that albuminuria disappeared shortly thereafter. Thus, he emphasized again that it was the lordotic position and not merely orthostatism that produced albuminuria.

Frank also measured glomerular filtration rate and renal blood flow in these individuals and found that both parameters decreased in the lordotic position. He commented that these changes possibly were related to changes in intrarenal hydrostatic pressure secondary to a positional reflex constriction of the renal artery.

His first publications after graduation addressed ongoing studies of kidney disease that were to lead to the coherent scheme of Franz Volhard (1872-1950) and Theodor Fahr (1877-1945) in framing the classification of kidney disease. This was a time when the kidney as a cause or culprit in hypertension was actively debated. In 1911, Frank published 2 reports in which he defined and described the terms hypertonische diathese and nephrogene hypertorie; in other words, essential hypertension and hypertension due to renal parenchymal disease. Based on the autopsy findings of a 46-year-old woman with severe hypertension (in whom rather than the expected small sclerotic kidneys, the kidneys showed minimal abnormalities and no sclerosis), he argued that the hypertension in this patient certainly was different from nephrogene hypertorie, suggesting that her hypertension was due to primary increased vascular tone (hypertonische diathese). He emphasized that clinically, this disorder usually begins in the early 40s and can result in cardiac and renal failure if untreated. He acknowledged that the cause of essential hypertension was unknown, but could be due to reflex activation originating from
the kidneys or its release of “renin,” but that these remained to be determined. In a subsequent publication, he considered other causes of hypertension, such as a higher set point for blood pressure control in the nervous system, sex hormones, and genetic factors.22

Another interest of Frank was renal glycosuria, specifically in pregnancy, which he began to address in 1913. He considered this “renal diabetes” a harmless condition due to a lower renal threshold for glucose absorption. However, he acknowledged that it could appear at the onset of diabetes or turn into diabetes subsequently.29

In addition, Frank contributed several articles on kidney function and disease to the Istanbul Contribution to Clinical Science that were detailed reviews of the literature. Importantly, he wrote the first Turkish textbook on the kidney and its diseases, titled Dahili Böbrek Hastalıkları Klinig˘i (Medical Kidney Diseases Clinics),25 which was published in 1941 by Istanbul University. This 277-page book was divided into 9 chapters and was a state-of-the-art text on kidney function and disease (Box 2; Fig 5).25

Contributions to Other Fields

Frank contributed to several fields in medicine other than nephrology, but most of his work centered in 4 areas.

Hematology

Some of Frank’s principal contributions in this field include the pathogenesis of aplastic anemia (1915), description of essential thrombocytopenia (1915), hypersplenism and the role of thrombocytes in anticoagulation (1915),30 and the first description of a potential factor deficiency in the pathogenesis of hemophilia (1927).31 After his move to Istanbul, Frank’s interest in hematology grew and he published several articles with his trainees on the prevalence of hematologic diseases in Turkey.

Diabetes

As a student and trainee in the department of Oskar Minkowski in Breslau, Frank had a long-standing and ongoing interest in diabetes. Over the years, he reported a micro-method for determining blood glucose levels, described a glucose tolerance test, and wrote an elegant article on the pathogenesis of diabetes mellitus.32 In addition, in 1925, he explored one of the very first oral biguanide antiabetes, Synthaline B,33,34 which did not gain wide acceptance because of its toxicity. He maintained this interest in diabetes after his move to Istanbul, focusing more on its dietary treatment. This accounts for his recruiting of Elsa Wolff and his concerted public health efforts in detecting, preventing, and treating diabetes in Turkey.

Endocrinology

Frank published several studies on the pathogenesis of diabetes insipidus. His 1912 report of a patient who developed polyuria after a gunshot wound to the head, in whom the bullet was located in the posterior pituitary, is considered the first clinical evidence of the role of the posterior pituitary in diabetes insipidus.9

Neurology

Frank was interested in the nervous system and published studies on muscular tone, the autonomic nervous system, and motor function.35,36

Before migrating to Turkey, Frank had published 43 articles, wrote a book on the autonomic nervous system in 1928, and contributed a book

Box 2. Table of contents of Frank’s textbook of nephrology “Medical Kidney Diseases Clinics” (Dahili Böbrek Hastalıkları Klinig˘i, 1941)25

2. Evaluation of kidney function. Concentrates on urea and creatinine clearance and their measurement.
3. Orthostatic proteinuria. Devoted to his long-standing interest in the subject.
5. Specific types of kidney disease. Includes renal changes in focal infections, bacterial endocarditis, and liver cirrhosis.
6. Nephrotic syndrome. Discusses cause, clinical manifestations, laboratory value abnormalities, and treatment of proteinuric nephropathies, including amyloidosis and pregnancy.
8. Uremia. Consists of 3 sections: renal ammonia production, chronic uremic syndrome, and acute uremia, in which a case of acute renal failure is reported.
chapter on hemorrhagic diatheses in 1925.37 After coming to Turkey, he authored 2 more books: one on nephrology (1941)25 and the other on carbohydrate metabolism (1949).38 He also published 38 original studies, 16 of which were co-authored with his trainees.

ERICH FRANK: THE TEACHER

During the 23 years that he worked in Turkey, Frank trained many young physicians and imbued them with the highest traditions of medicine and medical research. He lectured in German, which was translated simultaneously into Turkish by his residents. Over the years, he learned Turkish and communicated with his patients in Turkish, but continued to lecture in German or English. In his lectures, he described the clinical features of a disease, highlighting its pathophysiology and the rationale of its treatment.7 He taught at the bedside, expanding on and explaining the textbook description of a disease. During the lectures, his assistants took notes, which were collected, translated to Turkish, and published in 1951, 1952, and 1954 as 3 books titled Clinical Lessons in Internal Medicine by Prof. Dr. Erich Frank.39-41

Frank treated his last-year medical students as colleagues, giving them increasing responsibility in patient care in preparation for their entry into practice. After graduation, many of his students stayed on or returned for postgraduate training and research. Those who were unable to obtain a position at the university remained in close contact with Frank, who was always available to advise and collaborate with them in their studies. He followed their progress with interest and took pleasure in their achievements. He laid great emphasis on the formation of independent minds, encouraged the pursuit of research, and repeatedly emphasized that “a good educator should be

Figure 5. Illustration of (A) a nephron and (B) an osmometer from Erich Frank’s book, Dahili Böbrek Hastalıkları Kliniği (Medical Kidney Diseases Clinics), the first nephrology textbook in Turkish published in 1941.25 The Turkish text in parenthesis under the figure of the osmometers states, “Described in the section of nephrotic syndrome.” The 2 types of cellophane membrane osmometers shown were developed by August Krogh (1874-1949) and Paul Govaerts (1889-1960) to measure colloid osmotic pressure, which if low was considered diagnostic of nephrotic syndrome.
proud when the achievement of his students surpass his own work. He was addressed by all as Hocam, an endearing Turkish word meaning “My Master,” which implies deep respect and affection for a teacher.

The most eloquent testimony of Frank as a doctor was the love and reverence of his patients all over Turkey. To those who met him for the first time, he seemed rather aloof and awe inspiring, but all who knew him found him to be a delightful and easy companion who was a spirited conversationalist, with broad interests ranging from world politics to history, literature, the arts, and even sports. He was a friend of the young as well as the old and stimulated all who came in contact with him. He gave so much to everyone that his disciples felt utterly bereft when he passed away in 1957.

Frank was given a state funeral by the Turkish government. A first memorial service was held in Vakif Gureba Hospital, where he had worked. His coffin, covered by the Turkish flag, was carried by his colleagues, students, and patients to the Central University Building, some 5 km from the hospital, for another service. Along the way, people lining the streets were crying, praying, and applauding at the same time in appreciation of his many services. In accordance with his will, he was buried in Asıyan Asri Cemetery on the European coast of the Bosphorus in Istanbul. The epitaph on his tombstone, erected from donations of the Istanbul University Medical Faculty, reads “Rest in Peace Erich Frank. With the Gratitude and Thanks of Turkish Medicine” (Fig 6, left panel).

In 2007, the Turkish government issued a stamp commemorating the 50th anniversary of his death (Fig 6, right panel).

**CONCLUSION**

It is fair to conclude that Frank was instrumental in laying a solid foundation for several branches of Turkish medicine, including nephrology. As the author of the first textbook on kidney disease in Turkish and as the Hoca who taught and inspired several medical students of Istanbul University, some of whom went on to become the first generation of nephrologists in Turkey, clearly Frank was a pioneer in nephrology who helped launch the discipline in his adopted country.

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