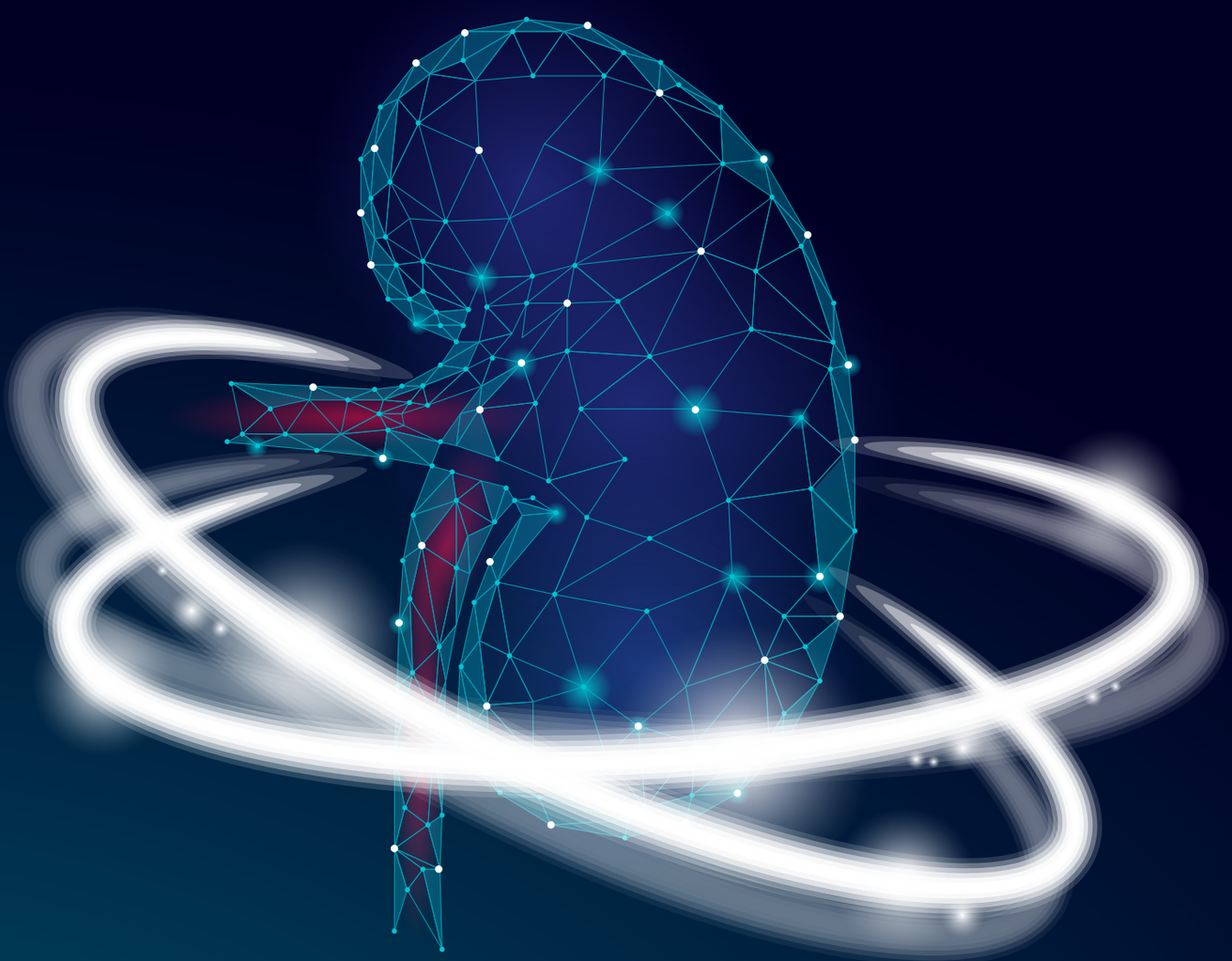
BREAKTHROUGH DISCOVERIES IN NEPHROLOGY



ISN
INTERNATIONAL SOCIETY OF NEPHROLOGY

In celebration of the 60th Anniversary of the ISN, the ISN Research Working Group (RWG), under the leadership of Chair, Adeera Levin, and Deputy Chair, Masaomi Nangaku, published a monthly series, “Breakthrough Discoveries.”

The series highlighted 60 + 1 historical discoveries of significant impact to the nephrology community. So that the selection of discoveries was globally representative, the leadership of the ten ISN Regional Boards were asked to provide references from their respective regions. Subsequently, Leon Fine, Pierre Ronco, and John Feehally were advisors, and the ISN RWG leadership and the ISN Executive Committee reviewed and voted for the final selection.

Every month in 2020, the ISN RWG, supported by the ISN Young Nephrologists Committee (YNC), highlighted and discussed five breakthrough discoveries. This series frames the year of celebratory activities and highlights ISN’s commitment to research, collaboration, and global community, as well as the achievements ISN has made through its members and supporters.

We want to thank the ISN Breakthrough Discoveries Narratives Contributors:

- *Abduzhappar Gaipov*
- *Caner Alperslan*
- *Daisuke Nakano*
- *Eishin Yaoita*
- *Enisa Mesic*
- *Fabian Braun*
- *Fumiaki Ando*
- *Georgina Irish*
- *Hirotaka Komaba*
- *Huang-Yu Yang*
- *HuiYi Shan*
- *Kate Robson*
- *Lani Shochet*
- *Lili Zhou*
- *Marco van Londen*
- *Mirna Aleckovic-Halilovic*
- *Mirha Pjanic*
- *Muzamil Hassan*
- *Nikolay Bulanov*
- *Rhys Evans*
- *Rolando Claure-Del Granado*
- *Sabine Karam*
- *Shankar Yadav*
- *Yosuke Hirakawa*

The ISN would like to particularly thank Masaomi Nangaku, ISN RWG Deputy Chair, on leading the publication of the monthly series, “Breakthrough Discoveries”, in collaboration with Yosuke Hirakawa, YNC member, to celebrate the 60th Anniversary of the ISN in 2020.

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JANUARY

FIRST MICROSCOPIC DESCRIPTION OF THE 'GLOMERULI'

By Sabine Karam MD
Saint George Hospital University Medical Center, Beirut, Lebanon

The Italian anatomist Marcello Malpighi (1628–1694), often referred to as the founder of microscopical anatomy, is credited for the first microscopic description of the glomeruli. He described them as dark, vascular structures resembling fruit suspended from a branch (… quae sanguineis vasis atro liquore turgidis in speciolae arbori formam productis, velut poma appenduntur). He demonstrated their continuity with the renal vasculature in 'De renibus,' a section of 'De Viscerum Structura Exercitatio Anatomica', originally published in Bologna, Italy, in 1666 and then in London, in 1669[1].

In 1782, Alexander Schlumlanski (1758-1795) described 'de Structura renum' in his dissertation as a connection between the circulation and the uriniferous tubules, deduced by experimenting on pig kidneys[2]. However, it was the surgeon and anatomist William Bowman (1816-1892) who elucidated the capillary architecture of the glomerulus and the continuity between its surrounding capsule and the proximal tubule in detail (see Discovery #3 by Lili Zhou). He presented his findings in the paper "On the Structure and Use of the Malpighian Bodies of the Kidney"[3]. Nonetheless, the term glomerulus would come into usage only a few years later in the mid-nineteenth century. It seems to be derived from the Latin word 'glomus', which means 'ball of thread'[4].

1 *M. M. De Viscerum Structura Exercitatio Anatomica. Londini: Typis T.R. Impensis Jo.Martyn;(London). MDCLXIX1669. p. 83–4.*
2 *A. S. Dissertatio inauguralis anatomica De Structura Renum MDCCLXXXII. : Argentorati (Strasbourg): Typis Lorenzii & Schuleri; 1782.*
3 *Todd Bentley R BW. The physiological anatomy and physiology of man. West Strand,London:John W Parker and sons. 1859;2:482-507.*
4 *Merriam Webster Dictionary. Glomerulus.*

IDENTIFICATION OF KIDNEY DISEASE

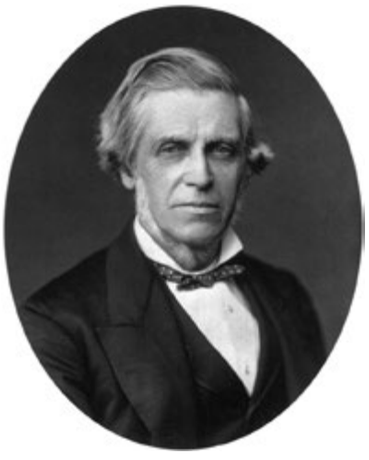
By Yosuke Hirakawa
Division of Nephrology and Endocrinology, the University of Tokyo Hospital, Japan

The symptoms of kidney disease are non-specific; therefore, diagnosis of kidney disease without laboratory testing is difficult. This was especially the case in the early 19th century. Surprisingly, the first identification of kidney disease was made by Richard Bright in 1827 before the identification of creatinine and routine measurement of urea. He extensively examined patients with proteinuria, anasarca, and uremia by checking urinary albumin and renal morbid anatomy in his work as a physician at Guy's Hospital in London[1,2]. Today, some of his cases would be diagnosed as having nephrotic syndrome caused by glomerulonephritis[3]. Identification of what became known as "Bright's disease" made a huge contribution to medicine. The most important aspect is the distinction Bright made between patients with kidney diseases and patients with cardiac diseases. After this differentiation, the characteristics of kidney disease patients started to be eagerly examined, and it was followed by increased urea and creatinine levels being identified shortly afterwards as major hallmarks of kidney disease.

1 *Boss J. Richard Bright's Reports of Medical Cases (1827): A sesquicentennial note. Bristol Med Chir J. 1978;93:5-6, 18.*
2 *Cameron JS. Bright's Disease Today: The Pathogenesis and Treatment of Glomerulonephritis – I. Br Med J. 1972;4:87-90.*
3 *Weller RO, Nester B. Histological reassessment of Three Kidneys Originally Described by Richard Bright in 1827-36. Br Med J. 1972 Jun 24;2:761-3.*

DESCRIPTION OF THE NEPHRON

By Lili Zhou
Division of Nephrology, Nanfang Hospital, Southern Medical University, China



The kidney is the most important organ in the human body to excrete urine and maintain the balance of water and electrolytes. These processes take place through the subtle mechanisms of the nephron, a tiny unit of workforce within the kidney. In 1842, after two years of exploration, Dr. William Bowman, a famous English surgeon and anatomist, discovered the nephron's true nature. Through repeated injections from the arteries, tubes, and veins in multiple species' kidneys, he found the real structure of the Malpighian bodies, as well as their connecting tubes and circulation. The Malpighian bodies, called glomerulus today, originate and gradually subdivide from the afferent artery terminal twigs to become two rounded capillary vessels tufts. These vessels ultimately converge to become one efferent channel (smaller in size than the afferent) to enter the capillary plexus surrounding the uriniferous tubes (proximal convoluted tubules, loop of Henle, and distal convoluted tubules). The interconnected capillary plexus surrounding the tubes serves as the portal system in contact with the tubes' basement membrane to renal veins. The tubes are the extension of Malpighian bodies' capsules (Bowman's capsule) and expand tortuously near the Malpighian bodies but straighten when proceeding toward the excretory channel (collecting duct). All these features retard blood flow and delay the excretion of nutrients into urine to maintain the balance of water, sugar, and electrolyte assimilation and excretion. This revolutionary discovery opened a new era in physiological and pathological research in kidneys[1].

1 *W. Bowman. On the Structure and Use of the Malpighian Bodies of the Kidney, with Observations on the Circulation through That Gland. Philosophical Transactions of the Royal Society of London Vol. 132 (1842), pp. 57-80.*

DESCRIPTION OF THE URINARY SEDIMENT AS A TOOL FOR THE DIAGNOSIS OF NEPHROPATHIES

By Rolando Claure
Universidad Mayor de San Simon School of Medicine, Cochabamba, Bolivia

Urinary sediment has been used as a diagnostic tool since the 17th century[1]and Pierre Rayer occupies a special place in the history of nephrology for his attempt to classify various diseases using this important diagnostic tool. Alongside his intern, Eugene Napoleon Vigla, Rayer revolutionized the study of kidney diseases by using microscopy to analyze urinary sediments, describing crystals, cells, casts, and yeasts[2,3].

At the Hôpital de la Charité, a microscope became available in 1835 and Rayer promptly set up a program to investigate urinary sediment findings in various forms of kidney diseases. His proposed classification was based on clinical findings, urinary microscopy, and gross specimens whenever possible. Renal diseases were divided into acute nephritis with many red blood cells and too much albumin in the urine, and chronic albuminuric nephritis corresponding to what is now known as nephrotic syndrome. There was also mention of suppurative forms of nephritis, with pus cells in the urine, the result of either blood-borne or ascending infection of the kidneys[4].

After this first description, routine chemical analysis of urine and microscopic examination of the sediment were introduced during the first half of the 19th century. After a first wave of interest, the use of urinary sediment has progressively decreased[5]; urinary microscopy analysis is now performed mostly in central laboratories and is infrequently performed by nephrologists who have lost the expertise to identify some types of casts and/or cells in order to perform clinical correlations[6]. Nephrologists should reclaim this noninvasive test, since combining it with a comprehensive clinical evaluation and new biomarkers would provide new insights into renal diseases[7].

1 *Armstrong JA. Urinalysis in Western culture: a brief history. Kidney Int. 2007;71(5):384-7.*
2 *Fogazzi GB, Cameron JS. The introduction of urine microscopy into clinical practice. Nephrol Dial Transplant. 1995;10(3):410-3.*
3 *Fogazzi GB, Cameron JS. Urinary microscopy from the seventeenth century to the present day. Kidney Int. 1996;50(3):1058-68.*
4 *Richet G. From Bright's disease to modern nephrology: Pierre Rayer's innovative method of clinical investigation. Kidney Int. 1991;39(4):787-92.*
5 *Eknoyan G. Looking at the urine: the renaissance of an unbroken tradition. Am J Kidney Dis. 2007;49(6):865-72.*
6 *Fogazzi GB, Garigali G. The clinical art and science of urine microscopy. Curr Opin Nephrol Hypertens. 2003;12(6):625-32.*
7 *Claure-Del Granado R, Macedo E, Mehta RL. Urine microscopy in acute kidney injury: time for a change. Am J Kidney Dis. 2011;57(5):657-60.*

ROUTINE MEASUREMENT OF UREA AND CREATININE IN CLINICAL PRACTICE

By Yosuke Hirakawa
Division of Nephrology and Endocrinology, the University of Tokyo Hospital, Japan

Routine measurement of urea and creatinine, sensitive indicators of renal function, forms the present-day basis of clinical nephrology. Around 1850, two important events related to measurement of urea and creatinine occurred.

The word “creatinine” was probably first used by Justus von Liebig in 1847[1,2]. He found the ingredient creatinine in beef tea. Beef tea was a traditional English remedy, made using only beef and salt, not tea leaves. It had previously been known that creatine, the precursor of creatinine, was abundant in animal muscle. Liebig, who established the Justus von Liebig’s Extract of Meat Company, found that the addition of hydrochloric acid to creatine resulted in the production of creatinine. Around this time, creatinine was not used as an indicator of renal function; researchers focused on urea as an indicator of renal function, with Joseph Picard having established the reproducible and sensitive method of urea measurement in 1856. He later found that urea concentration in the renal vein fell from that in the renal artery[3]. Around the same time, toxic mechanism came to be accepted as the etiology of uremic syndrome; therefore, the establishment of the urea measurement technique and the discovery of the urea fall in the renal vein led to the concept that urea was the causative substance of uremic syndrome. However, a brave study of urea loading in human patients performed in 1972 revealed that urea itself is not a uremic toxin[4].

1 *Pierre Delanaye (2012). “Serum Creatinine: An Old and Modern Marker of Renal Function” in Pierre Delanaye (ed.) Nephrology and Clinical Chemistry: The Essential Link pp9-20.*
2 *Kramer H, Rosas SE, Matsushita K. Beef Tea, Vitality, Creatinine, and the Estimated GFR. Am J Kidney Dis. 2016;67:169-72.*
3 *Gabriel Richet. Early history of uremia. Kidney Int 1988;33:1013-5*
4 *Johnson WJ, Hagge WW, Wagoner RD, Dinapoli RP, Rosevear JW. Effects of urea loading in patients with far-advanced renal failure. Mayo Clin Proc 1972;47:21-29*

FEBRUARY

DISCOVERY OF THE NEPHRON LOOP

By Yosuke Hirakawa
Division of Nephrology and Endocrinology, the University of Tokyo Hospital, Japan

In 1862, anatomist Jacob Henle presented the existence of nephron loops, widely known today as the loop of Henle[1]. He provided a morphological description; the importance of electrolyte reabsorption had not yet been determined and the existence of tubular reabsorption was only proved in the 1920s by Alfred Newton Richards. Henle is famous for his description of epithelial tissue: large sheets of cells free from blood vessels, blood components, and nerve endings. Henle described first epithelial tissue in the digestive tract followed by glandular and tubular organs, including the kidney[2]. In renal medulla, Henle found two tubular subtypes: one type was a papillary collecting duct with a diameter of 0.05-0.06 mm; the other type had a much smaller diameter of approximately 0.02-0.03 mm, running parallel to the collecting ducts but returning in a narrow hairpin curve toward the surface. The latter is the well-known loop of Henle. As an anatomist, Henle examined other epithelial tissues also: Henle's gland in the eyelids and Henle's layer in the hair follicle[3].

1 *Morel F. The loop of Henle, a turning-point in the history of kidney physiology. Nephrol Dial Transplant. 1999;14:2510-5*
2 *Kinne-Saffran E, Kinne RK. Jacob Henle: the kidney and beyond. Am J Nephrol. 1994;14:355-60.*
3 *Weyers W. Jacob Henle–a pioneer of dermatopathology. Am J Dermatopathol. 2009;31:6-12*

MICROPUNCTURE TECHNIQUE

By Yosuke Hirakawa
Division of Nephrology and Endocrinology, the University of Tokyo Hospital, Japan

It is now common knowledge that urine is produced by glomerular filtrate and tubular reabsorption of substances such as electrolytes and glucose. This phenomenon was initially understood by Alfred Newton Richards and his colleagues in the 1920s. At that time, many researchers had tried to observe glomerular circulation but did not have the capacity or methods to do so. Richards was the pioneer who decided to observe frog kidneys, which are thin and flat[1]. He investigated the effect of adrenaline on glomerular circulation with a micropipette introduced into glomerular space with the help of a micromanipulator. In the process, he obtained enough glomerular fluid for quantitative tests. He found that glomerular filtrate contained both chloride and sugar, detectable in blood but undetectable in bladder urine, leading to the conclusion that there must be 2 different processes: glomerular filtration and tubular reabsorption respectively. This description is thought to be one of the most important contributions in our understanding of renal physiology[2] on which subsequent understandings of glomerular filtration rate (GFR) and solute transport have been built. Richards' achievements are widely known and the ISN ensures that his outstanding and fundamental contribution to basic research is honored through the Alfred Newton Richards Award for basic science.

1 *Schmidt CF. Alfred Newton Richards 1876-1966. Ann Intern Med. 1969: Suppl 8:15-27.*
2 *Sands JM. Micropuncture: unlocking the secrets of renal function. Am J Physiol Renal Physiol. 2004; 287:F866-7.*

DEMONSTRATION OF RENAL PHYSIOLOGY

By Sabine Karam MD
Saint George Hospital University Medical Center, Beirut, Lebanon

Homer W. Smith (1895-1962), physiologist and medical writer, was a pioneer in renal physiology. He recognized the clinical importance of renal clearance methods, a concept initially introduced by Donald Van Slyke in 1928[1]. He introduced them as a tool for the precise measurement of renal function in medical practice and elaborated on the concepts of glomerular filtration, effective renal plasma flow, and intrarenal resistance[2]. Smith also played an essential role in elucidating tubular transport capacity, the reabsorption and secretion of various substances such as urea and creatinine, as well as providing novel insights into the mechanisms of the excretion of water and electrolytes[3]. Finally, he was instrumental in setting the perfect example of collaboration between basic scientists and clinicians, a model which has since been followed worldwide[2]. Dr. Smith's studies of the kidney culminated in 1951 with the authoritative summary, "The Kidney, Structure and Function in Health and Disease". He also had a remarkable career in philosophy and literature, as illustrated by the reflective essay, "From Fish to Philosopher," describing the evolutionary role of the kidney in enabling survival in both water and on land[4]. Today, his legacy endures through the Homer W. Smith annual award in renal physiology established by the American Society of Nephrology in 1964.

1 *SE B. Clearance concept in renal physiology. In: GOTrSCHALK CW BR, GIEBISCH GH, editor. Renal Physiology, People and Ideas. Bethesda: American Physiological society; 1987.*
2 *Baldwin DS, Neugarten J. Homer Smith: his contribution to the practice of nephrology. J Am Soc Nephrol. 1995;5(12):1993-9.*
3 *Giebisch G. Homer W. Smith's contribution to renal physiology. J Nephrol. 2004;17(1):159-65.*
4 *Fishman AP. Homer W. SMITH (1895-1962). Circulation. 1962;26:984-5.*

DESCRIPTION OF ACUTE RENAL FAILURE WITH CRUSH SYNDROME

By Mirna Aleckovic-Halilovic and Enisa Mesic
Clinic for Internal Diseases, Department of Nephrology, Dialysis and Renal Transplantation, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

In 1941, during the London Blitz, E.G. Bywaters and D. Beall described four victims of trauma-related crush syndrome, with limb edema and shock, who showed oliguria and brownish urine. All four patients died in about a week with nitrogen retention, and necropsy revealed pigment casts, polymorphonuclear invasion, and acute tubular necrosis in the kidney[1].

In 1943, using animal models, E.G. Bywaters & J.K. Stead identified myoglobin as the offending agent and formulated the first treatment plan[2]. It was later understood that crush syndrome is a systemic response to traumatic rhabdomyolysis and that acute kidney injury is one of its severest complications.

It was only after 25 000 people died in an Armenian Earthquake in 1988 that this entity got the attention it deserved through the establishment of ISN's Renal Disaster Relief Task Force and its recommendations for the management of crush victims in mass disasters[3]. Furthermore, this was the origin of the term 'disaster nephrology'[4,5].

This condition, first recognized as a single broad pathophysiologic entity in 1941, remains pertinent in the current era: The number of victims from natural and man-made disasters is growing, and crush syndrome is the second most common cause of death, after asphyxia, caused by these disasters[6]. Moreover, despite being rescued alive from the rubble. many crush victims die afterward due to the lack of access to dialysis.

1 *Bywaters EG and Beall D. Crush Injuries with Impairment of Renal Function. Br Med J. 1941 Mar 22;1(4185):427-32.*
2 *Bywaters EGL, Stead JK, The production of renal failure following injection of solutions containing myohaemoglobin. QJ Exp Physiol 1944;33:53*
3 *Sever MS, Vanholder R and the Workgroup. Recommendations for the management of crush victims in mass disasters. Nephrol Dial Transplant 2012; 27(Suppl 1): i1–67*
4 *Vanholder R, Sever MS, Erek E et al. Acute renal failure related to the crush syndrome: towards an era of seismo-nephrology? Nephrol Dial Transplant 2000; 15: 1517–1521*
5 *Gibney RT, Sever MS, Vanholder RC. Disaster nephrology: crush injury and beyond. Kidney Int 2014; 85: 1049–1057)*
6 *Ukai T. The Great Hanshin-Awaji Earthquake and the problems with emergency medical care. Ren Fail 1997; 19:633–645*

Since randomized control trials during mass disasters are unfeasible, the treatment recommendations in the guidelines[1] are based on observational data accrued from case reports and case series written by physicians in the field using physiological principles to treat these victims.

In honor of the achievements of Bywaters, the ISN established the Bywaters Award in 1991 to recognize outstanding contributions to the understanding and treatment of Acute Kidney Injury.

1 *Sever MS, Vanholder R and the Workgroup. Recommendations for the management of crush victims in mass disasters. Nephrol Dial Transplant 2012; 27(Suppl 1): i1–67*

LABORATORY METHODS FOR CLINICAL APPLICATION TO TREAT KIDNEY DISEASE

By Nikolay Bulanov
Sechenov First Moscow State Medical University, Russia

In 1886, Max Jaffe (1841 – 1911), a German physician and chemist, observed that creatinine produced an intensive red color in alkaline picrate solution and detected needle-formed crystals under the microscope which he reported in his landmark paper[1].

However, the quantitative analytical method used to assess creatinine concentration was developed in the first decade of the twentieth century by an outstanding Swedish-born American biochemist Otto Folin (1867 – 1934), who called it the "Jaffe method"[2]. Even over a century after its introduction into clinical practice, this procedure is still widely used to measure creatinine levels due to its simplicity and low-cost. However, several organic compounds called pseudochromogens (e.g. acetone, glucose) that were first recognized by Jaffe can also react with alkaline picrate and lead to an analytical bias.

In 1957, Alfred Free (1913 – 2000) and his co-authors working at the Ames Corporation published a paper describing a new colorimetric test for urinary protein[3]. The first dipstick was a yellow paper strip, impregnated with a citrate buffer and tetrabromphenol blue, which turns green in the presence of protein. Free et al tested their new method obtaining approximately 5000 turbid urine samples from patients and healthy subjects and demonstrated its adequate sensitivity and specificity. Today, urinary dipstick test is one of the most common screening techniques for early detection of kidney diseases.

In 1945, Bowling Barnes, David Richardson, John Berry, and Robert Hood introduced flame photometer to measure the low concentration of sodium and potassium in a solution[4]. Flame photometer measures the intensity of emitted light when a metal is introduced into the flame, giving information about the amount of the element present in the sample. This technology allows for cheap and simple measurements of electrolytes in serum and urine.

1 *Jaffe M. Ueber den Niederschlag welchen Pikrinsäure in normalen Harn erzeugt und über eine neue reaction des Kreatinins. Z Physiol Chem. 1886;10:391–400.*
2 *Shaffer PA. Otto Folin 1867-1934. Washington, DC: National academy of sciences;1952:47–82*
3 *Free AH, Rupe CO, Metzler I. Studies with a new colorimetric test for proteinuria. Clin Chem. 1957;3:716–727.*
4 *Barnes RB, Richardson D, Berry JW, Hood RL. Flame photometry; A rapid analytical procedure. Ind Eng Chem Anal Ed. 1945;17:605-11.*

MARCH

VOLHARD & FAHR'S BOOK

By Yosuke Hirakawa
Division of Nephrology and Endocrinology, the University of Tokyo Hospital, Japan

In 1914, Franz Volhard, a clinician, and Theodor Fahr, a pathologist, published the textbook, Die Brightsche Nierenkrankheit. Klinik, Pathologie und Atlas (Bright's disease. Clinical aspects, Pathology and illustrations)[1,2]. This is one of the most important textbooks because for the first time several pathological entities were described. 'Bright's disease' was categorized into nephrosis (nephrotic syndrome), nephritis, and arteriosclerotic renal disease; now recognized as focal segmental glomerulonephritis, crescentic glomerulonephritis, and membranoproliferative glomerulonephritis[3]. The original classification described by Volhard and Fahr formed the basis of current renal pathology constructs. This specific textbook is also notable as one of the last to be hand-illustrated in color. The beautiful drawings can be seen in the Nephrol Dial Transplant article from 1998.

1 *Fogazzi GB, Ritz E. Novel classification of glomerulonephritis in the monograph of Franz Volhard and Theodor Fahr. Nephrol Dial Transplant. 1998;13:2965-7.*
2 *Luft FC, Dietz R. Franz Volhard in historical perspective. Hypertension. 1993;22:253-6.*
3 *J Stewart Cameron. "Glomerular Disease – Before 1950" in John Feehally, Christopher McIntyre, J. Stewart Cameron (ed.). Landmark Papers in Nephrology (English Edition) 1st Edition. pp102-3.*

PERCUTAENOUS KIDNEY BIOPSY

By Caner Alparslan
Diyarbakır Gazi Yaşargil Training and Research Hospital, Turkey

The use of percutaneous kidney biopsy technique has become one of the most important tools in nephrology practice. In conjunction with the introduction of immunofluorescence and electron microscopy, the technique of percutaneous kidney biopsy has contributed to an improved understanding of kidney diseases. Nill Alwall performed the first percutaneous kidney biopsy in 1944. One year later, he presented preliminary results in Lund, Sweden. However, he stopped performing percutaneous kidney biopsies after one patient developed a hemorrhagic complication[1,2]. Nonetheless, Antonio Perez-ara in Cuba (in 1948), and Paul Iverson and Claus Brun in Copenhagen (in 1949), unaware of each other's work[3,4], began to perform percutaneous kidney biopsies. A liver biopsy aspiration needle was used by Iverson and Brun, whereas Perez-ara used a Vim-Silverman needle to perform the procedure. In following years, Robert M. Kark and Robert C. Muehrcke further developed the prone position percutaneous kidney biopsy technique which was subsequently adopted by many countries[5]. In children, the first documented attempts were made in 1955 in Cuba and 1957 in Europe[1].

Localizing the kidney is an important component of obtaining a sample(s) and, in part, reducing biopsy related complications. Until 1961, fluoroscopy and intravenous pyelography were used to localize the kidney. G.M. Berlyne suggested the use of ultrasound to localize kidneys, which subsequently became the standard in percutaneous kidney biopsy technique[1].

Today, with advances in technology and tools, disposable automatic biopsy needles and higher resolution in imaging aid in the performance of safe and useful percutaneous kidney biopsies to yield tissue samples. This tissue remains the ultimate tool to aid in diagnosis, management, and identification of new therapeutic targets in both pediatric and adult nephrology practice.

1 *Cameron JS, Hicks J. The introduction of renal biopsy into nephrology from 1901 to 1961: a paradigm of the forming of nephrology by technology. Am J Nephrol 1997;17:347-358.*
2 *Alwall N. Aspiration biopsy of the kidney, including report of a case of amyloidosis diagnosed in 1944 and investigated autopsy. Acta Med Scand 1952;143:430-435.*
3 *Iversen P, Brun C. Aspiration biopsy of the kidney. Am J Med 1951;11:324-330.*
4 *Perez-Ara A. La biopsia-punctural del rinon no megalico-consideraciones generales y aportacion de un nuevo metodo. Bol Liga Cubana Contra Cancer 1950;25:121-147.*
5 *Muehrcke RC, Kark RM, Pirani CL. Biopsy of the kidney in the diagnosis and management of renal disease. NEJM 1955;253:537-546.*

APPLICATION OF IMMUNE FLUORESCENCE TECHNIQUE TO KIDNEY BIOPSY – MELLORS 1950s

By Shankar Prasad Yadav
Department Of Pediatrics, B.P.Koirala Institute Of Health Sciences, Dharan, Nepal

The use of immunofluorescence techniques to detect specific tissue antigens using fluorescein-labeled antibody was first described in the 1940s by Albert Hewett Coons and colleagues. The antibody, coupled with fluorescein (immunochemical reagent), reacts with tissue containing antigen and produces a light emission visible through a fluorescence microscope. Coons used fluorescein to detect pneumococcal antigen in Aschoff nodules, a pathognomonic marker of rheumatic fever[1,2].

It was not until the 1950s, however, that the use of this principle in kidney biopsy was demonstrated by R.C. Mellors. The technique was modified to localize the antibody in kidney tissue. In this landmark study[3], fifteen healthy rabbits were injected with bovine gamma globulin, while four rabbits were used as a control group: this led to the description of different patterns of acute glomerulonephritis among twelve of the experimental animals. In the second part of the experiment, antibody was prepared from the globulin fraction of chicken anti-serum and rat immunoglobulin, which was coupled with fluorescence thiocyanate to generate fluorochrome reagent. The application of this reagent to kidney tissue, with subsequent fluorescent microscopy, demonstrated that there was increased intensity of immunofluorescence in the glomerulus of affected rabbits in comparison to tubules, or unaffected, or control group. These findings helped to conceptualize the antigen-antibody reaction as central in the pathogenesis of human glomerulonephritis.

Current use of immunofluorescence in diagnosing glomerulonephritis including IgA nephropathy, C3 glomerulonephritis, lupus nephritis, or detection of C4d in humoral anti-graft reactions are based on the fundamental principles elucidated by Mellors more than 60 years ago.

1 *Coons AH, Creech H J & Jones R N. Immunological properties of an antibody containing a fluorescent group. Soc. Expt. Biol. Med.47, 200–202 (1941).*

2 *Coons AH., Creech HJ., Jones RN. & Berliner E. The demonstration of pneumococcal antigen in tissues by the use of fluorescent antibody. Immunol.45, 159–170 (1942).*

3 *Mellors RC, Arias-Stella J, Siegei M, & Pressman D. Analytic Pathology II. Histopathologic demonstration of glomerular·localizing antibodies in experimental glomerulonephritis. Am. J. Path., In Press, 1955.*

APPLICATION OF ELECTRON MICROSCOPY TO ANALYZE ULTRASTRUCTURAL CHANGES OF THE KIDNEY

By Nikolay Bulanov
Sechenov First Moscow State Medical University, Russia

In 1957, American scientists Marilyn Farquhar, Robert Vernier, and Robert Good published the first paper describing the implications of a new technique of electron microscopy to study glomerular pathology[1]. They explored ultrastructural changes in the glomeruli of sixteen patients with 'nephrosis', seven patients with glomerulonephritis, and three patients with systemic lupus erythematosus. Electron microscopy revealed the effacement of podocyte foot processes in 'nephrosis,' and the glomerular basement membrane thickening in glomerulonephritis and lupus nephritis. Since then, electron microscopy is widely employed in clinical practice and has contributed to the discovery of several renal diseases, e.g. fibrillary glomerulonephritis. Today, electron microscopy is considered essential for definite diagnosis of glomerular diseases associated with mutations in type IV collagen genes, minimal change disease, and renal lesions associated with monoclonal gammopathy, etc. This technique reveals changes in cell structure, glomerular basement membrane, and localization of immune deposits that can't be visualized by light microscopy or immunofluorescence microscopy. However, electron microscopy requires special processing of tissue samples and is therefore relatively expensive, time-consuming, and not universally available in some countries.

1 *Farquhar MG, Vernier RL, Good RA. An electron microscope study of the glomerulus in nephrosis, glomerulonephritis, and lupus erythematosus. J Exp Med. 1957;106(5):649–660.*

STRUCTURE-FUNCTION CORRELATION IN THE GLOMERULUS

By Lili Zhou
Division of Nephrology, Nanfang Hospital, Southern Medical University, China

Glomerular capillary tufts are responsible for filtration. However, the structure and function of the different cell types within the glomerular capillary tufts were not well described until 1987. Described endothelial cells (ECs), as highly attenuated and fenestrated cells, could not be demonstrated to modulate blood flow. In 1987, Dr. Kriz Wilhelm discovered that mesangial cells (MCs) are important components that influence filtration dynamics. Filled with microtubules and intermediate filaments, these stellate-like MCs could contract and easily regulate the area size of mesangium. They also protrude tongue-like cell processes that extend to the mesangial angle (i.e. the sites where glomerular basement membrane (GBM) deviates from its pericapillary course and covers the mesangium). These processes can change the width of the GBM channel to permit the constriction and relaxation of capillaries and then modulate the intraglomerular blood flow and filtration. In addition to mesangial cells, he described podocytes, which sit outside the GBM. In 1995, Wilhelm summarized the podocyte structure-function relationships and those of other cell types. Through his work, a variety of cell types (MC, EC, podocytes) were described, and their structural relationship to the slit diaphragms and GBM with functional implications in the perfusion and filtration functions of the kidneys were subsequently elucidated[1,2,3,4].

1 *Sakai T, Kriz W. The structural relationship between mesangial cells and basement membrane of the renal glomerulus. Anat Embryol (Berl) 176 (3), 373-86. 1987.*
2 *Mundel P, Kriz W. Structure and function of podocytes: an update. Anat Embryol (Berl) 192 (5), 385-97. Nov 1995.*
3 *Kriz W. Maintenance and breakdown of glomerular tuft architecture. J Am Soc Nephrol 29 (4), 1075-1077. Apr 2018.*
4 *Kriz W. The inability of podocytes to proliferate: cause consequences and origin. Anat Rec (Hoboken) 2019 Oct 12*

APRIL

UNDERSTANDING OF ACID EXCRETION IN KIDNEY DISEASE

By Mirna Aleckovic-Halilovic and Enisa Mesic
Clinic for Internal Diseases, Department of Nephrology, Dialysis and Renal Transplantation, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

Fully understanding renal aspects of acid-base regulation has always been a challenge. A landmark paper that paved the way to current knowledge on acid excretion in different renal diseases and became a citation classic in 1979 was written by Oliver Wrong and H.E.F. Davies and published in 1959[1].

At the time, knowledge on acid excretion variation in different renal diseases was limited and there was a clear need for the development of a clinically useful test to detect impairment of kidney acid elimination. The authors devised a test, still widely used today, using ammonium chloride as an external acidification stimulus. They tested 10 subjects with normal renal function and 58 patients with different renal conditions. The cut-off point of pH 5.3 became the accepted criterion for defining a defect in renal acid excretion.

Contrary to accepted belief, they found that renal ability to acidify urine was not impaired in subjects with renal failure, and that systemic acidosis was, in fact, the result of greatly reduced excretion of ammonium and, to a lesser extent, reduced excretion of buffer and therefore reduced excretion of titratable acid, all due to reduced renal mass and nephron number.

On the other hand, they found that renal ability to acidify urine in renal tubular acidosis (RTA) was greatly impaired, and although buffer excretion was reduced, reflecting the reduced hydrogen ion secretion, urinary ammonium excretion was relatively well-preserved; this gave an explanation as to why many patients with RTA were not acidotic and had what the authors named “incomplete RTA”.

The authors further recognized that the form of RTA associated with features of renal Fanconi syndrome was different from the classical form, known today as distal RTA, and suggested an abnormality of proximal nephron function[2].

This first major work by Oliver Wrong[3], as well as his very last paper[4], was on RTA, a clinical disorder he returned to throughout his life. He was rightly named a ‘salt and water’ physician and a prize for innovative research in nephrology at the University College of London is named in his honor.

1 *Wrong O, Davies HE. The excretion of acid in renal disease. Q J Med. 1959;28(110):259-313.*
2 *Unwin, RJ (2012). “Back to the future: renal tubular acidosis then and now”. QJM. 105 (9): 915–916. doi:10.1093/qjmed/hcs134. PMID 22855286.*
3 *Wrong O, Davies HE. The excretion of acid in renal disease. Q J Med. 1959;28(110):259-313.*
4 *Khositseth S, Bruce LJ, Walsh SB, Bawazir WM, Ogle GD, Unwin RJ, et al. Tropical distal renal tubular acidosis: clinical and epidemiological studies in 78 patients. Q J Med 2012;105:861–77.*

PERFUSION OF ISOLATED TUBULES

By Nikolay Bulanov
Sechenov First Moscow State Medical University, Russia

Investigation of renal physiology is impossible without studying the function of different parts of the nephron. The first experiments on isolated tubules were described in 1924 by Wearn et al. who performed renal tubule micropuncture in vivo[1]. However, this technique was complicated and only able to assess surface tubule segments. In the 1950s, Maurice B. Burg began to consider the possibility of perfusing single renal tubules in vitro. After several years of hard work in the Laboratory of Kidney and Electrolyte Metabolism, Burg et al. published a paper describing the dissection of different tubule segments in single rabbit nephrons and their electrolyte and water composition[2]. They demonstrated that proximal tubules maintained transcellular gradients for sodium, potassium, and chloride ions. To assess transcellular transport, the authors measured the volume and composition of the effluent perfusion fluid. Decades later, Maurice Burg recalled that this experiment required considerable time, collaboration, and effort, including the development of special concentric perfusing micropipettes, and the application of a wide range of microdissection and analytical techniques[3]. This study contributed to a better understanding of cellular structure and function of both normal and diseased kidneys.

1 *Wearn JT, Richards AN. Observations on the composition of glomerular urine with particular reference to the problem of reabsorption in the renal tubules. Am J Physiol. 1924; 71:209–227.*

2 *Burg M, Grantham J, Abramow M, Orloff J. Preparation and study of fragments of single rabbit nephrons. Am J Physiol. 1966; 210:1293–1298.*

3 *Burg M. Introduction: Background and development of microperfusion technique. Kidney Int. 1982; 22:417–424.*

UNDERSTANDING OF NEPHRON MEMBRANE TRANSPORT SYSTEMS BY MEANS OF ISOLATED MEMBRANES AND CELLS

By Sabine Karam MD
Saint George Hospital University Medical Center, Beirut, Lebanon

Rolf Kinne from the Max Planck Institute of Molecular Physiology and Heini Murer from the University of Zurich made significant contributions to the understanding of transport mechanisms in human epithelial cells and, most notably, in the proximal tubular cells. They used the membrane-molecular approach[1,2] to isolate intestinal and renal brush-border-membrane vesicles in order to study their transport properties in vitro. Intestinal and renal brush-border membranes were found to contain an Na/H antiport system that catalyzes an electroneutral exchange of Na+ against protons and can subsequently produce a proton gradient in the presence of a concentration difference for Na+. They concluded that there was an active proton secretion in the small intestine and the proximal tubule of the kidney[3]. This technique allowed to localize transport elements situated in the two opposite sides of the cell (luminal and basolateral); and to characterize the driving forces, molecular properties, and regulatory influence of these transport elements. They summarized their findings in a seminal paper published in 1980[4].

1 *Kinne R, Schwartz IL. Isolated membrane vesicles in the evaluation of the nature, localization, and regulation of renal transport processes. Kidney Int. 1978;14(6):547-56. Epub 1978/12/01. doi: 10.1038/ki.1978.163. PubMed PMID: 219287.*

2 *Kinne R. Membrane-Cellular aspects of tubular transport. In: K.Thureau, editor. MTP International Review of Sciences Kidney and Urinary Tract Physiology, Vol11. London: Butterworths, Baltimore: University Park Press; 1976. p. 169-210.*

3 *Murer H, Hopfer U, Kinne R. Sodium/proton antiport in brush-border-membrane vesicles isolated from rat small intestine and kidney. Biochem J. 1976;154(3):597-604. Epub 1976/03/15. PubMed PMID: 942389; PubMed Central PMCID: PMCPMC1172760.*

4 *Murer H, Kinne R. The use of isolated membrane vesicles to study epithelial transport processes. J Membr Biol. 1980;55(2):81-95. Epub 1980/07/15. doi: 10.1007/bf01871151. PubMed PMID: 6997489.*

COUNTERCURRENT MULTIPLICATION SYSTEM WITHOUT ACTIVE TRANSPORT

By Rolando Claure-Del Granado
Universidad Mayor de San Simon School of Medicine, Cochabamba, Bolivia

Total body water content is largely determined by the total amount of salt in the body, and the kidneys ultimately control the salt and water concentration. Despite wide fluctuations in the intake of salt and water, the renal mechanisms maintain the serum sodium chloride concentration within a very narrow range. The kidneys can perform this critically important regulatory role by virtue of being the target organ of various stimuli regulating salt and water homeostasis. Our understanding of the mechanisms by which the kidney can generate both dilute and concentrated urine was made possible by a description of how the operation of the countercurrent multiplication system works.

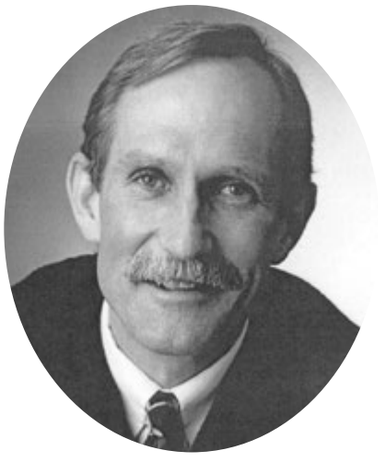
Wirtz et al. initially developed the general architecture of the renal countercurrent multiplication system in 1951[1]. Since that initial description, several alternate models of countercurrent multiplication systems were proposed; however, most of these models were advanced by theoretic arguments without experimental basis.

In 1972, Kokko and Rector[2] proposed a completely new model of the countercurrent multiplication system. The fundamental difference between this and previous models was that the new model removed the necessity of postulating active transport processes in the thin ascending limb. This model was therefore consistent with experimental results and satisfied the mathematical formulations simultaneously developed by Stephenson[3]. The model developed by Kokko and Rector stressed the importance of urea recirculation and allowed for an understanding of the pathophysiology behind many of the clinical states associated with a deranged balance of sodium and water.

1 *Kokko JP. The role of the renal concentrating mechanisms in the regulation of serum sodium concentration. Am J Med. 1977;62(2):165-9.*
2 *Kokko JP, Rector FC, Jr. Countercurrent multiplication system without active transport in inner medulla. Kidney Int. 1972;2(4):214-23.*
3 *Stephenson JL. Concentration of urine in a central core model of the renal counterflow system. Kidney Int. 1972;2(2):85-94.*

IDENTIFICATION OF MOLECULES

By Fumiaki Ando
Tokyo Medical and Dental University, Tokyo, Japan



Water and sodium homeostasis are closely interrelated and precisely regulated by the kidneys. The disruption of homeostatic balance is a common problem encountered in clinical practice. Water channels and amiloride-sensitive epithelial Na+ channel (ENaC) are representative molecules to determine body fluid-electrolyte parameters in blood and urine.

The first water channel, aquaporin-1 (AQP1), was identified as a 28-kDa membrane protein (CHIP28) in erythrocytes by Peter Agre and coworkers[1]. Agre was awarded the 2003 Nobel Prize in Chemistry for this discovery. AQP1 is a constitutively open water channel present at the luminal membrane of the proximal tubule cells and the descending thin limbs of the loop of Henle in the kidney. AQP2 is another important aquaporin localized in the renal collecting ducts (CD) that is critical in regulating urine volume[2]. In contrast to AQP1, AQP2 is dynamically regulated and is translocated from intracellular vesicles to the apical plasma membrane in response to dehydration leading to water reabsorption from urine via the luminal AQP2. Loss-of-function mutations in the AQP2 cause congenital nephrogenic diabetes insipidus.

ENaC is a plasma membrane protein localized primarily in the renal CD that plays a fundamental role in sodium reabsorption and regulates body sodium content and blood pressure. Canessa et al. found the first ENaC subunit (α), cloned from the colon of salt-deprived rats, in 1993[3]. Two other subunits (β and γ) were identified by functional complementation of the α subunit[4]. Liddle syndrome is caused by gain-of-function mutations in the ENaC that induce impairment of its degradation by the ubiquitin-proteasome system and a subsequent increase in ENaC expression.

1 *Preston GM, Carroll TP, Guggino WB, Agre P. Appearance of water channels in Xenopus oocytes expressing red cell CHIP28 protein. Science. 1992;256(5055):385-7.*

2 *Fushimi K, Uchida S, Hara Y, Hirata Y, Marumo F, Sasaki S. Cloning and expression of apical membrane water channel of rat kidney collecting tubule. Nature. 1993;361(6412):549-52.*

3 *Canessa CM, Horisberger JD, Rossier BC. Epithelial sodium channel related to proteins involved in neurodegeneration. Nature. 1993;361(6411):467-70.*

4 *Canessa CM, Schild L, Buell G, Thorens B, Gautschi I, Horisberger JD, Rossier BC. Amiloride-sensitive epithelial Na+ channel is made of three homologous subunits. Nature. 1994;367(6462):463-7.*

MAY

DESCRIPTION OF MINIMAL CHANGE NEPHROTIC SYNDROME, "LIPOID NEPHROSIS"

By Shankar Prasad Yadav
Department Of Pediatrics, B.P.Koirala Institute Of Health Sciences, Dharan, Nepal

The identification and description of each component of the clinical entity known as "nephrotic syndrome" have developed over centuries. Severe edema in children was described by Cornelius as far back as 1484, but he did not identify it as a kidney-related issue[1].Much later, in 1722, Theodore Zwinger postulated that this edema was related to pathological changes in the kidney[2]. However, it was R. Bright (1827) and his contemporaries who demonstrated the presence of proteinuria and then proposed the triad of edema, diseased kidney, and proteinuria as defining the clinical syndrome[3]. Subsequently, the presence of elevated lipids in the blood of such patients was discovered by R. Christison[4].

In 1905, the term "nephrosis", coined by Friedrich Muller, was used to describe the pathological lesion of such patient as degenerative rather than inflammatory and hence replaced "nephritis"[5]. In addition, Fritz Munk (1920) demonstrated lipid in the urine of such patients and reportedly used the term "lipoid nephrosis" to describe such conditions[6]. During this period, in kidney specimens observed through optical microscopy in patients with nephrosis, the gross appearance of glomeruli seemed almost normal; therefore, the idea of "pure nephrosis", or minimal change, emerged and it was conceded that the proteinuria resulted from tubular defect. The term "Nephrotic Syndrome" was gradually popularized in 1948[7].

1 *Chadwick J, Mann WN. The medical works of Hippocrates. London: Oxford University Press, 1950: 228 (Section 2, No 136), 240 (Section 13, No 266), 244 (Section 7, No 34).*
2 *Roelans C. Liber de aegritudinibus infantium. (c 1484). Reproduced in: Sudhoff KFJ. Erstlingeder padiatrischen Literatur. Munchen: Monchner Drucke, 1925: cxciii-cxciiii.*
3 *Bright R. Reports of medical cases selected with a view of illustrating the symptoms and cure of diseases by reference to morbid anatomy. London: Longman Green, 1827. Vol 1.*
4 *Christison R. On the cause of the milky and whey-like appearance sometimes observed in the blood. Edin Med Surg J 1830; 33: 274-280.*
5 *Muller F. Morbus Brightii. Verhandl Deutsch Path Gesellsch 1905; 9: 64-99.*
6 *Munk F. Klinische Diagnostik der degenerativen Nierenerkrankungen. Z Klin Med 1913; 78:1.52.*
7 *Bradley SE, Tyson CJ. The 'nephrotic syndrome'. N Engl J Med 1948; 238: 223-227, 260-266.*

CULTURE OF GLOMERULAR CELLS

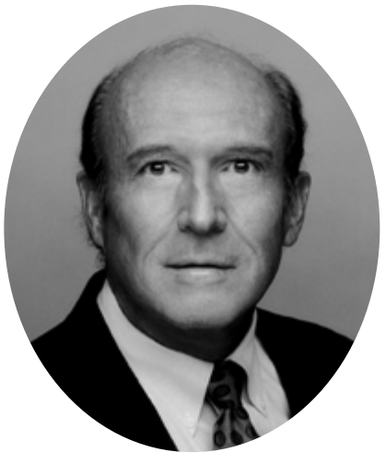
By Eishin Yaoita
Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

Cultured cells that reproduce phenotypes in vivo are essential elements in the study of biology and pathophysiology. The most important step for glomerular cell culture was the isolation of glomeruli. In 1950, S.A. Greenspon and C.A. Krakower first isolated large numbers of glomeruli by a sieving method using a stainless-steel screen[1]. In 1970, L. Quadracci and G.E. Striker applied glomeruli that had been isolated using a modified sieving method to cell-culture and reported three cell types in the culture[2]. Which cells came from podocytes remains controversial. P. Mundel et al. considered cobblestone-like polygonal cells to be dedifferentiated podocytes[3] and established podocyte cell lines using conditionally immortalized mice[4], which has had a great impact on podocyte research. In parallel, it has been suggested that polygonal cells originate from the parietal epithelial cells of Bowman's capsule as represented by J.O. Nørgaard's paper[5]. Few polygonal cells have actually been seen in outgrowths from glomeruli isolated by the innovative method invented by M. Takemoto et al., in which almost all glomeruli are decapsulated[6]. In addition, phenotypes very close to podocytes in vivo have been successfully restored using the outgrowths from glomeruli isolated by Takemoto's method[7], whereas phenotypes from polygonal cells from glomeruli isolated by the sieving method have not.

1 *Greenspon SA, Krakower CA. Direct evidence for the antigenicity of the glomeruli in the production of nephrotoxic serums. AMA Arch Pathol. 1950; 49:291-7.*
2 *Quadracci L, Striker GE. Growth and maintenance of glomerular cells in vitro. Proc Soc Exp Biol Med. 1970; 135:947-50.*
3 *Mundel P, Reiser J, Kriz W. Induction of differentiation in cultured rat and human podocytes. J Am Soc Nephrol. 1997; 8:697-705.*
4 *Mundel P, Reiser J, Zúñiga Mejía Borja A, Pavenstädt H, Davidson GR, Kriz W, Zeller R. Rearrangements of the cytoskeleton and cell contacts induce process formation during differentiation of conditionally immortalized mouse podocyte cell lines. Exp Cell Res. 1997; 236:248-58.*
5 *Nørgaard JO. Rat glomerular epithelial cells in culture. Parietal or visceral epithelial origin? Lab Invest. 1987; 57:277-90.*
6 *Takemoto M, Asker N, Gerhardt H, Lundkvist A, Johansson BR, Saito Y, Betsholtz C. A new method for large scale isolation of kidney glomeruli from mice. Am J Pathol. 2002; 161:799-805.*
7 *Yaoita E, Yoshida Y, Nameta M, Takimoto H, Fujinaka H. Induction of interdigitating cell processes in podocyte culture. Kidney Int. 2018; 93:519-24.*

IDENTIFICATION OF ANTIGEN OF MEMBRANOUS NEPHROPATHY

By Sabine Karam MD
Saint George Hospital University Medical Center, Beirut, Lebanon



Up until the late 1970s, it was thought that all forms of immune-complex glomerulonephritis were due to circulating immune complexes passively trapped in glomeruli. This theory was challenged by works done by W.G. Couser and B.J. Van Damme on Heymann nephritis, a rat model of experimental membranous nephropathy (MN) that showed that deposits in experimental MN formed in situ when circulating immunoglobulin G (IgG) antibodies bound to an unknown glomerular antigen located in the subepithelial space[1,2,3]. This hypothesis was only confirmed in a human model several years later when, in 2002, H.G. Debiec et al. described a case of neonatal MN in which transplacental passage of antineutral endopeptidase (NEP) antibodies from a pre-sensitized NEP-deficient mother bound to NEP on the baby's podocytes[4]. The pathogenesis of primary MN was finally elucidated in 2009 when D.J. Salant et al. found that the M-type phospholipase A2 receptor (PLA2R) expressed in podocytes of normal human glomeruli colocalized with IgG4 in immune deposits in the glomeruli of the majority of patients with idiopathic MN[5] and therefore constituted a major antigen in this disease. Salant had worked with Couser earlier in his career. Furthermore, this mechanism of adaptive immunity was found to have a genetic basis through the finding that the HLA-DQA1 allele on chromosome 6p21 was closely associated with idiopathic membranous nephropathy and could facilitate an autoimmune response against targets such as variants of PLA2R1[6].

Not only is the discovery seminal, but it's also notable that Dr. Couser was President of the ISN from 2005-2007 and won the 2020 Hamburger Award.

1 *Couser WG, Steinmuller DR, Stilmant MM, Salant DJ, Lowenstein LM. Experimental glomerulonephritis in the isolated perfused rat kidney. J Clin Invest. 1978;62(6):1275-87. Epub 1978/12/01. doi: 10.1172/JCI109248. PubMed PMID: 372233; PubMed Central PMCID: PMCPMC371893.*

2 *Van Damme BJ, Fleuren GJ, Bakker WW, Vernier RL, Hoedemaeker PJ. Experimental glomerulonephritis in the rat induced by antibodies directed against tubular antigens. V. Fixed glomerular antigens in the pathogenesis of heterologous immune complex glomerulonephritis. Lab Invest. 1978;38(4):502-10. Epub 1978/04/01. PubMed PMID: 147961.*

3 *Couser WG, Salant DJ. In situ immune complex formation and glomerular injury. Kidney Int. 1980;17(1):1-13. Epub 1980/01/01. doi: 10.1038/ki.1980.1. PubMed PMID: 6990087.*

4 *Debiec H, Guigonis V, Mougenot B, Decobert F, Haymann JP, Bensman A, et al. Antenatal membranous glomerulonephritis due to anti-neutral endopeptidase antibodies. N Engl J Med. 2002;346(26):2053-60. Epub 2002/06/28. doi: 10.1056/NEJMoa012895. PubMed PMID: 12087141.*

5 *Beck LH, Jr., Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;361(1):11-21. Epub 2009/07/03. doi: 10.1056/NEJMoa0810457. PubMed PMID: 19571279; PubMed Central PMCID: PMCPMC2762083.*

6 *Stanescu HC, Arcos-Burgos M, Medlar A, Bockenhauer D, Kottgen A, Dragomirescu L, et al. Risk HLA-DQA1 and PLA(2)R1 alleles in idiopathic membranous nephropathy. N Engl J Med. 2011;364(7):616-26. Epub 2011/02/18. doi: 10.1056/NEJMoa1009742. PubMed PMID: 21323541.*

FIRST DESCRIPTION OF IGA GLOMERULONEPHRITIS (BERGER'S DISEASE)

By Mirna Aleckovic-Halilovic and Enisa Mesic
Clinic for Internal Diseases, Department of Nephrology, Dialysis and Renal Transplantation, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

Jean Berger was the renal pathologist who first characterized IgA nephropathy alongside Nicole Hinglais in 1968, and then in 1969[1][2], although P. Galle and Berger had described "intercapillary fibrinoid deposits" earlier, in 1962[3]. This distinct clinicopathological entity with predominant mesangial IgA deposits was soon realized to be the most prevalent primary chronic glomerular disease and an important cause of kidney failure worldwide. Until this breakthrough[1], laboratories using immunofluorescence mostly used only anti-IgG reagents, as IgG was thought to be the predominant immunoglobulin class involved in the immunopathogenesis of nephritis[4].

Ever since the publication of this seminal paper, the presence of IgA nephropathy is established only by kidney biopsy. Furthermore, the immunofluorescence findings are the pathologic hallmark of this disease. The light microscopic features of IgA nephropathy may vary greatly among patients and within individual biopsy samples.

Enormous efforts were put into research to identify the etiology and pathogenesis of IgA nephropathy. While they are still poorly understood, recent studies shed some light on the pathogenesis (see the narrative: "IgA hinge glycosylation in IgA nephropathy and IgA vasculitis"). Some studies have shown the efficacy of steroids and inhibition of the renin-angiotensin system, but there is no single therapeutic strategy shown to be effective against this disease.

The current state of knowledge regarding pathogenesis is that an initiating event is likely and that the main feature defining this glomerulonephritis is dominant or codominant mesangial deposits of IgA. Hence, Berger and his associates were the first to describe IgA nephropathy, and their work remains the backbone of diagnostics and today's understanding of it.

While we are striving, in all areas of medicine, to move away from eponyms in naming diseases in pursuit of a better understanding of the underlying mechanisms, we acknowledge that, for many, IgA nephropathy will remain Berger's disease.

1 *Berger J, Hinglais N. Les dépôts intercapillaires d'IgA-IgG. J Urol Nephrol 1968; 74: 694–695.*
2 *Berger J. IgA glomerular deposits in renal disease. Transplant Proc 1969; 1: 939–944..*
3 *GALLE P, BERGER J: Depots fibrinoides intercapillaires. J Urol Nephrol (Paris) 68:123—127, 1962.*
4 *Jean Berger (1930–2011) Feehally, John et al. **Kidney International**, Volume 80, Issue 5, 437 – 438.*

IGA HINGE GLYCOSYLATION IN IGA NEPHROPATHY AND IGA VASCULITIS

By Nikolay Bulanov
Sechenov First Moscow State Medical University, Russia

Immunoglobulin A (IgA) deposits in the glomeruli – the hallmark feature of IgA nephropathy – were first described in 1968 by Jean Berger and Nicole Hinglais[1]. However, the underlying mechanisms of mesangial IgA deposition in the glomeruli couldn't be explained until the mid-90s. In 1995, Alice C. Allen et al. studied serum IgA1, IgG, and C1 inhibitor glycosylation in several patients with biopsy-proven IgA nephropathy (IgAN) and healthy controls. IgAl from patients with IgAN showed significantly higher binding than controls to lectins specific for O-linked N-acetyl galactosamine that indicated reduced terminal galactosylation of the hinge region O-linked moieties[2]. In 1998, Allen et al. found a similar increase in IgA1 lectin binding in both adults and children with Henoch-Schönlein purpura (currently known as IgA vasculitis) with kidney involvement compared to other forms of glomerulonephritis and controls[3]. In 1999, Milan Tomana et al. showed that circulating immune complexes (CICs) isolated from sera of patients with IgAN consisted of undergalactosylated polymeric IgA1 and IgG antibodies specific for N-acetyl galactosamine residues in O-linked glycans of the hinge region of IgA1 heavy chains[4]. These studies provided insights into immunological abnormalities resulting in the formation of CICs containing aberrantly glycosylated IgA1 that escape removal through the reticuloendothelial system and form mesangial deposits in IgAN and IgA vasculitis.

1 *Berger J, Hinglais N. Les depots intercapillaires d'IgA-IgG. J Urol Nephrol. 1968; 74:694–95.*
2 *Allen AC, Harper SJ, Feehally J. Galactosylation of N- and O-linked carbohydrate moieties of IgA1 and IgG in IgA nephropathy. Clin Exp Immunol. 1995; 100:470–474.*
3 *Allen AC, Willis FR, Beattie TJ, Feehally J. Abnormal IgA glycosylation in Henoch-Schönlein purpura restricted to patients with clinical nephritis. Nephrol Dialysis Transplant. 1998; 13:930–934.*
4 *Tomana M, Novak J, Julian BA, et al. Circulating immune complexes in IgA nephropathy consist of IgA with galactose-deficient hinge region and antiglycan antibodies. J Clin Invest. 1999; 104:73–81.*

JUNE

DISCOVERY OF THE LINK BETWEEN KIDNEY DISEASE AND HYPERTENSION

By Rhys D. R. Evans,
Department of Renal Medicine, University College London, UK

Measurement of blood pressure is an integral part of the assessment of a patient with kidney disease due to the recognition of hypertension as a key clinical manifestation of impaired renal function. Richard Bright (1789-1858),provided the earliest descriptions of kidney disease in a series of patients with 'dropsy' (oedema) in 1827[1]. The triad of dropsy, albuminuria, and kidney disease became known as "Bright's Disease". However, it was another English Physician, Frederick Henry Horatio Akbar Mahomed (1849-1884), who is thought to have been the first to make the link between hypertension and kidney disease. After developing techniques to measure blood pressure as a medical student,in 1874,he published his observations of hypertension being an early clinical feature of acute and chronic kidney (Bright's) disease[2].

One of hisearliest observations with the sphygmograph was that 'the pulse of acute Bright's disease closely resembles that which had previously been described as occurring in chronic Bright's disease, or, more strictly speaking, with cirrhosis of the kidney". He found that both conditions were accompanied by a pulse of high tension.

He went on to note: "that previous to the commencement of any kidney change, or to the appearance of albumin in the urine, the first condition observable is high tension in the arterial system".

Hence the link between hypertension and kidney disease had been made.

1 *Dr. Bright's Reports of Medical Cases in Guy's Hospital. Medico-Chir. Rev.8, 90–103 (1828).*
2 *Mahomed, F. A. The Etiology of Bright's Disease and the Prealbuminuric Stage. Medico-Chir. Trans.57, 197–228 (1874).*

EXPERIMENTAL HYPERTENSION

By Abduzhappar Gaipov
Nazarbayev University School of Medicine, Nur-Sultan, Kazakhstan

In the early 1900s, several authors tried to demonstrate the renal cause of hypertension.However, most of the studies were controversial[1]. In 1934, Harry Goldblatt (1891–1977), professor of experimental pathology at the Case-Western Reserve University School of Medicine, Cleveland, established a successful experimental model of hypertension[2]. From a careful examination of autopsy specimens, Dr. Goldblatt noted the narrowing of the renal arteries and enlargement of the heart in patients who died from hypertension and renal failure. He suggested that a decrease in blood flow in the kidneys, and consequently reduced oxygen supply to the kidneys (ischemia), might be the cause of hypertension[3]. Goldblatt performed experimental studies on dogs and demonstrated renal ischemia-induced hypertension by constricting both renal arteries with a self-styled adjustable silver clamp, which resulted in an elevation of blood pressure[2,4]. The clamping of other arteries (splenic or femoral) did not result in hypertension, which showed the specific role of kidneys in hypertension. Further, this experimental model became the basis for identifying the role of the renin-angiotensin system in the regulation of blood pressure[5,6].

1 *Goldblatt H. Experimental Hypertension Induced by Renal Ischemia: Harvey Lecture, May 19, 1938. Bull N Y Acad Med. 1938;14(9):523-53.*
2 *Goldblatt H, Lynch J, Hanzal RF, Summerville WW. Studies on Experimental Hypertension: I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia. J Exp Med. 1934;59(3):347-79.*
3 *Van Epps HL. Harry Goldblatt and the discovery of renin. J Exp Med. 2005;201(9):1351.*
4 *Gerbi C, Rubenstein BB, Goldblatt H. Studies on Experimental Hypertension: X. The Oxygen Consumption of the Ischemic Kidney. J Exp Med. 1940;71(1):71-6.*
5 *Katz YJ, Goldblatt H. Studies on Experimental Hypertension: Xxi. The Purification of Renin. J Exp Med. 1943;78(1):67-74.*
6 *Goldblatt H, Katz YJ, Lewis HA, Richardson E. Studies on Experimental Hypertension: Xx. The Bioassay of Renin. J Exp Med. 1943;77(4):309-13.*

MACULA DENSA

By Daisuke Nakano
Department of Pharmacology, Kagawa University, Japan

In 1889, Golgi[1] initially reported that Henle's loop regularly returns to its originating glomerulus and makes close anatomical contact with the vascular pole. At the site of contact, 5–15 cells are packed more closely to each other than at adjacent sections of the distal tubule. In 1933, Karl Zimmermann[2] named this portion of epithelium with prominent nuclei "macula densa." Today, macula densa cells are well known as the tubular component of juxtaglomerular apparatusand control tubuloglomerular feedback (TGF). In the 1930s, given the observation of the closeanatomical contact, it was hypothesized that juxtaglomerular apparatus, including macula densa, affects tonus of afferent/efferent arterioles[3]. In 1964, K. Thurau and J. Schnermann[4] demonstrated the function of macula densa using a micropuncture technique. They observed thatan increase in luminal Na+ concentration at the tubules near macula densa reduced GFR in a renin-dependent manner, accounting for the term TGF. Thus, over a period of 70 years, the role of the macula densa, in a variety of important functions, was described.

1 *Golgi C. Annotazioni intorno all' Istologia dei reni dell' uomo e dialtri mammiferi e sull' Istogenesi dei canalicoli oriniferi. Atti R.Accad Lincei Rend.1889; 5: 334-342.*

2 *Zimmermann K. Ueber den Bau des Glomerulus der Saeugerniere: Weittere Mitteilunger. Ztschr Mikrosk Anat Forsch. 1933;32:176-278.*

3 *Goormaghtigh N. L'appareil neuro-myo-artériel juxtaglomérulaire du rein: ses réactions en pathologie et ses rapports avec le tube urinifère, Compt Rend Soc Biol, 1937;129:293-296.*

4 *Thurau K und Schermann J. Die Natriumkonzentration an den Macula densa-Zellen als regulierender Faktor für das Glomerulumfiltrat (Mikropunctionsversuche). Klinische Wochenschrift. 1964;43:410-413.*

EXPRESSION OF GLOMERULAR RECEPTOR FOR ANGIOTENSIN II

By Lili Zhou
Division of Nephrology, Nanfang Hospital, Southern Medical University, China

As the vasoactive hormone effector of the renin–angiotensin–aldosterone system (RAAS), angiotensin II (AngII) was first found to induce vasoconstriction of the glomerular capillaries in 1972, suggesting the potential existence of its receptors in glomerular mesangium[1]. However, the specific AngII receptors in isolated glomeruli were not well characterized until 1974[2]. The AngII receptors turned out to localize on the mesangial cells and induce a contractile response[3]. There are two subtypes of AngII receptors, AT1 and AT2. In 1992,using antagonist-inhibited 125I-AngII binding, D. Chansel et al. found that AT1 primarily mediates the vasoconstrictive properties of AngII on mesangial cells through increases in intracellular calcium concentration[4]. In 1993, the localization of AT1 in mesangium was directly visualized by in situ hybridization[5]. Subsequently, the more widespread distribution of Ang II receptors, possibly including in podocytes, was hypothesized by W. Kriz et al.[6] based on data from Yamada et al.[7]. The presence of both AT1 and AT2 receptors in podocytes was subsequently verified by Sharma et al. in 1998[8]. AT1 was found to be more abundant (~75%) than AT2 inpodocytes[9], and responsible for structural podocyte damage and cell stress induced by AngII[10]. The discovery of AT1 and its function in mesangial cells and podocytes over the last 30 years has led to a rationale as to the importance of AngII on glomerular microcirculation and ultrafiltration originally described in 1976[11]. Since then, additional functions of AT1 and AT2 have been elucidated, and the elegant contribution to the coordination and regulation of glomerular functions described.

1 *Hornych H, Beaufils M, Richet G.The effect of exogenous angiotensin on superficial and deep glomeruli in the rat kidney.Kidney Int. 1972 Dec;2(6):336-43.*
2 *Sraer JD, Sraer J, Ardaillou R, Mimoune O.Evidence for renal glomerular receptors for angiotensin II.Kidney Int. 1974 Oct;6(4):241-6.*
3 *Foidart J, Sraer J, Delarue F, Mahieu P, Ardaillou R.Evidence for mesangial glomerular receptors for angiotensin II linked to mesangial cell contractility.FEBS Lett. 1980 Dec 1;121(2):333-9.*
4 *Chansel D, Czekalski S, Pham P, Ardaillou R.Characterization of angiotensin II receptor subtypes in human glomeruli and mesangial cells.Am J Physiol. 1992 Mar;262(3 Pt 2):F432-41.*
5 *Kakinuma Y, Fogo A, Inagami T, Ichikawa I.Intrarenal localization of angiotensin II type 1 receptor mRNA in the rat.Kidney Int. 1993 Jun;43(6):1229-35.*
6 *Kriz W, Hackenthal E, Nobiling R, Sakai T, Elger M, Hähnel B.A role for podocytes to counteract capillary wall distension.Kidney Int. 1994 Feb;45(2):369-76.*
7 *Yamada H, Sexton PM, Chai SY, Adam WR, Mendelsohn FA.Angiotensin II receptors in the kidney. Localization and physiological significance.Am J Hypertens. 1990 Mar;3(3):250-5.*
8 *Sharma M, Sharma R, Greene AS, McCarthy ET, Savin VJ.Documentation of angiotensin II receptors in glomerular epithelial cells. Am J Physiol. 1998 Mar;274(3 Pt 2):F623-7.*
9 *Wang L, Flannery PJ, Spurney RF.Characterization of angiotensin II-receptor subtypes in podocytes.J Lab Clin Med. 2003 Nov;142(5):313-21.*
10 *Hoffmann S, Podlich D, Hähnel B, Kriz W, Gretz N.Angiotensin II type 1 receptor overexpression in podocytes induces glomerulosclerosis in transgenic rats.J Am Soc Nephrol. 2004 Jun;15(6):1475-87.*
11 *Blantz RC, Konnen KS, Tucker BJ.Angiotensin II effects upon the glomerular microcirculation and ultrafiltration coefficient of the rat.J Clin Invest. 1976 Feb;57(2):419-34.*

DISCOVERY OF RENIN

By Shankar Prasad Yadav
Department Of Pediatrics, B.P.Koirala Institute Of Health Sciences, Dharan, Nepal

Current knowledge and understanding of the Renin-Angiotensin-Aldosterone System (RAAS) and its effects on organ systems are based on the discovery of renin made by Robert Tigerstedt in the 1890s. Tigerstedt, a professor of physiology, alongside his student P.G. Bergman, conducted experiments to prove the hypothesis that kidneys contribute to hypertension[1].

Firstly, tissue extracts were methodically prepared from rabbit kidneys and subsequently injected into the jugular veins of rabbits. A rise in blood pressure followed each injection. Other important findings included the observation that the extract from the cortex led to a rise in blood pressure, while an extract from the medullary portion did not. This observation, based on a simple experiment, allowed the conclusion that the substance causing hypertension originated from the cortex. Tigerstedt and Bergman also demonstrated that in a nephrectomized rabbit, blood injected from the renal arteries increased the blood pressure, leading to the conclusion that the substances causing hypertension are secreted into the bloodstream. Interestingly, during the experiment, it was noted that there was no altered activity in the heart and that this pressure effect was not neurally mediated. These conclusions were based on the observation that the pressure increased despite the high cervical section or crushing of the spinal cord. Since the substance and the effect were predominantly related to the kidney (renal), the term “renin” was coined[1,2].

It was not until 1939 when renin was found to be an enzyme rather an effector, and responsible for the production of angiotensin II, that the actual vasoconstrictor responsible for hypertension was properly understood[3].

1 *Tigerstedt R, Bergman PG. Niere und Kreislauf. Skand Arch Physiol. 1898(8):223–271*
2 *Philips M.I, Schmidt-Ott KM. The discovery of renin 100 years ago. News Phsiol. Sci 1999(14). 271-274*
3 *Braun-Menendez E, and I. H. Page. Suggested revision of nomenclature: angiotensin. Science 1958:127: 242*

JULY

DESCRIPTION OF FAMILIAL KIDNEY DISEASE

By Yosuke Hirakawa
Division of Nephrology and Endocrinology, the University of Tokyo Hospital, Japan

Alport syndrome, characterized by progressive renal failure, hearing impairment, and ocular changes, is a representative genetic kidney disease interpreted nowadays as a glomerular disease arising from genetic mutations in Col4A3, Col4A4, or Col4A5. Alport syndrome has a long history, dating back to 1927 when Arthur Cecil Alport, a South African physician, identified this disease in a British family[1]. Cases of familial nephritis, however, were reported even earlier; William Howship Dickinson was an English physician who published several case reports of kidney diseases at that time[2]. He described familial cases of albuminuria as early as 1875. Dr. Dickinson was “a well-rounded physician,” and because of his involvement in a children’s hospital, he described hereditary albuminuria in four generations of a single family[3]. His observations on familial albuminuria highlighted genetic cases of kidney diseases and contributed to the discovery of Alport’s disease.

1 *Alport Cecil A. Hereditary Familial Congenital Haemorrhagic Nephritis, Br Med J. 1927; 1(3454): 504–506.*
2 *Dickinson W. H. Notes of four cases of intermittent haematuria. Lancet 1865;1: 568-9.*
3 *Obituary. William Howship Dickenson, M.D.Cantab., F.R.C.P.Lond. Br Med J 1913;1:141*

DESCRIPTION OF ALPORT SYNDROME

By Yosuke Hirakawa
Division of Nephrology and Endocrinology, the University of Tokyo Hospital, Japan

In 1924, Arthur Cecil Alport reviewed the family history of a 14-year-old boy he was examining. He found that almost all children in three generations of this family had hematuria, nephritis, and deafness. He re-examined a family previously reported by Guthrie in 1902, and Hurst in 1915, to have familial nephritis. In 1927, Alport published his study on what earlier physicians had called “hereditary familial congenital haemorrhagic nephritis,” reporting a familial case of nephritis and deafness.

He described that (i) affected members originated from one deaf female over four generations, (ii) deafness was a marked feature, and (iii) affected male members developed nephritis and deafness and died before they reached adulthood[1].

At that time, they could not determine whether this disease was congenital or not, and the researchers focused on the possibility of a bacterial contribution. Approximately 60 years later, it was demonstrated that a Col4A5 mutation causes X-linked Alport syndrome, and a Col4A3 or Col4A4 mutation causes autosomal dominant Alport syndrome[2,3]. In “thin basement membrane nephropathy,” the family history may test positive for hematuria, but kidney failure and deafness are typically absent or occur relatively late in life. Some experts consider this to be a variant of Alport syndrome. Despite the long history of describing this condition, effective treatment for Alport syndrome has not been established. While promising molecules are under investigation, researchers continue to look for novel pharmaceutical or genetic treatments[4,5].

1 *Alport AC. HEREDITARY FAMILIAL CONGENITAL HAEMORRHAGIC NEPHRITIS. Br Med J. 1927;1:504-6*
2 *Barker DF, Hostikka SL, Zhou J, et al. Identification of mutations in the COL4A5 collagen gene in Alport syndrome. Science 248:1224-1227,1990*
3 *Mochizuki T, Lemmink HH, Mariyama M, et al. Identification of mutations in the alpha 3(IV) and alpha 4(IV) collagen genes in autosomal recessive Alport syndrome. Nat Genet 8:77-81, 1994*
4 *Briggs JP and Hostetter TH. Editorial Note: From Both Sides Now. J Am Soc Nephrol. 2018;29:355-356.*
5 *Yamamura T, Horinouchi T, Adachi T, et al. Development of an exon skipping therapy for X-linked Alport syndrome with truncating variants in COL4A5. Nat Commun 2020;11:2777.*

APOL1 AND KIDNEY DISEASE

By Muzamil Olamide Hassan
Renal Unit, Department of Medicine,
Obafemi Awolowo University Teaching Hospital, Nigeria

To date, there have been relatively few actionable discoveries in genomics and nephrology. *APOL1* risk variants are among the most powerful common risk variants identified as increasing the risk for chronic kidney disease. In 2010, two coding sequence variants in the *APOL1* gene on chromosome 22 (identified in the 1000 Genomes Project) demonstrated by far the strongest association with chronic kidney disease. The first variant is two amino acid substitutions (S342G and I384M) near the C terminus that almost always occur together. Referred to as G1 and G2, the latter is a 6 base-pair deletion resulting in the loss of two amino acid residues, N388 and Y389.

These two single nucleotide polymorphisms together confer resistance to *Trypanosoma brucei* infections and are common in West African populations. The G1 and G2 variants greatly increase the risk of human immunodeficiency virus-associated nephropathy, focal segmental glomerulosclerosis, chronic kidney disease attributed to hypertension, and non-diabetic kidney disease. Given the recent advances in understanding the role of *APOL1* and its genetic variants in human kidney disease, it is believed that these discoveries will lead to important changes in clinical care, ultimately reducing the burden of kidney disease in patients of African descent.[1,2,3,4,5]

1 *Kopp JB, Smith MW, Nelson GW, Johnson RC, Freedman BI, et al. MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. Nat. Genet. 2008,40:1175–84*
2 *Kao WH, Klag MJ, Meoni LA, Reich D, Berthier-Schaad Y, et al. MYH9 is associated with nondiabetic end-stage renal disease in African Americans. Nat.Genet.2008, 40:1185–92*
3 *Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science 2010, 329:841–45*
4 *Tzur S, Rosset S, Shemer R, Yudkovsky G, Selig S, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. Hum. Genet. 2010, 128:345–50.*
5 *Friedman DJ, Pollak MR. APOL1 and Kidney Disease: From Genetics to Biology. Annu.Rev.Physiol.2020.82:323–42*

CLONING OF NEPHRIN

By Fabian Braun
University Medical Center Hamburg-Eppendorf, Germany

One ever-evolving field of research is the functional study of the glomerular filtration barrier. While electron microscopy analyses in the early days delineated the three major components – fenestrated endothelium, glomerular basement membrane, and podocyte foot processes – the molecular basis for the retainment of large macromolecules was poorly understood for many years. Karl Tryggvason and his group changed this when they successfully cloned a gene, *NPHS1*, encoding a glomerular transmembrane protein of the immunoglobin superfamily they termed "nephrin"[1]. In the same study, they identified mutations altering the transcription of nephrin to be the basis for congenital nephrotic syndrome of the Finnish type. In a follow-up investigation, they were able to determine the localization of nephrin to the podocytes and specifically to the slit diaphragm (SD)[2]. Tryggvason's group has thus shaped our understanding of the interaction between SD proteins and podocyte ultrastructure, and thereby how we appreciate the development of proteinuria. The meticulous analyses, which identified additional slit diaphragm proteins, deepened our understanding of the precise structure of the glomerular filtration barrier.

1 *Kestilä M. et al. Positionally Cloned Gene for a Novel Glomerular Protein—Nephrin—Is Mutated in Congenital Nephrotic Syndrome. Mol Cell 1, 575–582 (1998).*

2 *Ruotsalainen V. et al. Nephrin is specifically located at the slit diaphragm of glomerular podocytes. Proceedings of the National Academy of Sciences of the United States of America 96, 7962–7967 (1999).*

CLONING OF PKD1 AND PKD2 AND TREATMENT OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

By Sabine Karam MD
Saint George Hospital University Medical Center, Beirut, Lebanon

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common monogenic disorders in humans, affecting 1 in 1000 individuals. Mutations in the *PKD1* gene located on chromosome 16 are the most common cause of ADPKD.

The *PKD1* sequence was first described in 1995, after obtaining the genomic sequence of the *PKD1* locus and ascertaining the assembly of a *PKD1* transcript from the sequence of 46 exons[1]. The 14.5 kb *PKD1* transcript was found to encode a 4304 amino acid protein that was identified as polycystin 1, an integral membrane protein involved in cell-cell/matrix interactions[2]. The second gene, *PKD2*, that accounts for 15% of affected families, was localized on chromosome 4q21-23[3,4]. Truncating mutations were identified in 1996[5], leading to the discovery of polycystin 2. Both polycystins were found to have a role in the regulation of intracellular calcium[6,7] and, as a result, affect the concentration of adenosine-3′,5′-cyclic monophosphate (cAMP) which plays a major role in cystogenesis[8,9]. These insights accelerated a broader understanding of the disease and moved the field toward directed therapeutic clinical trials for ADPKD. In 2004, the first therapeutic agent was identified. Known then as the vasopressin V2 receptor (VPV2R) antagonist OPC31260, the molecule was shown in a mouse model of ADPKD to reduce renal cyclic AMP (cAMP) levels with marked inhibition of cystogenesis[10]. Shortly afterward, a randomized placebo-

1 *Polycystic kidney disease: the complete structure of the PKD1 gene and its protein. The International Polycystic Kidney Disease Consortium. Cell. 1995;81(2):289-98. Epub 1995/04/21. doi: 10.1016/0092-8674(95)90339-9. PubMed PMID: 7736581.*

2 *Hughes J, Ward CJ, Peral B, Aspinwall R, Clark K, San Millan JL, et al. The polycystic kidney disease 1 (PKD1) gene encodes a novel protein with multiple cell recognition domains. Nat Genet. 1995;10(2):151-60. Epub 1995/06/01. doi: 10.1038/ng0695-151. PubMed PMID: 7663510.*

3 *Kimberling WJ, Kumar S, Gabow PA, Kenyon JB, Connolly CJ, Somlo S. Autosomal dominant polycystic kidney disease: localization of the second gene to chromosome 4q13-q23. Genomics. 1993;18(3):467-72. Epub 1993/12/01. doi: 10.1016/s0888-7543(11)80001-7. PubMed PMID: 8307555.*

4 *Peters DJ, Spruit L, Saris JJ, Ravine D, Sandkuijl LA, Fossdal R, et al. Chromosome 4 localization of a second gene for autosomal dominant polycystic kidney disease. Nat Genet. 1993;5(4):359-62. Epub 1993/12/01. doi: 10.1038/ng1293-359. PubMed PMID: 8298643.*

5 *Mochizuki T, Wu G, Hayashi T, Xenophontos SL, Veldhuisen B, Saris JJ, et al. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. Science. 1996;272(5266):1339-42. Epub 1996/05/31. doi: 10.1126/science.272.5266.1339. PubMed PMID: 8650545.*

6 *Koulen P, Cai Y, Geng L, Maeda Y, Nishimura S, Witzgall R, et al. Polycystin-2 is an intracellular calcium release channel. Nat Cell Biol. 2002;4(3):191-7. Epub 2002/02/21. doi: 10.1038/ncb754. PubMed PMID: 11854751.*

7 *Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X, et al. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. Nat Genet. 2003;33(2):129-37. Epub 2003/01/07. doi: 10.1038/ng1076. PubMed PMID: 12514735.*

8 *Yamaguchi T, Pelling JC, Ramaswamy NT, Eppler JW, Wallace DP, Nagao S, et al. cAMP stimulates the in vitro proliferation of renal cyst epithelial cells by activating the extracellular signal-regulated kinase pathway. Kidney Int. 2000;57(4):1460-71. Epub 2000/04/12. doi: 10.1046/j.1523-1755.2000.00991.x. PubMed PMID: 10760082.*

9 *Hanaoka K, Guggino WB. cAMP regulates cell proliferation and cyst formation in autosomal polycystic kidney disease cells. J Am Soc Nephrol. 2000;11(7):1179-87. Epub 2000/06/23. PubMed PMID: 10864573.*

10 *Torres VE, Wang X, Qian Q, Somlo S, Harris PC, Gattone VH, 2nd. Effective treatment of an orthologous model of autosomal dominant polycystic kidney disease. Nat Med. 2004;10(4):363-4. Epub 2004/03/03. doi: 10.1038/nm1004. PubMed PMID:*

controlled trial was launched – the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4. This study was completed in 2012 and demonstrated that the modification of ADPKD progression was achievable following twice-daily oral dosing with tolvaptan, an oral selective vasopressin V2-receptor antagonist[1].

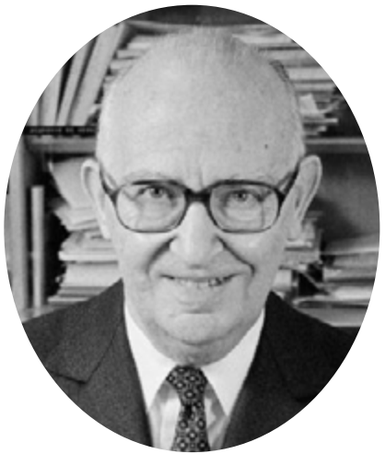
14991049.

1 *Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367(25):2407-18. Epub 2012/11/06. doi: 10.1056/NEJMoa1205511. PubMed PMID: 23121377; PubMed Central PMCID: PMCPMC3760207.*

AUGUST

KIDNEY TRANSPLANTATION

By Georgina L. Irish and Philip A. Clayton
Central and Northern Adelaide Renal and Transplantation Service,
Royal Adelaide Hospital, Adelaide, Australia



Kidney transplantation is the best treatment for most patients with end-stage kidney disease, delivering improved quality of life and survival while using fewer resources[1,2,3]. Prior to the 1950s, despite many attempts, no kidney transplants had functioned successfully[4,5]. In 1952, the first temporarily successful kidney transplant was performed by Jean Hamburger, the founding president of the ISN, in Paris, France[6]. A 16-year-old boy received a living kidney transplant from his mother, which functioned for 22 days before failing due to acute rejection[7]. This accomplishment was followed by another milestone: the first successful long-term kidney transplant in Boston, USA. In 1954, John Merrill and Joseph Murray performed a kidney transplant between monozygotic twins[8,9]. This kidney functioned for eight years. For this, and his career in organ transplantation, Joseph Murray was awarded the Nobel Prize for Medicine in 1990. These early successes paved the way for many subsequent milestones in kidney transplantation and have transformed the lives of millions of patients with kidney disease.

1 *Wolfe RA, Ashby VB, Milford EL et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;341(23):1725-1730.*
2 *Tonelli M, Wiebe N, Knoll G et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. American Journal of Transplantation 2011;11(10):2093-2109.*
3 *Laupacis A, Keown P, Pus N et al. A study of the quality of life and cost-utility of renal transplantation. Kidney Int. 1996;50(1):235-242.*
4 *Hume DM, Merrill JP, Miller BF et al. Experiences with renal homotransplantation in the human: report of nine cases. J Clin Invest.1955;34(2):327-382.*
5 *Morris PJ. Transplantation–a medical miracle of the 20th century. N Engl J Med. 2004;351(26):2678-2680.*
6 *Michon L, Hamburger J, Oeconomos N et al. [An attempted kidney transplantation in man: medical and biological aspects]. Presse Med. 1953;61(70):1419-1423.*
7 *Richet G. Hamburger's achievement with early renal transplants. Am J Nephrol. 1997;17(3-4):315-317.*
8 *Harrison JH, Merrill JP, Murray JE. Renal homotransplantation in identical twins. Surg Forum 1956;6:432-436.*
9 *Merrill JP, Murray JE, Harrison JH et al. Successful homotransplantation of the human kidney between identical twins. Journal of the American Medical Association 1956;160(4):277-282.*

KNIGHTS OF HEMODIALYSIS

By Mirna Aleckovic-Halilovic and Enisa Mesic
Clinic for Internal Diseases, Department of Nephrology, Dialysis and Renal Transplantation, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

In the early 1940s, the pathophysiological and clinical knowledge of the natural course of acute and chronic kidney failure was already at such a level that physicians and researchers in Europe and North America could begin constructing an artificial kidney. The foundations for such work began as early as the middle of the 19th century when the famous Thomas Graham described dialysis[1]. The development of a functional dialyzer resulted from the cumulative effect of numerous experiments: Abel (1914), Haas (1924), and Thalhimer (1937)[2,3,4,5]. Based on such achievements, three major researchers, independently of each other, constructed hemodialysis (HD) machines sufficiently efficient and safe for human use. In 1943, during World War II, Willem Kolff (1911-2009) in the Netherlands made a rotating drum with a cellophane membrane and described the recovery of patients with acute kidney failure for the first time[6,7]. Nils Alwall (1904-1986) constructed a vertical "rotating drum" HD machine in Sweden a few years later and was responsible for the concept of ultrafiltration[8,9]. The first HD machines in North America were designed by Gordon Murray (1894-1976) in Canada: the "coil" machine in 1945-1946 and a second-generation "flat-plate" model in 1952-1953[10]. Nils Alwall established a special Department of Nephrology at Lund University, where many future nephrologists from Europe and the world were educated. His merits and engagement in the nephrology community ultimately led him to two important leadership positions: President of ERA-EDTA and the ISN[11]. Willem Kolff left the Netherlands after the war and selflessly shared several of his HD machines with colleagues in Europe and the United States. In 2002, he was awarded the highly regarded Albert Lasker Clinical Medical Research Award, alongside Belding Scribner,

1 *Graham T. The Bakerian lecture: Osmotic force. Philos Trans R Soc London. 1854; 144: 177-228. Available from: Graham T. The Bakerian lecture: Osmotic force. Philos Trans R Soc London. 1854;144:177-228.*
2 *Abel JJ, Rowntree LG, Turner BB. On the removal of diffusible substances from the circulating blood of living animals by dialysis. J Pharmacol Exp Ther. 1914;5(6):611-623.*
3 *Haas G. Versuche der Blutauswaschung am Lebenden mit Hilfe der Dialyse. Klin Wochenschr. 1925;4(1):13-14.*
4 *Benedum J. Georg Haas (1886-1971): Pionier der Hemodialse (in German). Med Hist J. 1979;14:196.*
5 *Thalhimer W. Experimental Exchange Transfusions for Reducing Azotemia. Use of Artificial Kidney for This Purpose. Exp Biol Med. 1938;37 (4):641-643.*
6 *Kolff W, Berk H. De kunstmatige nier: een dialysator met groot oppervlak (in Dutch). Ned Tijdschr Geneeskd. 1943;87:1684.*
7 *Kolff W, Berk H, Welle NM, van der Ley A, van Dijk E, van Noordwijk J. The Artificial Kidney: a dialyser with a great area. Acta Med Scand. 1944;117(2):121-134.*
8 *Alwall N. On the Artificial Kidney. I Apparatus for Dialysis of the Blood in vivo. Acta Med Scand. 1947;128(4):317-325.*
9 *Alwall N. Therapeutic and Diagnostic Problems in Severe Renal Failure: Clinical and Experimental Studies … Stockholm: Thomas; 1964.*
10 *McKellar S. Gordon Murrey and the artificial kidney in Canada. Nephrol Dial Transplant 1999; 14: 2766-2770.*
11 *Kjellstrand CM. Dedication to Nils Alwal. Nephron 1985; 39: 71-72.*

for his work reversing kidney disease prognosis from fatal to curable, changing the fate of kidney patients. Willem Kolff received the first Jean Hamburger Award from the ISN, which recognizes outstanding research in nephrology with a clinical emphasis. Although they all faced various difficulties, and often misunderstandings from colleagues, the achievements of these three "knights of hemodialysis" were the beginning of what is a necessary medical reality today: artificial renal replacement therapy[1]. Exceptional innovation, perseverance, patience, continuous learning, and the exchange of knowledge should be inexhaustible motives for young colleagues in further improving HD technology, enabling organ transplantation, and treating acute and chronic kidney patients.

1 *Vienken J. "Bioengineering for life": a tribute to Willem Johan Kolff. Nephrol Dial Transplant 2009; 24: 2299-2301.*

VASCULAR ACCESS

By Abduzhappar Gaipov
Nazarbayev University School of Medicine, Nur-Sultan, Kazakhstan

The history of vascular access in dialysis has evolved in parallel with the development of vascular surgery and dialysis techniques. Dr. Georg Haas (Germany) first performed temporary vascular access using a glass cannula to connect extracorporeal circuits from the radial artery to the cubital vein during the first hemodialysis in 1924[1]. There were isolated attempts to perform hemodialysis using different vascular cannulations from the femoral or radial artery; however, the existing dialysis techniques could not provide effective purification. In the 1960s, when technical devices were available for regular hemodialysis treatments, Quinton, Dillard, and Scribner (USA) developed an arteriovenous (AV) Teflon shunt, modifying it further over the following years[2]. At the same time, Stanley Shaldon (UK) developed the percutaneous intravenous insertion of catheters by Seldinger's technique into different main arteries and veins. Later this technique was used for immediate vascular access via femoral or subclavian veins leading to fewer complications. Dr. Rob Uldall, based in Toronto, Canada, developed the 'Uldall catheter,' available commercially in the 1980s. In 1965, Dr. Appell (USA) created the first arteriovenous fistula for maintenance hemodialysis, which is currently in common use with subsequent modifications[3]. This technique made long-term maintenance hemodialysis feasible and significantly impacted the ability to save lives by offering safe and sustainable vascular access. Since the 1970s, ongoing modifications to vascular access techniques, grafts, and procedures have been introduced into clinical practice[4].

1 *Haas G. Versuche der blutauswaschung am lebenden mit hilfe der dialyse. Klinische Wochenschrift. 1925;4(1):13-4.*
2 *Quinton W, Dillard D, Scribner BH. Cannulation of blood vessels for prolonged hemodialysis. ASAIO Journal. 1960;6(1):104-13.*
3 *Brescia MJ, Cimino JE, Appel K, Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. New England Journal of Medicine. 1966;275(20):1089-92.*
4 *Santoro D, Benedetto F, Mondello P, Pipitò N, Barillà D, Spinelli F, et al. Vascular access for hemodialysis: current perspectives. International Journal of Nephrology and Renovascular Disease. 2014;7:281.*

PERITONEAL DIALYSIS

Designing the Flexible PD Catheter

First Description of CAPD as an Effective Therapy

By Shankar Prasad Yadav
Department Of Pediatrics, B.P.Koirala Institute Of Health Sciences, Dharan, Nepal

Ganter (1923) first conducted peritoneal dialysis (PD) by instilling hypertonic saline and then draining it in two cases of kidney failure[1]. Since then, there have been a series of modifications in the catheter, dialysis fluids, and the procedure for performing peritoneal dialysis. Two important milestones are designing a flexible PD catheter and the start of continuous ambulatory peritoneal dialysis (CAPD).

Henry Tenckhoff (1968) improvised flexible PD catheter material as well as the procedure itself. The catheter was made of silastic, and the two cuffs were made of Dacron. He also designed trocars for introducing the catheter. Tenckhoff recommended inserting the catheter so that a slightly arcuate subcutaneous course would give the external and intraperitoneal segment a caudal direction. One cuff was placed just above the ***linea alba***, and the other just beneath the exit-site[2].Tenckhoff's catheter and technique, with marginal modifications, is widely used today.

Popovich (1978) developed the technique of continuous ambulatory peritoneal dialysis (CAPD), which he tested on nine patients over 136 weeks[3]. Notably, patients themselves were taught to carry out the procedure. CAPD allowed excellent control of blood chemistry and edema, and manageable protein loss[4]. CAPD gradually developed to become the standard modality of renal replacement therapy with comparable outcomes to other dialysis modalities. Dimitrios Oreopoulos (1977), a Greek nephrologist based in Canada, developed a system of container bags made of lightweight plastic, which enabled peritoneal dialysis treatments to be easily administered in a home setting. The development of these techniques, the catheter's design, proof of effectiveness, and the ability to deliver solutions in a patient-friendly manner, contributed to the successful implementation and uptake of peritoneal dialysis.

1 *Ganter G. Ueber die Beseitigung giftiger Stoffe aus demBlute durch Dialyse (On the elimination of toxic substances from the blood by dialysis). Münch Med Wochenschr 1923; 70: 1478-80.*
2 *Tenckhoff H, Schechter H. A bacteriologically safe peritoneal access device. Trans Am Soc Artif Intern Organs 1968; 14: 181-7.*
3 *Twardowski Z. History of peritoneal access development. The International Journal of Artificial Organ 2006; 29: 2-40.*
4 *Popovich R, Moncrief J, Nolph K, Ghods A, Twardowski Z, Pyle W. Continuous Ambulatory Peritoneal Dialysis. Annals Intern Med. 1978; 88: 449-56*

FIRST CONTINUOUS RENAL REPLACEMENT TREATMENT (CRRT)

By Rolando Claure-Del Granado
Universidad Mayor de San Simon School of Medicine, Cochabamba, Bolivia

About forty years ago, Peter Kramer treated the first patient with continuous arteriovenous hemofiltration (CAVH) in the intensive care unit (ICU) of Gottingen, Germany[1]. Before that, acute kidney injury (AKI) was mostly treated with peritoneal dialysis or hemodialysis, but in critically ill patients, these modalities were often contraindicated or precluded due to severe cardiovascular instability. CAVH was well tolerated and easy to set up in ICUs where hemodialysis was not routinely performed. Following the first description of CAVH, a significant evolution of acute dialysis for critically ill patients with AKI and related technology occurred, leading to the modern techniques of continuous renal replacement therapy (CRRT). A remarkable increase in treatment efficiency and urea removal was achieved with the addition of diffusion. New filters with two ports in the dialysate/filtrate compartment allowed the use of counter-current flow of dialysate, giving birth to continuous arteriovenous hemodiafiltration or hemodialysis (CAVHDF or CAVHD)[2]. CAVHD and CAVHDF made it possible to treat hyper-catabolic patients. In the case of excessive ultrafiltration, fluid losses were wholly or partially replaced, allowing accurate fluid balance control. The problem of arterial cannulation was still the main drawback of the technique. Manual control of ultrafiltration was initially achieved by positioning the filtrate bag at different heights, thus modifying the negative pressure generated by the filtrate column. Delivery of replacement fluid was initially regulated manually, and later new systems were designed to provide automatic fluid balance[3]. The systems operated by gravity, using scales and electronic clamps, although peristaltic pumps soon replaced these simple mechanisms with more advanced equipment. The evolution from arterial cannulation to venous cannulation and the subsequent adaptation of CAVHD/DF to CVVHD has enabled safe and effective delivery of continuous replacement therapies and refined technologies in critical care settings.

1 *Kramer P, Schrader J, Bohnsack W, Grieben G, Grone HJ, Scheler F. Continuous arteriovenous haemofiltration. A new kidney replacement therapy. Proc Eur Dial Transplant Assoc. 1981;18:743-9.*

2 *Ronco C. Arterio-venous hemodiafiltration (A-V HDF): a possible way to increase urea removal during C.A.V.H. Int J Artif Organs. 1985;8(1):61-2.*

3 *Ronco C, Fabris A, Feriani M, Chiaramonte S, Brendolan A, Bragantini L, et al. Technical and clinical evaluation of a new system for ultrafiltration control during hemodialysis. ASAIO Trans. 1988;34(3):613-6.*

SEPTEMBER

DEVELOPMENT OF THE ANIMAL MODEL OF NEPHROTOXIC SERUM NEPHRITIS

By Lani Shochet
Centre for Inflammatory Diseases, Monash University Department of Medicine, and Department of Nephrology, Monash Health, Australia

Nephrotoxic serum nephritis is notable for its contribution to the knowledge and understanding of renal pathology. Initially described by Masugi in the 1930s after experiments in rats, it was among the first models to elucidate the immune system's role in the pathogenesis of glomerulonephritis, and to identify the glomerulus, rather than the tubules, as the target[1]. In this model, transferred autologous anti-kidney antibodies (nephrotoxic serum) bind to the glomerular basement membrane, inducing severe crescentic glomerular damage bearing a resemblance to human disease.

While initial contributions to the understanding of renal pathology regarded the immune mechanisms of the acute phase of the disease, nephrotoxic nephritis can also model renal scarring and glomerulosclerosis[2,3]. This ability to observe the various phases of crescentic glomerulonephritis, with the appreciation of the specific membrane targets, immune cells, and systems involved at each step[4,5], pave the way for the development of new treatments with potential translation into clinical use. As such, it remains an important animal model of human renal disease, almost a century after it was first described.

1 *Masugi, M. Ueber die experimentelle Glomerulonephritis durch das spezifischen Antinierenserum. Beitr Pathol Anat Aig Pathol 92:429—466, 1934*
2 *Shirato, I., Hosser, H., Kriz, W. et al.The development of focal segmental glomerulosclerosis in Masugi nephritis is based on progressive podocyte damage. Vichows Archiv A Pathol Anat 429, 255–273 (1996)*
3 *Tam FW, Smith J, Morel D, et al. Development of scarring and renal failure in a rat model of crescentic glomerulonephritis. Nephrol Dial Transplant. 1999;14(7):1658-1666. doi:10.1093/ndt/14.7.1658*
4 *Shigematsu H. Glomerular events during the initial phase of rat Masugi nephritis. Virchows Arch B Cell Pathol. 1970;5(3):187-200.*
5 *Cochrane CG, Unanue ER, Dixon FJ (1965) A role for polymorphonuclear leukocytes and complement in nephrotoxic nephritis. J Exp Med 122:99–116*

IMMUNE TOLERANCE

By Kate J. Robson
Centre for Inflammatory Diseases, Monash University Department of Medicine,
and Department of Nephrology, Monash Health, Australia

Tolerance – the lack of immune response to an antigen – protects our own tissues from immune attack, curbs reactivity to allergens and commensals, and enables pregnancy. The immune system's mechanisms of distinguishing between host and foreign tissue are fundamental to nephrology, underpinning the challenges we navigate in allograft transplantation and autoimmune disease.

Australian Sir Frank Macfarlane Burnet introduced the concept of 'self' and 'non-self' in 1949 with Frank Fenner[1]. While preceding work on antibodies focused on chemical and structural questions, Burnet drew on cell biology and 'population genetics' to define the concept he recognized as 'probably the basis of immunology.'[2] After Ray Owen's 1945 report that non-identical twin cattle sharing a common placenta tolerated each other's different blood groups without reaction[3], Burnet and Fenner hypothesized that the capacity to distinguish between self and foreign antigens was not inherited, but acquired in embryonic life. Sir Peter Medawar and colleagues substantiated this theory in 1953, demonstrating that fetal mice inoculated with cells from a different strain accepted skin grafts from that strain in adulthood without rejection[4].

Burnet and Medawar were awarded the 1960 Nobel Prize in Physiology or Medicine for the 'discovery of acquired immune tolerance.'[5] This breakthrough transformed immunobiology and paved the way for organ transplantation.

1 *Burnet FM, Fenner F. The production of antibodies 2nd ed (1949).*
2 *Burnet FM, Fenner F. Genetics and Immunology. 2, 289-324 (1948).*
3 *Owen RD. Immunogenetic consequences of vascular anastomoses between bovine twins. 102, 400-401 (1943).*
4 *Billingham RE, Brent L, Medawar PB. Actively acquired tolerance of foreign cells. 172, 603-606.*
5 *The Nobel Prize in Physiology or Medicine 1960 www.nobelprize.org/prizes/medicine/1960/summary*

INTRODUCTION OF AZATHIOPRINE AND CYCLOSPORIN

By Rolando Claure-Del Granado
Universidad Mayor de San Simon School of Medicine, Cochabamba, Bolivia

George Herbert Hitchings and Gertrude Elion first synthesized Azathioprine (AZA) in 1957 as a slow-release formulation of mercaptopurine (6-MP) in a metabolically active, but masked, form called BW 57-322. It was initially used as a chemotherapy drug[1]. Azathioprine is an anti-metabolite pro-drug that converts 6-mercaptopurine to tissue inhibitors of metalloproteinase, which convert to thioguanine nucleotides that interfere with DNA synthesis. Other possible mechanisms include converting co-stimulation into an apoptotic signal.

Robert Schwartz investigated AZA's effect on the immune response in 1958 and discovered that it profoundly suppresses the formation of antibodies when given to rabbits together with antigens[2]. Following this discovery, and the work done by Sir Peter Medawar and Gertrude Elion in discovering the immunological basis of rejection of transplanted tissues and organs, Sir Roy Calne, a British pioneer in transplantation, introduced AZA as an experimental immunosuppressant for kidney and heart transplants[3]. Azathioprine was the first immunosuppressive agent used in organ transplantation, and its developers were rewarded with a share in the 1988 Nobel Prize in Physiology or Medicine. It is used to maintain immunosuppression; however, it became a second-line drug after cyclosporine was introduced. Because AZA is 6 to 10 times cheaper than mycophenolate mofetil, AZA is still used in some parts of the world for tacrolimus-based immunosuppression and as an immunosuppressive drug in living-donor kidney transplantation.

The pharmacological development of cyclosporin was conducted by Jean Borel and colleagues in the 1970s. Cyclosporin decreases the function of lymphocytes by forming a complex with cyclophilin to block the phosphatase activity of calcineurin. In 1978, Sir Roy Calne reported the first successful results when using cyclosporin in kidney transplantation[4]. Cyclosporin made a considerable contribution to preventing organ rejection in kidney transplants.

1 *Elion GB. The purine path to chemotherapy. Science. 1989;244(4900):41-7.*
2 *Schwartz R, Stack J, Dameshek W. Effect of 6-mercaptopurine on antibody production. Proc Soc Exp Biol Med. 1958;99(1):164-7.*
3 *Calne RY. The rejection of renal homografts. Inhibition in dogs by 6-mercaptopurine. Lancet. 1960;1(7121):417-8.*
4 *Calne RY, White DJ, Thiru S, et al. Cyclosporin A in patients receiving renal allografts from cadaver donors. Lancet. 1978;2(8104-5):1323-7.*

RITUXIMAB THERAPY FOR RENAL DISEASES

By Nikolay Bulanov
Sechenov First Moscow State Medical University, Russia

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen of the B-lymphocytes; it was registered in 1997 to treat non-Hodgkin's lymphoma[1]. In 2002, Giuseppe Remuzzi et al. published the first case series studying the efficacy of four weekly infusions of rituximab (375 mg/m2) in eight patients with idiopathic membranous nephropathy (iMN) with persistent nephrotic syndrome[2]. They found that 24 h urinary protein excretion rates were significantly reduced during the treatment period from 8.6 g/24 h at study entry to 3.7 g/24 h at week 20. Since this initial success, the efficacy of rituximab for the treatment of iMN was confirmed in two randomized control trials (RCTs): GEMRITUX and MENTOR[3,4]. Recently, rituximab has been included, among other options, in KDIGO guidelines for the treatment of iMN. Another approved indication for rituximab is the therapy of ANCA-associated vasculitis. The RAVE and RITUXVAS protocols were the first RCTs that proved the non-inferiority of rituximab for induction therapy of ANCA-associated vasculitis compared to traditional cytotoxic regimens[5,6]. However, rituximab's efficacy in cases of severe renal involvement in ANCA-associated vasculitis is still under debate. Rituximab has been proposed for the treatment of focal segmental glomerulosclerosis, minimal change disease, mixed essential cryoglobulinemia, lupus nephritis, and several other autoimmune renal disorders. The list of its possible applications in nephrology is still expanding; however, high-quality RCTs for additional applications are currently lacking.

1 *Maloney DG, Grillo-López AJ, White CA, et al. (September 1997). "IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma". Blood. 90(6):2188–2195.*

2 *Remuzzi G, Chiurchiu C, Abbate M, et al. Rituximab for idiopathic membranous nephropathy. Lancet. 2002;360:923-924.*

3 *Dahan K, Debiec H, Plaisier E, et al. Rituximab for Severe Membranous Nephropathy: A 6-Month Trial with Extended Follow-Up. J Am Soc Nephrol. 2017;28:348-358.*

4 *Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. N Engl J Med. 2019;381:36-46.*

5 *Stone JH, Merkel PA, Spiera R, et al. Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis. N Engl J Med. 2010;363:221-232.*

6 *Rachel B. Jones, Jan Willem Cohen Tervaert, Thomas Hauser, et al. Rituximab versus Cyclophosphamide in ANCA-Associated Renal Vasculitis. N Engl J Med. 2010;363:211-220.*

IMMUNE COMPLEX-MEDIATED GLOMERULONEPHRITIS

By Caner Alparslan
Diyarbakır Gazi Yaşargil Training and Research Hospital, Turkey

Immune complex-mediated glomerulonephritis includes various diseases such as membranoproliferative glomerulonephritis, lupus nephritis, IgA nephropathy, and post-infectious glomerulonephritis[1,2,3,4].

In the early 1900s, Schick and Von Pirquet observed a hypersensitive reaction after streptococcal infection[5,6]. With the introduction of the immunofluorescence in kidney pathology, immune complexes were demonstrated in glomeruli. Because the kidney is a particularly susceptible target for immune deposit formation, passive trapping of preformed immune complexes was thought to be responsible for many forms of human glomerulonephritis. The best example of circulating immune complex disease is the classic acute serum sickness model in rabbits. Germuth et al.[7] and Dixon et al.[8] showed that immune complexes cause glomerular injury formed in circulation so that complexes settled target tissues and activated further cascades.

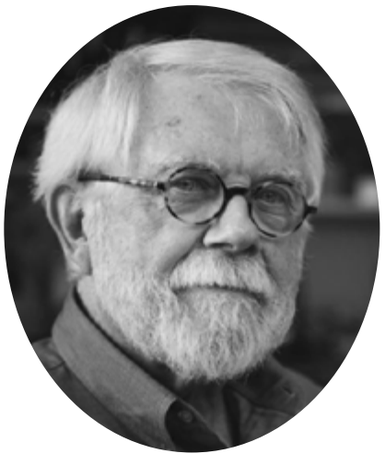
In the early 1980s, there was considerable debate regarding the relative importance of circulating immune complexes versus the in situ formation of immune deposits. The Heymann nephritis model of membranous nephropathy served an important role in clarifying this issue. Between 1978 and 1983, groups led by Hoedemaeker and Couser[9,10,11] almost simultaneously reported studies that showed subepithelial immune complex formation following the direct perfusion of bloodless kidneys with pathogenic IgG antibodies, thus establishing that subepithelial immune deposits in this classic model of membranous nephropathy developed through a novel mechanism, referred to as in situ immune-complex formation.

1 *Couser WG, Salant DJ. In situ immune complex formation and glomerular injury. Kidney Int 1980; 71:1-13.*
2 *Couser WG. Mechanisms of glomerular injury in immune-complex disease. Kidney Int 1985; 28:569-583.*
3 *Wilson CB. Immunologic glomerular injury. Postgraduate Medicine 1973; 54:157-164.*
4 *Schick B. Die nachkrankheiten des scharlachs. Jahrb f Kinderheit 1907; 65:132-173.*
5 *Salant DJ. Immune complex glomerulonephritis. Clin Exp Nephrol 1998; 2:271-275.*
6 *Von Pirquet CE. Allergy. Arch Intern Med 1911; 259-288, 383-436.*
7 *Germuth FG, McKinnon GE. Studies on the biological properties of antigen-antibody complexes: I. The anaphylactic shock induced by soluble antigen-antibody complexes in unsensitized normal guinea pigs. Johns Hopkins Med J 1953; 101:13-43.*
8 *Dixon FJ. The pathogenesis of glomerulonephritis. Am J Med 1969; 94:493-498.*
9 *Couser WG, Steinmuller DR, Stilmant NM, Salant DJ, Lowenstein LM. Experimental glomerulonephritis in the isolated perfused rat kidney. J Clin Invest 1978;62:1275–87*
10 *Van Damme BJC, Fleuren GJ, Bakker WW, Vernier RL, Hoedemaeker Ph J. Experimental glomerulonephritis in the rat induced by antibodies directed against tubular antigens. V. Fixed glomerular antigens in the pathogenesis of heterologous immune complex glomerulonephritis. Lab invest 1978;38:502–10*
11 *Madaio MP, Salant DJ, Cohen AJ, Adler S, Couser WG. Comparative study of in situ immune deposit formation in active and passive Heymann nephritis. Kidney Int 1983;23:498–505*

OCTOBER

HISTORIC BREAKTHROUGHS IN PREECLAMPSIA

By Hui Yi Shan
Division of Nephrology and Hypertension, Keck School of Medicine of University of Southern California, USA



The concept of toxemia in women with preeclampsia was first introduced in 1849. In the 1960s, physicians gained a deeper understanding of preeclampsia pathology by examining placental bed biopsies[1,2]. They observed that the presence of shallow trophoblast invasion and narrow spiral arteries resulted in placental perfusion reduction. In 1989, J. M. Roberts et al. hypothesized that ischemic placenta released a damaging factor into maternal circulation and led to endothelial disorder. Over the past few decades, major advances have improved our understanding of the causal mechanisms of preeclampsia; Oxidative stress pathways, immunologic intolerance at the maternal-fetal interface, and angiogenic factor imbalance have been described. Of specific interest, an anti-angiogenic protein, sFlt-1 (soluble Fms-like tyrosine kinase-1), first characterized in 2003 by the Karumanchi group[3], is a protein that is made in the placenta and released into the maternal circulation that antagonizes the activity of vascular endothelial and placental growth factor signaling in the vasculature. The presence of this protein results in endothelial dysfunction and produces clinical features of hypertension and proteinuria that are observed in preeclampsia. sFlt-1, in combination with other angiogenic factors, has been further utilized to aid the diagnosis and prognosis of preeclampsia. In 2011, Thadhani et al. prolonged the gestation of women with preeclampsia by lowering the level of sFlt-1 using targeted apheresis methods[4]. Thus, through improved understanding of mechanisms and targeted interventions, improvements in outcomes have been described.

1 *Bell M. A historical overview of preeclampsia-eclampsia. J Obstet Gynecol Neonatal Nurs.2010;39 510-518.*
2 *Phipps EA, Thadhani R, Benzing T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. Nat Rev Nephrol. 2019;15:275-289.*
3 *Maynard SE, Min JY, Merchan J, Lim KH, Li J, Mondal S, Libermann TA, Morgan JP, Sellke FW, Stillman IE, Epstein FH, Sukhatme VP, Karumanchi SA. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia J. Clin. Invest. 2003; 111:649–658.*
4 *Thadhani R, Kisner T, Hagmann H, Bossung V, Noack S, Schaarschmidt W, Jank A, Kribs A, Cornely O, Kreyssig C, Hemphill L, Rigby A, Khedkar S, Lindner T, Mallmann P, Stepan H, Karumanchi SA, Benzing T. Pilot study of extracorporeal removal of soluble fms-like tyrosine kinase 1 in preeclampsia. Circulation. 2011;124:940-950.*

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

By Nikolay Bulanov
Sechenov First Moscow State Medical University, Russia

The clinical presentation of granulomatosis with polyangiitis (previously called Wegener's granulomatosis) was first described in 1936[1]. However, the underlying immunological diseases and processes were poorly understood until the 1980s. In 1985, Fokke Johannes van der Woude (1953-2006) and colleagues published an article describing the prevalence of immunoglobulin G autoantibodies against extranuclear components of polymorphonuclear granulocytes in patients with polyangiitis[2]. Indirect immunofluorescence tests showed that these antibodies, known as antineutrophil cytoplasmic antibodies (ANCA), were present in 25 out of 27 serum samples from patients with active disease and in only 4 out of 32 samples from patients without disease activity. The authors prospectively assessed 19 patients and recognized that antibodies titers were strongly associated with disease activity. The study's importance cannot be understated; it contributed to the recognition of a new group of systemic autoimmune diseases – ANCA-associated vasculitides, that were later shown to be the most common cause of rapidly progressive glomerulonephritis in adults[3]. Since 1985, sensitive antigen-specific assays (ELISA) have been developed for ANCA detection, and the pathogenetic role of these antibodies has been proven in experimental studies[4]. Subsequently, the associations between ANCA types (depending on whether the ANCA is directed against proteinase-3 or myeloperoxidase), clinical features, and relapse rates of ANCA-associated vasculitides have been demonstrated and can now guide clinical understanding and follow-up[5].

1 *Wegener F. Ueber generalisierte septische Gefäßerkrankungen [About generalised septic vascular diseases], Verh Deut Pathol Ges. 1936;29:202-210.*

2 *Van der Woude FJ, Rasmussen N, Lobatto S, et al. Autoantibodies against neutrophils and monocytes: Tool for diagnosis and marker of disease activity in Wegener's granulomatosis. Lancet. 1985;1:425-429.*

3 *Jennette JC. Rapidly progressive crescentic glomerulonephritis. Kidney Int. 2003;63(3):1164-1177.*

4 *Xiao H, Heeringa P, Hu P, et al. Antineutrophil cytoplasmic autoantibodies specific for myeloperoxidase cause glomerulonephritis and vasculitis in mice. J Clin Invest. 2002;110:955–963.*

5 *Lionaki S, Blyth ER, Hogan SL, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis and Rheumatism. 2012;64(10):3452–3462.*

PLASMA EXCHANGE FOR TTP AND ANTI-GBM NEPHRITIS

By Rolando Claure-Del Granado
Universidad Mayor de San Simon School of Medicine, Cochabamba, Bolivia

Plasma exchange refers to the removal of large quantities of plasma (usually 2 to 5 L) from a patient for replacement by either fresh frozen or stored plasma. The procedure is frequently referred to as “plasmapheresis,” when a solution other than plasma (e.g., isotonic saline) is used as replacement fluid (“apheresis” from the Greek “to remove” or “to take away”). Manual plasmapheresis was first described in 1914 in animal experiments. Apheresis technology was initially developed in the 1950s to harvest peripheral blood cells from healthy donors for transfusion into patients[1] and was first used therapeutically in 1952 to control hyperviscosity in multiple myeloma. The advent of the automated cell separator in the 1960s led to its later application in therapeutic plasmapheresis.

Subsequently, the techniques were widely introduced, usually based on anecdotal or uncontrolled studies, as a primary or adjunctive treatment for a range of human conditions in which “circulating factors” were believed to contribute to disease pathophysiology. The technique was most frequently used to modulate humoral components of the immune response and rapidly lower circulating titers of autoantibodies as in anti-glomerular basement membrane disease. In 1975, Lockwood et al. used plasmapheresis and immunosuppression to successfully treat pulmonary hemorrhage and renal failure in Goodpasture syndrome, now called anti-GBM disease[2]. Plasma exchange is also utilized to remove components other than immunoglobulin, such as thrombotic factors like thrombotic thrombocytopenic purpura[3]. In 1977, Bukowski et al. used plasma exchange to successfully treat two patients with thrombotic thrombocytopenic purpura (TTP), renal impairment, hematuria, and proteinuria[4]. Since then, plasma exchange has been employed in a variety of kidney and systemic disorders.

1 *Shumak KH, Rock GA. Therapeutic plasma exchange. N Engl J Med. 1984;310(12):762-71.*
2 *Lockwood CM, Boulton-Jones JM, Lowenthal RM, Simpson IJ, Peters DK. Recovery from Goodpasture’s syndrome after immunosuppressive treatment and plasmapheresis. Br Med J. 1975;2(5965):252-4.*
3 *Byrnes JJ, Khurana M. Treatment of thrombotic thrombocytopenic purpura with plasma. N Engl J Med. 1977;297(25):1386-9.*
4 *Bukowski RM, King JW, Hewlett JS. Plasmapheresis in the treatment of thrombotic thrombocytopenic purpura. Blood. 1977;50(3):413-7.*

DIABETIC KIDNEY DISEASE

By Sabine Karam MD
Saint George Hospital University Medical Center, Beirut, Lebanon

Diabetic kidney disease (DKD) is the leading cause of CKD worldwide, with a similar risk in patients with type 1 and type 2 diabetes mellitus[1]. Fortunately, the continuing increase in global prevalence has prompted many efforts to tackle mechanisms of progression. The effects of early aggressive antihypertensive treatment on kidney function in diabetic nephropathy were first established in 1983 when an improvement in eGFR decline and a decrease in urinary albumin excretion was shown in ten insulin-dependent diabetics over a period of 39 months[2]. A year later, microalbuminuria in patients with type II diabetes was found to be predictive of clinical proteinuria and increased mortality[3]. Subsequently, a landmark study by Taguma and colleagues showed kidney protection by ACE inhibitors for the first time[4]. A subsequent randomized controlled trial established the protective effect of captopril in delaying the progression of diabetic kidney disease independently of blood pressure control[5]. Furthermore, the Diabetes Control and Complications Trial, a multicenter, randomized clinical trial designed to compare intensive with conventional diabetes therapy, demonstrated that intensive glycemic control treatment delays the onset and slows the progression of retinopathy, nephropathy, and neuropathy[6,7]. Finally, agents such as SGLT2 inhibitors and GLP1 receptor agonists have emerged as reno and cardio-protective in patients living with kidney disease, independent of their anti-glycemic effects[8,9].

1 *Hasslacher C, Ritz E, Wahl P, Michael C. Similar risks of nephropathy in patients with type I or type II diabetes mellitus. Nephrol Dial Transplant. 1989;4(10):859-63. Epub 1989/01/01. doi: 10.1093/ndt/4.10.859. PubMed PMID: 2515489.*

2 *Parving HH, Andersen AR, Smidt UM, Svendsen PA. Early aggressive antihypertensive treatment reduces rate of decline in kidney function in diabetic nephropathy. Lancet. 1983;1(8335):1175-9. Epub 1983/05/28. doi: 10.1016/s0140-6736(83)92462-5. PubMed PMID: 6133986.*

3 *Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med. 1984;310(6):356-60. Epub 1984/02/09. doi: 10.1056/NEJM198402093100605. PubMed PMID: 6690964.*

4 *Taguma Y, Kitamoto Y, Futaki G et al. Effect of captopril on heavy proteinuria in azotemic diabetics. N Engl J Med. 1985 Dec 26;313(26):1617-20*

5 *Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329(20):1456-62. Epub 1993/11/11. doi: 10.1056/NEJM199311113292004. PubMed PMID: 8413456.*

6 *Diabetes C, Complications Trial Research G, Nathan DM, Genuth S, Lachin J, Cleary P, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86. Epub 1993/09/30. doi: 10.1056/NEJM199309303291401. PubMed PMID: 8366922.*

7 *Diabetes C, Complications Trial Research G, Nathan DM, Genuth S, Lachin J, Cleary P, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86. Epub 1993/09/30. doi: 10.1056/NEJM199309303291401. PubMed PMID: 8366922.*

8 *von Scholten BJ, Hansen TW, Goetze JP, Persson F, Rossing P. Glucagon-like peptide 1 receptor agonist (GLP-1 RA): long-term effect on kidney function in patients with type 2 diabetes. J Diabetes Complications. 2015;29(5):670-4. Epub 2015/05/04. doi: 10.1016/j.jdiacomp.2015.04.004. PubMed PMID: 25935863.*

9 *Kluger AY, Tecson KM, Lee AY, Lerma EV, Rangaswami J, Lepor NE, et al. Class effects of SGLT2 inhibitors on cardiorenal outcomes. Cardiovasc Diabetol. 2019;18(1):99. Epub 2019/08/07. doi: 10.1186/s12933-019-0903-4. PubMed PMID: 31382965; PubMed Central PMCID: PMCPMC6683461.*

ARISTOLOCHIC ACID NEPHROPATHY

By Huang-Yu Yang
Kidney Research Institute, Nephrology Department, Chang Gung Memorial Hospital, Taiwan

Approximately three decades ago, women in Belgium taking an herbal slimming regimen suffered from rapidly progressive renal failure. The nephropathy was characterized by acellular, extensive interstitial fibrosis without glomerular lesions and was later named Chinese-herb nephropathy (CHN) or aristolochic acid nephropathy (AAN)[1]. After further investigation, scientists discovered that Stephania tetrandra had inadvertently been substituted with Aristolochia fangchi, thus exposing individuals to aristolochic acid (AA) in their diet. Follow-up studies described high levels of urothelial carcinoma (almost 50%) in patients consuming these Chinese herbs[2,3,4].

Balkan endemic nephropathy (BEN), a tubulointerstitial nephropathy affecting rural farmers in the Balkan area, had been described in 1956[5], but no cause had been found. Subsequently, it was determined that chronic dietary exposure to AA through contaminated crops or water led to endemic nephropathy[6,7,8]. The difference in dose and duration of exposure accounted for BEN patients' slower progression toward ESKD compared to the trajectories within the Belgian cohort[9]. BEN is also associated with pper urinary tract urothelial cancer[10]. Through careful review, a common etiology of CHN and BEN, the exposure to AAN, was therefore described[11].

AA is a powerful nephrotoxin and human carcinogen that causes many adverse effects[12]. Although the sale of AA-containing products is banned in most countries due to the risk of AAN, some herbal products still contain AA and are reported to be in use globally[13,14,15,16,17].

1 *Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women: association with slimming regimen including Chinese herbs. Lancet 1993; 341: 387-391.*
2 *Cosyns JP, Jadoul M, Squifflet JP, et al. Urothelial malignancy in nephropathy due to Chinese herbs. Lancet 1994; 344: 188.*
3 *Schmeiser HH, Bieler CA, Wiessler M, et al. Detection of DNA adducts formed by aristolochic acid in renal tissue from patients with Chinese herbs nephropathy. Cancer Res 1996; 56: 2025-2028.*
4 *Nortier JL, Martinez MC, Schmeiser HH, et al. Urothelial carcinoma associated with the use of a Chinese herb (Aristolochia fangchi). The New England journal of medicine 2000; 342: 1686-1692.*
5 *Tanchev I, Ts E, Dorosiev D, et al. [Study of nephritis in Vrattsa district]. Suvr Med (Sofiia) 1956; 7: 14-29.*
6 *Ivic M. [Etiology of endemic nephropathy]. Lijec Vjesn 1969; 91: 1273-1281.*
7 *Jelakovic B, Karanovic S, Vukovic-Lela I, et al. Aristolactam-DNA adducts are a biomarker of environmental exposure to aristolochic acid. Kidney Int 2012; 81: 559-567.*
8 *Gruia AT, Oprean C, Ivan A, et al. Balkan endemic nephropathy and aristolochic acid I: an investigation into the role of soil and soil organic matter contamination, as a potential natural exposure pathway. Environ Geochem Health 2018; 40: 1437-1448.*
9 *De Broe ME. Chinese herbs nephropathy and Balkan endemic nephropathy: toward a single entity, aristolochic acid nephropathy. Kidney Int 2012; 81: 513-515.*
10 *Stefanovic V, Polenakovic M. Fifty years of research in Balkan endemic nephropathy: where are we now? Nephron Clin Pract 2009; 112: c51-56.*
11 *De Broe ME. Chinese herbs nephropathy and Balkan endemic nephropathy: toward a single entity, aristolochic acid nephropathy. Kidney Int 2012; 81: 513-515.*
12 *Vanhaelen M, Vanhaelen-Fastre R, But P, et al. Identification of aristolochic acid in Chinese herbs. Lancet 1994; 343: 174.*
13 *Yang HY, Lin JL, Chen KH, et al. Aristolochic acid-related nephropathy associated with the popular Chinese herb Xi Xin. J Nephrol 2006; 19: 111-114.*
14 *Ban TH, Min JW, Seo C, et al. Update of aristolochic acid nephropathy in Korea. Korean J Intern Med 2018; 33: 961-969.*
15 *Vaclavik L, Krynitsky AJ, Rader JI. Quantification of aristolochic acids I and II in herbal dietary supplements by ultra-high-performance liquid chromatography-multistage fragmentation mass spectrometry. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2014; 31: 784-791.*
16 *Wu FL, Chen YM, Lai TS, et al. Does Chinese herb nephropathy account for the high incidence of end-stage renal disease in Taiwan? Nephron Clin Pract 2012; 120: c215-222.*
17 *Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. Kidney Int 2008; 74: 158-169.*

NOVEMBER

eGFR

By Mirna Aleckovic-Halilovic and Enisa Mesic
Clinic for Internal Diseases, Department of Nephrology, Dialysis and Renal Transplantation, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

Among the many diverse functions of the kidney, glomerular filtration is a key function. Glomerular filtration rate (GFR) is recognized as the gold standard for assessing overall kidney function[1]. Accurate measurement of GFR using inulin clearance or isoptic techniques is time-consuming and expensive. Thus, equations have been developed to facilitate estimation of GFR in clinical practice. The first equation based on serum creatinine (sCr) for estimating the kidney function was developed in 1957 but was mainly intended to estimate renal drug clearance for dosage adjustments[1]. It was not until 1976 that Donald W. Cockroft and M. Henry Gault (at that time, respirology and nephrology residents) derived a formula for predicting creatinine clearance (CrCl) from sCr, age, and body weight. The novel idea to use an sCr-based formula to estimate kidney function became widespread among physicians[2]. They compared values of CrCl calculated by the formula above and four other published methods with the mean values of the two measured CrCl's for 236 patients and found a correlation coefficient of 0.83. The difference between two paired measured CrCl's was similar to the one between calculated and measured values, suggesting that prediction error was not greater than the difference between two measured CrCl in the same individual. The CG formula for estimating kidney function was used extensively from 1973 until the early 2000s. It is still cited in major pharmacy compendiums and forms the basis of chemotherapeutic and anti-coagulation dosing. In 1999, Andrew S. Levey et al. developed a new sCr-based estimation formula for GFR from the extensive database of the Modification of Diet in Renal Disease (MDRD) Study, marking the start of a modern era in the field of estimated GFR (eGFR) equations[3]. They performed extensive statistical analyses using stepwise multiple regression, including many different variables in predicting GFR, resulting in an equation to estimate GFR, rather than using CrCl measurement, which was easier to apply in laboratory-based systems. Both equations (CG and MDRD) were limited to some extent by the populations used to derive the formulas, but both equations performed well in various scenarios and served the purpose of enabling

1 *Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013; 3: 1-150*

2 *Effersøe, P. Relationship between endogenous 24-hour creatinine clearance and serum creatinine concentration in patients with chronic renal disease. Acta Med. Scand. 156, 429–434 (1957).*

3 *Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 16, 31–41 (1976).*

clinical estimation of GFR and a better understanding of kidney function than simple serum creatinine values. The eGFR is a simple and essential tool for decision making in nephrology and the broader medical field that should be further qualified by applying a uniform 'gold standard' calibration of sCr measurements. Developing the precision and accuracy of estimating equations has formed a significant work component since 2000. The key is the value of the eGFR in that it facilitates the interpretation of serum creatinine within individual patient contexts, providing the clinician and patient with a better appreciation of true kidney function[1,2,3].

1 *Levey, A. S. et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann. Intern. Med. 130, 461–470 (1999).*

2 *Matsuo, S. et al. Revised equations for estimated GFR from serum creatinine in Japan. Am. J. Kidney Dis. 53, 982-92 (2009)*

3 *Ling-I Chen et al. Modification of diet in renal disease (MDRD) study and CKD epidemiology collaboration (CKD-EPI) equations for Taiwanese adults. PLoS One. 2014;9:e99645.*

CKD CLASSIFICATION AND STAGING

By Sabine Karam MD
Saint George Hospital University Medical Center, Beirut, Lebanon

In 2002, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) published " Clinical Practice Guidelines for Chronic Kidney Disease (CKD) for evaluation, classification, and stratification of CKD"[1]. This landmark initiative has had far-reaching and dramatic consequences for clinical practice, research, and public health worldwide. More than standardizing the definition of CKD to replace previous terminology (comprising a confusing array of terms), it also established that kidney health is not only about care for late-stage kidney failure but rather that CKD is a very common epidemiologic entity with important public health repercussions requiring prevention and detection at early stages. Furthermore, using large representative databases of both referred and non-referred patients and evidence-based examination of the literature, the KDOQI working group, including Adeera Levin (former ISN president) and colleagues, defined five stages of kidney disease according to the level of glomerular filtration rate (GFR) and the prevalence of co-morbidities associated with kidney disease[2]. The emphasis on estimating GFR from formulas rather than using simple serum creatinine values was an attempt to recognize the limitations of serum creatinine as a marker of kidney function. Following a decade of intense data analysis and collaboration, data from the CKD Prognosis Consortium showed a steep increase of risk at GFR <45 mL/min/1.73 m 2, and that proteinuria stages were also powerful predictors for cardiovascular disease and mortality[3]. The culmination of these findings led to a revision of this classification with a subdivision of GFR stage 3 into GFR stage 3a and stage 3b and incorporation of cause and albuminuria categories as classification criteria by a KDIGO CKD Guideline Work Group in 2012[4]. Ongoing use of the classification system has led to improved communication for patients, primary care physicians, and other specialists and defines entry criteria into clinical trials.

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1 *National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39(2 Suppl 1):S1-266. Epub 2002/03/21. PubMed PMID: 11904577.*

2 *Levin A. The advantage of a uniform terminology and staging system for chronic kidney disease (CKD). Nephrol Dial Transplant. 2003;18(8):1446-51. Epub 2003/08/05. doi: 10.1093/ndt/gfg241. PubMed PMID: 12897079.*

3 *Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17-28. Epub 2010/12/15. doi: 10.1038/ki.2010.483. PubMed PMID: 21150873.*

4 *Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group*

KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013; 3: 1-150

PURIFICATION OF ERYTHROPOIETIN

By Caner Alparslan
Diyarbakır Gazi Yaşargil Training and Research Hospital, Turkey

Erythropoietin (EPO) is an important hormone that contributes to erythropoiesis and serves as an anti-apoptotic hormone. Receptors for the hormone exist on the vasculature and in various organ systems. The development of EPO to address clinical issues identified in kidney patients is surely an important milestone for modern-day nephrology[1]. In 1906, Carnot and Deflandre[2] detected increasing erythropoiesis in rabbits when given hypoxic rabbit serum. They defined that factor as a hemopoietin, with the more specific name “erythropoietin” provided by Bonsdorff[3]. In 1943, Krumdieck[4] and 1953, Erslev[5] modified Carnot and Deflandre’s experiment by adding a reticulocyte count and showed increasing erythropoiesis within 3 – 6 days of injection of anemic rabbit serum[6].

Through rat studies in 1957 and 1964, respectively, Jacobson[7] and Nathan[8] revealed that kidneys are the primary organs for EPO secretion . In the following years, Eugene Goldwasser began intense and prolonged efforts to isolate EPO. First, he studied anemic sheep and obtained 200 µcg of EPO in 1/10 purity in 1970. Later, he examined the urine from anemic patients in Argentina. Finally, in 1977 Takaji Miyake purified 8 mg of EPO using 2.5 t of urine from Japanese aplastic anemic patients[9,10]. In subsequent years, Jacobs et al.[11] and Lin et al.[12] achieved molecular cloning of the EPO gene that led to the production of recombinant EPO in 1985. Recombinant EPO, used to treat anemia in CKD, turned out to be a most successful bioengineered drug[13].

1 *Eschbach JW The anemia of chronic renal failure: pathophysiology and the effects of recombinant. Kidney Int 1989;35:134-148.*
2 *Carnot P, Deflandre C. Sur l’activité hémopo’iétique du sérum au cours de la régénération du sang. Copmt rend Acad Sci, 1906; 143: 384-386.*
3 *Bonsdorff E. On the presence of erythropoietin in the plasma from sheep foetuses during the latter half of gestation. Acta Physiol Scandinav, 1949; 18:51-62.*
4 *Krumdieck N. Erythropoietic substance in the serum of anemic animals. Proc Soc Exp Biol Med, 1943; 54: 14–17.*
5 *Erslev A. Humoral regulation of red cell production. Blood, 1953; 8: 349–357.*
6 *Bunn HF. Erythropoietin. Cold Spring Harb Perspect Med, 2013; 3:a011619.*
7 *Jacobson LO, Marks E, Gaston E, Goldwasser E. Role of the kidney in erythropoiesis. Nature, 1957; 179: 633–634.*
8 *Nathan DG, Schupak E, Stohlman F Jr, Merrill JP. Erythropoiesis in anephric man. J Clin Invest, 1964; 43: 2158–2165.*
9 *Miyake T, Kung CKH, Goldwasser E. Purification of human erythropoietin. J Biol Chem, 1977; 252: 5558-5564.*
10 *Goldwasser E. Erythropoietin: a somewhat personal history. Perspectives in Biology and Medicine, 1996; 40(1): 18-32.*
11 *Jacobs K, Shoemaker C, Rudersdorf R, Neill SD, Kaufman RJ, Mufson A, Seehra J, Jones SS, Hewick R, Fritsch EF, et al. Isolation and characterization of genomic and cDNA clones of human erythropoietin. Nature, 1985; 313: 806–810.*
12 *Lin F-K, Suggs S, Lin C-H, Browne JK, Smalling R, Egrie JC, Chen KK, Fox GM, Martin F, Stabinsky Z, et al. Cloning and expression of the human erythropoietin gene. Proc Natl Acad Sci, 1985; 82: 7580–7584.*
13 *Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med. 1987;316(2):73-8.*

As recombinant EPO and their relatives, erythropoietic stimulating agents (ESA), are relatively safe, large clinical trials were performed to clarify whether hemoglobin normalization improves prognosis and quality of life in CKD patients. However, the Normal Hematocrit Study in hemodialysis patients[1] and three large clinical trials in non-dialysis dependent CKD patients, CREATE[2], CHOIR[3], and TREAT[4], showed association of adverse events with high target hemoglobin levels in patients treated with ESA. Subsequent analysis showed that hyporesponsiveness to ESA, rather than high target hemoglobin levels per se, played a critical role in increased adverse events[5].

1 *Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998 Aug 27;339(9):584-90.*

2 *Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006 Nov 16;355(20):2071-84.*

3 *Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006 Nov 16;355(20):2085-98.*

4 *Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, Remuzzi G, Singh AK, Solomon SD, Toto R; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009 Nov 19;361(21):2019-32.*

5 *Solomon SD, Uno H, Lewis EF, Eckardt KU, Lin J, Burdmann EA, de Zeeuw D, Ivanovich P, Levey AS, Parfrey P, Remuzzi G, Singh AK, Toto R, Huang F, Rossert J, McMurray JJ, Pfeffer MA; Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) Investigators. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010 Sep 16;363(12):1146-55.*

RENAL OSTEODYSTROPHY AND CKD-MBD

By Hirotaka Komaba
Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan

There has been a long evolution in understanding the complex relationship between kidney disease and bone disease. Renal bone disease was first recognized by Virchow in 1855[1]. However, it was not until 1943 – before the introduction of dialysis treatment – that the term "renal osteodystrophy" was first used[2].

Interest in bone metabolism in various states had predominantly been in the context of endocrinology and metabolism. In the late 1960s, with the number of kidney disease patients increasing, Bricker's group proposed the concept that became known as the "trade-off hypothesis"[3], which described that with increasing nephron loss and reduction in phosphate excretion, higher levels of PTH were needed to facilitate the excretion of phosphate. This simple but plausible theory overlooked the more complex relationship between vitamin D and PTH. The Bricker group was unaware that the kidney is the principal site of 1,25-dihydroxyvitamin D synthesis and that relative 125OH2D3 deficiency also drives PTH elevation. This was revealed in the early 1970s by two groups led by DeLuca[4] and by Fraser and Kodicek[5]. Subsequently, the demonstration that 1,25-dihydroxyvitamin D suppresses parathyroid hormone synthesis[6] stimulated the clinical use of active vitamin D to treat secondary hyperparathyroidism.

Treatment paradigms for excess phosphate and HPTH included aluminum. In the 1970s and 80s, aluminum used as a phosphate binder was eventually found to induce osteomalacia and neurological toxicity[7], further contributing to bone disease. This led to the alternative use of calcium-based binders over the next 20+ years, but these agents have also faced controversy as excessive calcium use is associated with accelerated vascular calcification (in vivo and in vitro). However, these treatments

1 *Virchow R. Kalk-Metastasen. Archiv f pathol Anat. 1855;8(1):103-113.*
2 *Liu SH, Chu HI. Studies of calcium and phosphorus metabolism with special reference to pathogenesis and effects of dihydrotachysterol (A.T.10) and iron. Medicine. 1943;22(2):103-162.*
3 *Bricker NS, Slatopolsky E, Reiss E, et al. Calcium, phosphorus, and bone in renal disease and transplantation. Arch Intern Med. 1969;123(5):543-553.*
4 *Holick MF, Schnoes HK, DeLuca HF, et al. Isolation and identification of 1,25-dihydroxycholecalciferol. A metabolite of vitamin D active in intestine. Biochemistry. 1971;10(14):2799-2804.*
5 *Fraser DR, Kodicek E. Unique biosynthesis by kidney of a biological active vitamin D metabolite. Nature. 1970;228(5273):764-766.*
6 *Silver J, Naveh-Many T, Mayer H, et al. Regulation by vitamin D metabolites of parathyroid hormone gene transcription in vivo in the rat. J Clin Invest. 1986;78(5):1296-1301*
7 *Alfrey AC, LeGendre GR, Kaehny WD. The dialysis encephalopathy syndrome. Possible aluminum intoxication. N Engl J Med. 1976;294(4):184-188.*

were in the context of deranged phosphate metabolism, and appreciation of the complexity of the biological relationship only began to emerge in the 2000s. With increased understanding and need for treatment came the development of non-calcium-based binders, along with the introduction of the concept "chronic kidney disease-mineral bone disorder (CKD-MBD)." CKD MBD describes the totality of the impact of CKD MBD, not just bone parameters, and incorporates extraskeletal calcification as one of its components[1]. The term attempted to convey the complexity of the relationship and stimulated more basic and clinical research in the area.

The identification of calcium-sensing receptors by Brown and colleagues in 1993[2] represented a major step forward in our understanding of PTH regulation, and ultimately the development of drugs targeting this receptor. Parathyroid hormone-lowering therapy that does not cause hypercalcemia or hyperphosphatemia led to the development and availability of calcimimetics in the 2000s[3].

The discovery of the fibroblast growth factor 23-Klotho system in the 2000s[4,5] considerably advanced our understanding of CKD-MBD. Research is ongoing to determine whether this system can be therapeutically targeted in patients with kidney disease[6,7].

1 *Moe S, Drüeke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006;69(11):1945-1953.*

2 *Brown EM, Gamba G, Riccardi D, et al. Cloning and characterization of an extracellular Ca(2+)-sensing receptor from bovine parathyroid. Nature. 1993;366(6455):575-580.*

3 *Block GA, Martin KJ, de Francisco AL, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. N Engl J Med. 2004;350(15):1516-1525*

4 *Kuro-o M, Matsumura Y, Aizawa H, et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature. 1997;390(6655):45-51.*

5 *Urakawa I, Yamazaki Y, Shimada T, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature. 2006;444(7120):770-774.*

6 *Gutiérrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med. 2008;359(6):584-592.*

7 *Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. J Clin Invest. 2011;121(11):4393-4408.*

CARDIO-RENAL ASSOCIATION

By Muzamil Olamide Hassan
Renal Unit, Department of Medicine,
Obafemi Awolowo University Teaching Hospital, Nigeria

In 1836, Dr. Richard Bright at Guy's Hospital, London, England, was the first to describe the association between chronic kidney disease and cardiovascular disease when he discovered an enlarged left ventricle in the autopsies of several kidney disease patients[1]. Since then, several epidemiological studies have confirmed and extended this finding[2,3,4,5]. The term 'cardiorenal' as relating to human disease was first used in 1913 by Thomas Lewis[6]. Around 2004, the term 'cardio-renal syndrome' was used to describe the pathophysiological condition in which cardiac and renal disease co-exist. The Working Group of the National Heart, Lung, and Blood Institute first attempted to formally define cardio-renal syndrome (CRS) in 2004[7]. Subsequently, at a consensus conference of the Acute Dialysis Quality Initiative in 2008, CRS was defined as comprising a spectrum of disorders involving the heart and kidneys in which acute or chronic dysfunction in one organ may cause acute or chronic dysfunction in another organ, and was classified into five subtypes based on the organ that is primarily responsible[8,9]. Given that the mechanisms underlying the cross-talk between the kidney and heart are multifactorial and parts of these mechanisms remain undetermined, further studies are necessary to address these research gaps.

1 *Keith NM, Keys TE. Contributions of Richard Bright and his associates to renal disease. AMA archives of internal medicine. 1954; 94(1):5-21.*

2 *Foley RN, Parfrey PS, Harnett JD, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int. 1995; 47:186-92.*

3 *Go AS, Chertow GM, Fan D et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351:1296–305. doi:10.1056/NEJMoa041031*

4 *Daly C. Is early chronic kidney disease an important risk factor for cardiovascular disease? A background paper prepared for the UK Consensus Conference on early chronic kidney disease. Neph Dial Transplant. 2007;22(Suppl.9):19-25.*

5 *Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003; 108:2154–69.*

6 *Lewis T. A Clinical Lecture ON PAROXYSMAL DYSPNOEA IN CARDIORENAL PATIENTS: WITH SPECIAL REFERENCE TO "CARDIAC" AND "URAEMIC" ASTHMA: Delivered at University College Hospital, London, November 12, 1913. Br Med J. 1913;2(2761):1417-1420. doi:10.1136/bmj.2.2761.1417*

7 *National Heart, Lung, and Blood Institute. NHLBI Working Group: cardio-renal connections in heart failure and cardiovascular disease, 2004. 2004. https://www.nhlbi.nih.gov/events/2004/cardio-renal-connections-heart-failure-and-cardiovascular-disease. Accessed August 3, 2020.*

8 *Ronco C, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P. Cardio-renal syndromes: report from the Consensus Conference of the Acute Dialysis Quality Initiative. Eur Heart J. 2010; 31:703–711.*

9 *Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008; 52:1527–1539. doi: 10.1016/j.jacc.2008.07.051.*

DECEMBER

CORTICOSTEROIDS AS EFFECTIVE (AND THEREFORE LIFESAVING) IN NEPHROTIC SYNDROME IN CHILDREN

By Shankar Prasad Yadav
Department Of Pediatrics, B.P.Koirala Institute Of Health Sciences, Dharan, Nepall

Steroid hormones were first isolated and identified in 1936. Cortisone was prepared by partial synthesis from bile acids by 1946, while adrenocorticotropic hormone (ACTH) was extracted from pig and sheep pituitary glands by isoelectric precipitation in the 1940s[1]. A few hallmark studies reported the use of either ACTH or cortisone via the intramuscular route in a small cohort of children with Nephrotic Syndrome administered from between 5 days to 2 weeks. These hormonal therapies induced diuresis, reduction of edema, decrease in albuminuria, and improvement in serum cholesterol in the majority of children both during and after therapy[2,3]. Arneil preferred cortisone over ACTH, considering possible contamination of ACTH with antidiuretic hormone (ADH). High-dose intramuscular cortisone, based on children's weight, was given over five days and abruptly stopped. It produced the desired effect for a few days in 4 out of 6 cases. One patient was effectively treated with oral cortisone[4]. Later on, prednisone synthesized by oxidation of cortisone became available, and oral prednisone gradually emerged as first-line therapy[5]. This may be due to the cost and administration route, as well as the factors described above. With the advent of steroid therapy, mortality from nephrotic syndrome dramatically decreased.

1 *Pal A, Kaskel F. History of Nephrotic Syndrome and Evolution of its Treatment. Front Pediatr 2016; 4: 56*
2 *Barnett Hl, Mcnamara H, Mccrory W, et al. The Effects Of ACTH And Cortisone On The Nephrotic Syndrome. Ama Am J Dis Child. 1950;80(3):519-520*
3 *Mccall MF, Ross A, Wolman B, Burns Ad, Harpur Em, Goldbloom A. The Nephrotic Syndrome In Children Treated With ACTH And Cortisone. Arch Dis Child. 1952 Aug;27(134):309-21.*
4 *Arneil G, Wilson H. Archives Of Disease In Childhood 1952; 27: 322*
5 *Chaudhuri JN, Ghosal SP. Observations on prednisolone treated cases of nephrotic syndrome. Indian J Pediatr (1958) 25(5):201–9*

HYPERFILTRATION THEORY

by Marco van Londen
University Medical Center Groningen, The Netherlands

In the 1980s, Barry M. Brenner, nephrologist at Brigham and Women's Hospital in Boston, presented a novel concept called the hyperfiltration theory[1]. In patients with loss of nephrons due to kidney disease, nephrectomy, or reduced nephron endowment at birth, the remnant nephrons increase the single nephron glomerular filtration (snGFR) as an adaptive response to maintain overall GFR. High protein and/or salt intake further aggravate hyperfiltration and, accordingly, kidney damage. We now know how tubuloglomerular feedback drives hyperfiltration. Individuals with prolonged high snGFR develop maladaptive changes to glomerular capillaries and in podocytes, initiating and perpetuating disease progression in CKD. In living kidney donors, a higher snGFR was independently associated with larger nephrons on biopsy and more glomerulosclerosis and arteriosclerosis than would be expected for age[2]. Concurrently, albuminuria was discovered as a major mechanism accelerating CKD progression.

Although lack of long-term human data remains a drawback, Brenner's theory set the stage for studies on prevention and treatment of CKD: RAS inhibitors ameliorate hyperfiltration, and improve long-term kidney outcomes, especially during moderate salt intake[3]. The recently discovered SGLT-2 inhibitors ameliorate hyperfiltration in CKD through an effect on tubuloglomerular feedback[4].

In conjunction with meticulously conducted animal experiments, subsequent human observations, and clinical trials, Barry Brenner's hyperfiltration theory has changed the state of the art and science of nephrology over the last three decades.

1 *Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: A paradigm shift in nephrology. Kidney Int. 1996; 49(6):1774-7.*
2 *Denic A, Mathew J, Lerman LO, Lieske JC, Larson JJ, Alexander MP, Poggio E, Glassock RJ, Rule AD. Single-Nephron Glomerular Filtration Rate in Healthy Adults. N Engl J Med 2017; 376:2349-2357.*
3 *Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P. Sodium intake, ACE inhibition, and progression to ESRD. J Am Soc Nephrol. 2012;23(1):165-173.*
4 *Fioretto P, Zambon A, Rossato M, Busetto L, Vettor R. SGLT2 Inhibitors and the Diabetic Kidney. Diabetes Care. 2016;39 Suppl 2:S165-S171.*

KIDNEY PROTECTION BY RAS INHIBITION

By Nikolay Bulanov
Sechenov First Moscow State Medical University, Russia

Currently, inhibition of the renin-angiotensin system (RAS) is the standard of care in the management of diabetic and non-diabetic chronic kidney disease (CKD).

Initially, RAS inhibition was considered contraindicated in patients with CKD because it leads to an initial dip in GFR. However, Taguma and colleagues reported kidney protection by captopril in patients with diabetic kidney disease in 1985[1]. While kidney protection by RAS inhibition was not considered viable at that time, hallmark studies by Edmund Lewis et al. in 1993 demonstrated that captopril reduced the risk of doubling serum creatinine concentration in insulin-dependent diabetic nephropathy in a randomized control trial[2]. In a larger, more diverse group of patients, data reported on the renoprotective effect of RAS inhibition in those with type 2 diabetes and proteinuria. The Irbesartan Diabetic Nephropathy Trial (IDNT) described 'hard end-points'[3], such as doubling of serum creatinine, ESRD, or death, as the primary outcomes, and it was significantly lower in the irbesartan treatment group than in the placebo and amlodipine groups. Most importantly, this effect was independent of the reduction in blood pressure. Similar results were obtained by Brenner et al. in the RENAAL study[4] and Parving et al. in the IRMA-2 study[5], published in the same issue of The New England Journal of Medicine. Remuzzi et al. also showed the prevention of microalbuminuria in diabetics in the BENEDICT study[6].

The first RCT that demonstrated the benefit of RAS inhibition in non-diabetic CKD was the Ramipril in Non-diabetic Renal Failure (REIN) study conducted by the GISEN group and published in 1997[7]. The authors showed that treatment with ramipril was associated with slower GFR decline and a significantly lower risk of doubling the

1 *Taguma Y, Kitamoto Y, Futaki G et al. Effect of captopril on heavy proteinuria in azotemic diabetics. N Engl J Med. 1985;313:1617-1620.*
2 *Lewis EJ, Hunsicker LG, Bain BP, Rohde RD. The Effect of Angiotensin-Converting-Enzyme Inhibition on Diabetic Nephropathy. N Engl J Med. 1993;329:1456-1462.*
3 *Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes. N Engl J Med. 2001;345:851-860.*
4 *Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy. N Engl J Med. 2001;345:861-869.*
5 *Parving HH, Lehnert H, Bröchner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med. 2001;345:870-878.*
6 *Ruggenenti P, Fassi A, Ilieva AP, et al. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004;351:1941-51.*
7 *The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet. 1997;349(9069):1857-1863.*

serum creatinine concentration or ESRD in chronic non-diabetic nephropathies with proteinuria of ≥3 g/24 h independently of blood pressure reduction.

All these studies contributed to a paradigm shift in diabetic and non-diabetic CKD management, providing evidence for future studies of the role of RAS in the progression of kidney diseases. Note that all studies included those with proteinuric kidney diseases. To our knowledge, there has not been a study examining non-proteinuric kidney disease.

HIF AND HYPOXIA OF THE KIDNEY

By Lili Zhou
Division of Nephrology, Nanfang Hospital, Southern Medical University, China

Oxygen homeostasis is critical to cell vitality and depends on its transportation via binding with hemoglobin. In response to hypoxia, the hormone erythropoietin (EPO) is induced to increase erythropoiesis and oxygen delivery. However, EPO regulation was not well characterized until 1992, when Gregg Semenza discovered the key transcriptional factor, hypoxia-inducible factor (HIF)[1]. HIF consists of a constitutive β subunit and an oxygen-dependent α-subunit[2]. Sir Peter J. Ratcliffe clarified the mechanism of oxygen-dependent regulation of HIF, revealing the critical role of oxygen-dependent hydroxylation of specific prolyl residues in HIF-α through HIF-prolyl hydroxylase (HIF-PH)[3,4]. William Kaelin Jr. demonstrated the essential role of von Hippel-Lindau (VHL) E3 ligase in proteolysis of hydroxylated HIF-α[5]. Under hypoxia or PHD inhibition, HIF-α translocates into nuclei and heterodimerizes with HIF-β to initiate the transcription of EPO (a specific HIF-2α target) and other targets. In states of reduced kidney function, EPO-producing cells in the kidney lose their ability to produce EPO, leading to a reduction in hematopoiesis and, thus, lower hemoglobin values. The Nobel Assembly at Karolinska Institute jointly awarded the 2019 Nobel Prize in Physiology or Medicine to Sir Peter J. Ratcliffe, Gregg L. Semenza, and William G. Kaelin Jr. for their important discovery of how cells sense and adapt to oxygen availability. Sir Peter Ratcliffe thus became the first nephrologist to receive a Nobel laureate. Pharmacological interventions using HIF-PH inhibitors now serve as a novel therapeutic modality for anemia in CKD[6,7].

Of note, hypoxia and HIF regulation are involved in numerous pathophysiological

1 *Semenza GL, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. Mol Cell Biol. 1992;12:5447-54.*

2 *Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci U S A. 1995;92:5510-4.*

3 *Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, von Kriegsheim A, Hebestreit HF, Mukherji M, Schofield CJ, Maxwell PH, Pugh CW, Ratcliffe PJ. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science. 2001;292:468-72.*

4 *Epstein AC, Gleadle JM, McNeill LA, Hewitson KS, O'Rourke J, Mole DR, Mukherji M, Metzen E, Wilson MI, Dhanda A, Tian YM, Masson N, Hamilton DL, Jaakkola P, Barstead R, Hodgkin J, Maxwell PH, Pugh CW, Schofield CJ, Ratcliffe PJ. C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. Cell. 2001;107:43-54.*

5 *Ivan M, Kondo K, Yang H, Kim W, Valiando J, Ohh M, Salic A, Asara JM, Lane WS, Kaelin WG Jr. HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. Science. 2001;292:464-8.*

6 *Chen N, Hao C, Peng X, Lin H, Yin A, Hao L, Tao Y, Liang X, Liu Z, Xing C, Chen J, Luo L, Zuo L, Liao Y, Liu BC, Leong R, Wang C, Liu C, Neff T, Szczech L, Yu KP. Roxadustat for Anemia in Patients with Kidney Disease Not Receiving Dialysis. N Engl J Med. 2019;381:1001-1010.*

7 *Chen N, Hao C, Liu BC, Lin H, Wang C, Xing C, Liang X, Jiang G, Liu Z, Li X, Zuo L, Luo L, Wang J, Zhao MH, Liu Z, Cai GY, Hao L, Leong R, Wang C, Liu C, Neff T, Szczech L, Yu KP. Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis. N Engl J Med. 2019;381:1011-1022.*

processes, including kidney disease. Chronic Hypoxia Hypothesis," initially proposed by Leon Fine, emphasized that chronic hypoxia in the tubulointerstitial compartment may be a final common pathway to end-stage kidney disease[1]. This concept was extended and verified in experimental studies by Masaomi Nangaku and Kai-Uwe Eckardt independently[2,3]. Recent advances in technology have enabled scientists to monitor intracellular oxygen tensions in live animals and further clarify the crucial role of hypoxia in kidney disease[4]. Now chronic hypoxia in the kidney is thought to be an important target for therapeutic approaches. HIF activation may be a useful therapy, not only as a treatment of anemia in CKD but potentially ameliorating progressive kidney decline itself.

1 *Fine LG, Orphanides C, Norman JT. Progressive renal disease: the chronic hypoxia hypothesis. Kidney Int Suppl. 1998 Apr;65:S74-8.*

2 *Nangaku M. Chronic hypoxia and tubulointerstitial injury: a final common pathway to end-stage renal failure. J Am Soc Nephrol. 2006;17:17-25.*

3 *Eckardt KU, Bernhardt WM, Weidemann A, Warnecke C, Rosenberger C, Wiesener MS, Willam C. Role of hypoxia in the pathogenesis of renal disease. Kidney Int Suppl. 2005;(99):S46-51.*

4 *Hirakawa Y, Mizukami K, Yoshihara T, Takahashi I, Khulan P, Honda T, Mimura I, Tanaka T, Tobita S, Nangaku M. Intravital phosphorescence lifetime imaging of the renal cortex accurately measures renal hypoxia. Kidney Int. 2018;93:1483-1489.*

IDENTIFICATION OF SGLT2 AND CLINICAL APPLICATION OF ITS INHIBITOR

By Sabine Karam MD
Saint George Hospital University Medical Center, Beirut, Lebanon

In humans, the kidneys filter ≈180g of d-glucose from plasma each day, all of which is reabsorbed. In the 1980s and 90s, Wright and colleagues postulated that the major reabsorptive mechanism involved a low-affinity, high-capacity Na+/glucose cotransporter located in the early proximal convoluted tubule segment S1, and with a Na+ to glucose coupling ratio of 1:1. They named it SGLT2, as opposed to SGLT1 expressed in the intestine, kidney, heart, and skeletal muscle[1]. The first molecular evidence for this renal D-glucose reabsorptive mechanism was provided by Kanai et al. in 1994[2]. Of interest, as early as 1835, and subsequent to its isolation from the bark of apple trees by French chemists[3], phlorizin was found to produce glucosuria by Von Mering in 1886[4]. A century later, phlorizin's binding affinity for the renal glucose transporter was found to be 1000 to 3000 times the affinity of glucose for this carrier[5], leading to an increased interest to use it or its analogs as pharmaceutical tools to lower glycemia by promoting glycosuria.

Initially designed for just that purpose, the class of SGLT2 transport inhibitors was found to have pleiotropic effects. Several landmark trials such as the Empagliflozin, Cardiovascular Outcomes, and Mortality in type 2 diabetes (T2DM) (EMPA-REG OUTCOME) trial[6], the Canagliflozin Cardiovascular Assessment Study (CANVAS)[7] and the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial[8], showed significant reductions in cardiovascular events suggesting significant renoprotective effects. Although these studies were large, landmark international trials, they were cardiovascular outcome trials, and most of the recruited patients did not have kidney disease at the time of recruitment. It was the CREDENCE trial that established the potent

1 *Wells RG, Pajor AM, Kanai Y, Turk E, Wright EM, Hediger MA. Cloning of a human kidney cDNA with similarity to the sodium-glucose cotransporter. Am J Physiol. 1992;263(3 Pt 2):F459-65. Epub 1992/09/01. doi: 10.1152/ajprenal.1992.263.3.F459. PubMed PMID: 1415574.*

2 *Kanai Y, Lee WS, You G, Brown D, Hediger MA. The human kidney low affinity Na+/glucose cotransporter SGLT2. Delineation of the major renal reabsorptive mechanism for D-glucose. J Clin Invest. 1994;93(1):397-404. Epub 1994/01/01. doi: 10.1172/JCI116972. PubMed PMID: 8282810; PubMed Central PMCID: PMCPMC293794.*

3 *Petersen C. Analyse des phloridzins. Ann Acad Sci Fr. 1835;15:178.*

4 *J. VM. Ueber kunstlichen Diabetes. Centralbl Med Wiss. 1886;xxii:531.*

5 *Vick H, Diedrich DF, Baumann K. Reevaluation of renal tubular glucose transport inhibition by phlorizin analogs. Am J Physiol. 1973;224(3):552-7. Epub 1973/03/01. doi: 10.1152/ajplegacy.1973.224.3.552. PubMed PMID: 4691268.*

6 *Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015;373(22):2117-28. Epub 2015/09/18. doi: 10.1056/NEJMoa1504720. PubMed PMID: 26378978.*

7 *Neal B, Perkovic V, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(21):2099. Epub 2017/11/23. doi: 10.1056/NEJMc1712572. PubMed PMID: 29166232.*

8 *Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-57. Epub 2018/11/13. doi: 10.1056/NEJMoa1812389. PubMed PMID: 30415602.*

renoprotective effect of this class of medications unequivocally by showing that canagliflozin reduces the risk of end-stage kidney disease and death from renal or cardiovascular disease by 32% when compared to placebo among patients with T2DM and diabetic nephropathy[1] with proteinuria.

Because of the unexpectedly marked benefits of SGLT2 inhibition in diabetic kidney disease, the next important question was whether SGLT2 inhibition would also be effective in non-diabetic kidney disease. The DAPA-CKD trial revealed that the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo among patients with CKD, regardless of the presence or absence of diabetes[2], those with eGFR's as low as 25, and with proteinuria. Another large international study, EMPA-KIDNEY, conducted by Will Herrington et al. from Oxford, is expected to further extend these observations to those with no-diabetic kidney disease at lower GFR levels irrespective of proteinuria.

1 *Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. N Engl J Med. 2019;380(24):2295-306. Epub 2019/04/17. doi: 10.1056/NEJMoa1811744. PubMed PMID: 30990260.*

2 *Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020 Oct 8;383(15):1436-1446.*

SIXTY PLUS ONE:
AN OVERVIEW OF RECENT DISCOVERIES AS POTENTIAL BREAKTHROUGHS TO FUTURE KNOWLEDGE

By Yosuke Hirakawa
Division of Nephrology and Endocrinology, the University of Tokyo Hospital, Japan

Read the full article here.

kidney INTERNATIONAL

In addition to the 60 historical breakthroughs presented throughout 2020, we wanted to note some potential breakthroughs that await future validation. Although too recent to be included in the 60 preceding narratives, we believe they are just as important and decided to mention these as "sixty plus one."

Reprogramming of mature cells to become pluripotent

In 2012, the Nobel Prize in Physiology or Medicine 2012 was jointly awarded to **John B. Gurdon and Shinya Yamanaka for the discovery that mature cells can be reprogrammed to become pluripotent**. The application of induced pluripotent stem cells (iPS cells) to kidney research is rapidly advancing the field, in which Melissa Little and Ryuichi Nishinakamura are leaders. They developed methods to independently establish kidney organoids, giving hope of applying their methods to novel drug screening, disease modeling, and regenerative therapy[1,2].

Next-generation sequencing to improve sophistication of understanding of kidney cell types

Advances in next-generation sequencing is another example of a recent breakthrough. Katalin Susztak et al. applied single-cell RNA sequencing to nephron-constituent cells, identifying 20 types of nephron component cells[3]. Their study illustrated the characteristics of each cell type precisely and discovered two cell clusters that had not previously been identified. Katalin Susztak also created an expression quantitative trait loci (eQTL) atlas for the glomerular and tubular compartments of the human kidney and integrated eQTL with the CKD GWAS, single-cell RNA sequencing, and regulatory region maps to identify novel genes for CKD[4]. The clinical application of genome sequencing is also widely applicable. Ali Gharavi et al. revealed that a significant proportion of chronic kidney disease patients have causal genome mutations[5].

1 *Takasato M, Er PX, Chiu HS, Maier B, Baillie GJ, Ferguson C, Parton RG, Wolvetang EJ, Roost MS, Lopes SM, Little MH. Kidney Organoids From Human iPS Cells Contain Multiple Lineages and Model Human Nephrogenesis. Nature. 2015;526:564-8.*

2 *Taguchi A, Kaku Y, Ohmori T, Sharmin S, Ogawa M, Sasaki H, Nishinakamura R. Redefining the in vivo origin of metanephric nephron progenitors enables generation of complex kidney structures from pluripotent stem cells. Cell Stem Cell. 2014;14:53-67.*

3 *Park J, Shrestha R, Qiu C, Kondo A, Huang S, Werth M, Li M, Barasch J, Suszták K. Single-cell transcriptomics of the mouse kidney reveals potential cellular targets of kidney disease. Science. 2018;360:758-763.*

4 *Qiu C, Huang S, Park J, Park Y, Ko YA, Seasock MJ, Bryer JS, Xu XX, Song WC, Palmer M, Hill J, Guarnieri P, Hawkins J, Boustany-Kari CM, Pullen SS, Brown CD, Susztak K. Renal compartment-specific genetic variation analyses identify new pathways in chronic kidney disease. Nat Med. 2018 Nov;24(11):1721-1731.*

5 *Groopman EE, Marasa M, Cameron-Christie S, Petrovski S, Aggarwal VS, Milo-Rasouly H, Li Y, Zhang J, Nestor J, Krithivasan P, Lam WY, Mitrotti A, Piva S, Kil BH, Chatterjee D, Reingold R, Bradbury D, DiVecchia M, Snyder H, Mu X, Mehl K, Balderes O, Fasel DA, Weng C, Radhakrishnan J, Canetta P, Appel GB, Bomback AS, Ahn W, Uy NS, Alam S, Cohen DJ, Crew RJ, Dube GK, Rao MK, Kamalakaran S, Copeland B, Ren Z, Bridgers J, Malone CD, Mebane CM, Dagaonkar N, Fellström BC, Haefliger C, Mohan S, Sanna-Cherchi S, Kiryluk K, Fleckner J, March R, Platt A, Goldstein DB, Gharavi AG. Diagnostic Utility of Exome Sequencing for Kidney Disease. N Engl J Med. 2019;380:142-151.*

Collaborations across disciplines: Bioengineering and nephrology

Other potential breakthroughs can be achieved by collaboration within different fields, such as technology and engineering. Kidney-on-a-chip, developed by Jonathan Himmelfarb and others, may serve as an important tool in the future[1].

Telemedicine, EMR, and care delivery

COVID-19 forced us to recognize the importance of telenephrology[2]. Database-driven studxies using electronic health records are producing important insights[3].

1 *Weber EJ, Lidberg KA, Wang L, Bammler TK, MacDonald JW, Li MJ, Redhair M, Atkins WM, Tran C, Hines KM, Herron J, Xu L, Monteiro MB, Ramm S, Vaidya V, Vaara M, Vaara T, Himmelfarb J, Kelly EJ. Human kidney on a chip assessment of polymyxin antibiotic nephrotoxicity. JCI Insight. 2018 Dec 20;3(24):e123673.*

2 *Rohatgi R, Ross MJ, Majoni SW. Telenephrology: current perspectives and future directions. Kidney Int. 2017 Dec;92(6):1328-1333.*

3 *Nakagawa N, Sofue T, Kanda E, Nagasu H, Matsushita K, Nangaku M, Maruyama S, Wada T, Terada Y, Yamagata K, Narita I, Yanagita M, Sugiyama H, Shigematsu T, Ito T, Tamura K, Isaka Y, Okada H, Tsuruya K, Yokoyama H, Nakashima N, Kataoka H, Ohe K, Okada M, Kashihara N. J-CKD-DB: a nationwide multicentre electronic health record-based chronic kidney disease database in Japan. Sci Rep. 2020 Apr 30;10(1):7351.*

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