RENAL

RETROSPECTIVE

HOMER W. SMITH 1895-1962

Robert Levy, MD and Michael Moran, MD

Homer W. Smith

U.S. National Library of Medicine

Homer W. Smith is an iconic figure in medicine and physiology; it is impossible to imagine a world without his science. Yet, he remains somewhat unknown in a modern era saturated with new scientific discoveries. Smith was born in Denver, Colorado and attended college at the University of Denver. He went on to study at Johns Hopkins where he received his Sc.D. degree in physiology, then studied medicine for another two years there. He received the Passano and Lasker Awards, the Presidential Medal of Merit as well as being named a Guggenheim Fellow. The following is a memoir of Homer Smith written by Robert I. Levy, MD who knew him personally:

INTRODUCTION

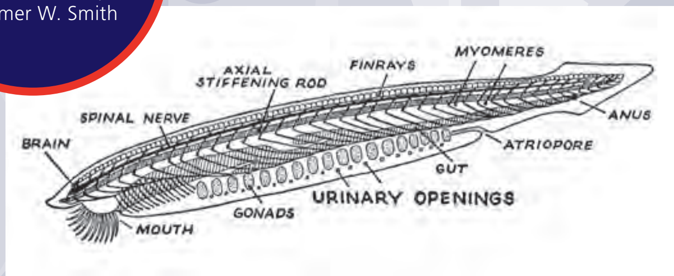
Homer W. Smith was a dominate influence on the developing field of renal physiology from 1918 through 1962. He was instrumental in developing the use of Inulin and Para amino hippuric acid clearances as measures of glomerular filtration rate and renal blood flow. He wrote over 150 published articles on renal physiology and related topics. Early studies included those on camels, lung fish and the history of the evolution of the functional architecture of the kidney over geological time. His department of physiology at New York University welcomed many physicians who studied clinical nephrology problems such as hypertension and renal failure. His laboratory was a training ground for many clinicians and laboratory scientists such as William Goldring, Herbert Chasis, Robert Pitts and Robert Berliner. He also wrote many philosophical books and articles, such as ***Kamongo*** - describing the lung fish of Africa and ***Man and His Gods*** - with an introduction by Albert Einstein. I was first introduced to Dr. Smith when I was in medical school by the publication of his textbook, *The Kidney; Structure and Function in Health and Disease* published in 1951 by Oxford University Press.

EARLY LIFE

Homer Smith spent his childhood in the small town of Cripple Creek in central Colorado. He later joined the armed forces and transferred to the Chemical Warfare Station of the American University in Washington, DC under Dr. E. K. Marshall to study the biological effects of nerve gases. Dr. Marshall was my Professor of Pharmacology at Johns Hopkins in 1950. Smith and Marshall developed a lifelong friendship and Smith's first three published papers on mustard gas were published with Marshall in 1918 and 1919. After the war, Marshall arranged for Smith to undertake graduate studies at the Johns Hopkins School of Hygiene and Public Health obtaining a Sc.D. in 1921 under William H. Howell, Professor of Physiology. The fourth published collaboration between Smith and Marshall was a long paper in the Biological Bulletin entitled *The Glomerular Development of the Vertebrate Kidney in relation to Habitat* in 1930, providing evidence that the '*provertebrate kidney was aglomerular and that the glomerulus was evolved as an adaptation to a fresh-water habitat.*'

The hypothetical protovertebrate

From Fish to Philosopher by Homer W. Smith



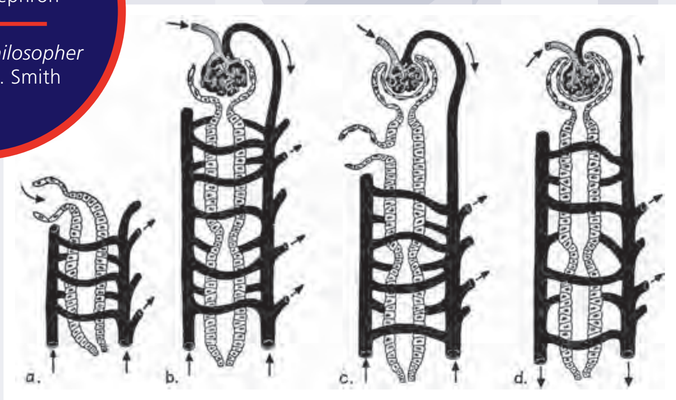
FURTHER TRAINING AND INTRODUCTION TO THE KIDNEY

Working in the laboratory of Dr. Walter B. Cannon (1921-1923) and then as chairman of the Department of Physiology at the University of Virginia College of Medicine (1925-1928), Smith continued to work in the fields of physical chemistry and cellular physiology. It was not until 1928 that he published his first paper on a renal subject, *Note on the nitrogen excretion of camels*, in the *Journal of Biological Chemistry*. That year, he was appointed Professor of Physiology and Director of the Physiological Laboratories at the New York University College of Medicine, a position he held until 1961. This short, two and one half page article was a rather mundane correction to a previous article in the Journal by authors who had found no urea in the urine of camels, whereas Smith and his colleague Silvette found that the "camel excretes urea in amounts comparable with other herbivorous animals." This was a rather insignificant correction and gave no inkling of his more important papers to follow on renal function.

KAMONGO

Homer Smith was not only interested in science and renal function but in philosophical subjects such as man's place in the universe and belief in God. His paper on the metabolism of the lung-fish in 1930, a fish whose gills are reduced in function and can live out of water by burrowing in the mud— obtaining air in a state of hibernation or estivation— became a background for his first novel, *Kamongo*, an African word meaning *Lung-fish*. This 1932 book is in the form of a dialogue between a priest and a scientist, and their conversation is recorded while on a slow boat trip returning from Africa. The book became immediately popular and won many book awards for its artistry and philosophical discussion. I remember hearing Dr. Smith give scientific lectures in Baltimore and St. Louis after which we were invited to attend informal discussions on the philosophic topics that were simply and skillfully presented in his narrative.

> *The most important constituents in the body fluid of all vertebrates are water and sodium chloride- ordinary table salt, the primary salt of the sea and of all plants and animals. One cannot, in connection with living organisms, think of water without salt or salt without water. All marine invertebrates are isosmotic with their environment- in other words, their body fluids have the same salt content, and hence the osmotic pressure as the sea water in which they live.*
>
> – HOMER W. SMITH



Four stages in the evolution of the vertebrate nephron

From Fish to Philosopher by Homer W. Smith

MAN AND HIS GODS

Another somewhat controversial book by Smith published in 1952, *Man and His Gods*, contains a foreword written by Albert Einstein: "*The work is a broadly conceived attempt to portray man's fear-induced animistic and mythic ideas… and the causal relationships by which they have become crystallized into organized religion.*" I reviewed in the archives of the New York University Hospital the letters that Dr. Smith received concerning this comprehensive book of almost 500 pages. About 90% of the entries concerning this book had criticisms of the general tenor of this book, in sharp contrast to the enthusiasm for *Komongo*, published 20years earlier.

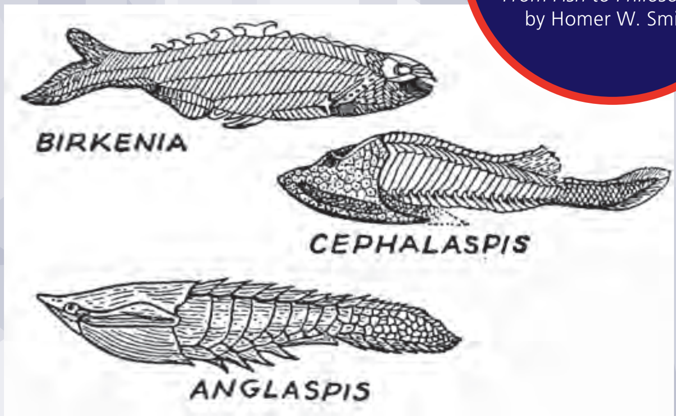
PORTER LECTURE OF 1939

The Porter Lecture of 1939, delivered at the University of Kansas Medical School, was entitled *The Evolution of the Kidney*. Dr. Smith gave the ninth such lecture in this series in 1939 and provided a brilliant analysis of how the functional architecture of the human kidney, the glomerulus and the various parts of the tubule, are related to the evolution of the vertebrates, first in salt water, then fresh water and then on to dry land all in relation to geological history over the last six thousand years. Smith wrote, "*the* *very matrix of life is water and the evolution of the kidney is essentially the story of the evolution of the regulation of water content of the body.*" And "*The composition of the blood is determined not by what the mouth ingests but by what the kidneys keep.*"

Smith points out that the marine invertebrates, worms, star fish and mollusks were in osmotic equilibrium with the sea and faced no problem of water regulation, but only the problem of the excretion of nitrogenous waste. These marine ancestors of the chordates had a pair of open tubules that connected the body cavity to the exterior, derived originally from gonaducts serving to carry the eggs and sperm out of the body to the exterior.

He further explains that as the first chordates entered fresh waters in the Silurian-Devonian period, encased in heavy armor, perhaps to insulate the body from the relatively hypotonic new environment, it was necessary to devise a filtering device by bringing together arteries and these coelomic tubules to form a glomerulus. "*The important point is that the renal glomerulus was evolved independently of and long after the evolution of the renal tubule.*" However, it was necessary to modify the tubules so that they could reabsorb the osmotically active constituents of the plasma, glucose, chloride, phosphate, etc., except for the protein which did not pass through the filtering bed of the glomerulus. "*Thus as a concomitant of the evolution of the glomerulus, there came into existence a tubule capable of reabsorbing large quantities of glucose and similar valuable substances including salt producing a urine hypotonic to the blood.*"

As reptiles with tough hides and long legs crawled onto the dry land, they changed their degradation of protein nitrogen from urea to uric acid,



Three types of armored fishes or ostracoderms from the Devonian

From Fish to Philosopher by Homer W. Smith

which is almost insoluble in water. The reptiles secrete uric acid in the tubular urine as a concentrated supersaturated solution. As the urine passes to the cloaca the uric acid precipitates out, leaving most of the water in the urine free to be reabsorbed into the blood, while the uric acid itself is expelled as an almost dry paste. "*This same uric acid adaptation is found in birds, for the birds are but warm blooded reptiles wit feathers and wings.*" How close does Smith come to our modern understanding that birds are just specialized dinosaurs, more specifically therapod dinosaurs?

> *If the two million tubules in the two human kidneys were connected end to end, they would stretch for nearly fifty miles.*
> – HOMER W. SMITH

During the Mesozoic era, the reptiles were prominent and the mammals remained in the background. These thick-skinned animals, culminating in the great dinosaurs suddenly disappeared. The mammals, not having the propensity to degrade protein nitrogen to uric acid, continued to produce urea and developed increased circulation of blood as an adaption for frigidity of the environment. This resulted in increased filtration rate, entailing an increased need for conserving water by reabsorbing it from the newly emerging thin segment of the tubule, the major contribution of the mammals over the last million years.

RENAL PHYSIOLOGY BETWEEN TWO WARS

Homer Smith did not coin the expression, ***clearance***, to explain a function of the kidney. In Smith's lecture on *Renal Physiology between the Two Wars*, delivered at the Mount Sinai Hospital in 1943, he attributes the genesis of the term to Donald D. Van Slyke, working at the Rockefellar Institute. Van Slyke had devised a somewhat complicated mathematical formula to express the excretory efficiency of the kidney, UV/P:

> *In 1926 Van Slyke had been on his way to Baltimore to give an address to the Hopkins doctors on kidney function, and on the train his courage failed him when he thought of facing an audience again with a mathematical equation. He had learned what every lecturer must ultimately learn, that only experts can visualize and comprehend the true realities which the unreal symbols of a mathematical equation are intended to represent; the simplest equation has the fearsome power of completely dispelling the comprehension of an audience at least in the fields of mathematics for the benefit of the medical profession, it occurred to him that all that the equation for high urine flows said was that in effect some constant volume of blood was being '**cleared**' of urea in each minute of time.*

In the very next paragraph Smith indicates, "*In my opinion this word (clearance) has been more useful to renal physiology than all the equations ever written.*"

CLINICAL STUDIES ON RENAL FUNCTION AS PROFESSOR OF PHYSIOLOGY AT NEW YORK UNIVERSITY IN 1928

It was a matter of developing a more reliable measurement of glomerular filtration rate that next occupied the attention of Homer Smith and his clinical associates. Studies to obtain this led to the evaluation of inulin, a non-metabolized polysaccharide containing fructose which is neither reabsorbed nor excreted by the renal tubules which proved to be an excellent choice. Para-aminohippuric acid (PAH) also proved to be a similarly reliable agent to evaluate renal blood flow as well as estimations of tubular mass which followed. With these methods Smith and his clinical colleagues at NYU developed a close association between the medical clinic and the physiology department that resulted in a wide variety of studies on basic renal physiology as well as consideration of renal function in a wide variety of clinical conditions such as hypertension, renal insufficiency and glomerulonephritis.

HOMER W. SMITH'S SCIENTIFIC MONOGRAPHS RELATED TO RENAL FUNCTION AND DISEASE

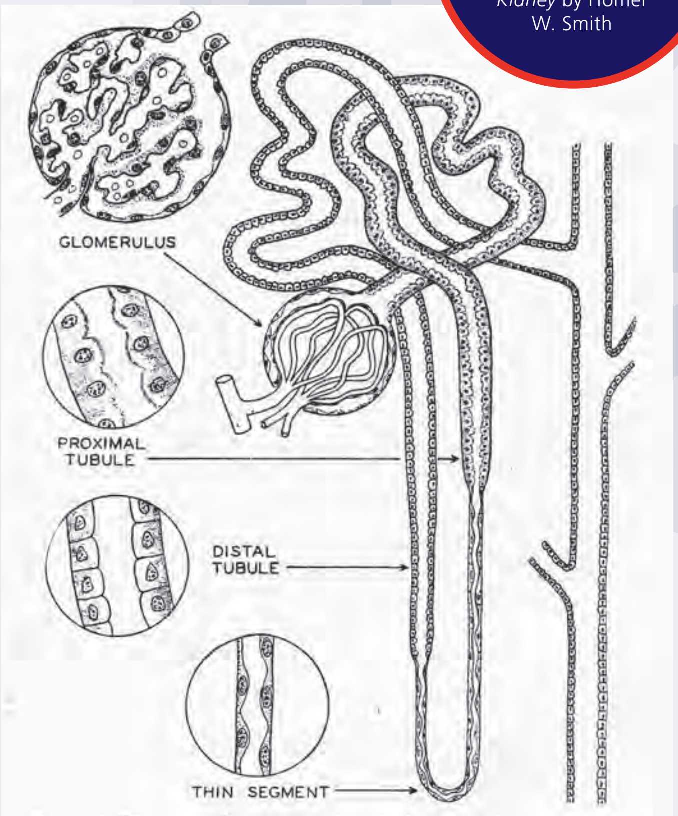
The Physiology of the Kidney, published in 1937, summarized a current analysis for both the scientific investigator and clinician. This was the first comparable summary since the earlier publication of the British pharmacologist Arthur R. Cushny's publication, *The Secretion of the Urine* in 1917.

Smith's *The Physiology of the Kidney* included the evidence for tubular secretion as first described by Marshall and Crane in 1924.

Smith's second (and really his monumental treatise) was entitled *The Kidney: Structure and Function in Health and Disease*, published in 1951. This book covered clinical and basic science advances in great detail. A smaller monograph, a concise, readable account of current concepts of renal function, Principles of Renal Physiology, was published in 1956. Homer W. Smith was working on a revision to this book at the time of his death in 1962.

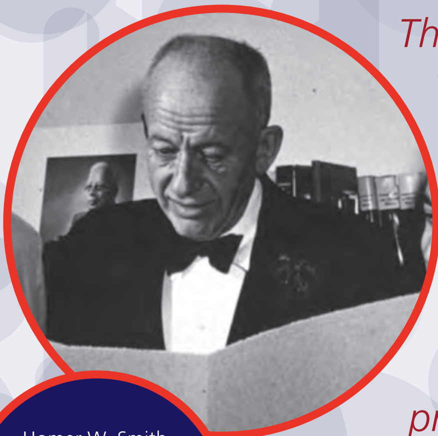
Diagrammatic representation of a human nephron.

The Physiology of the Kidney by Homer W. Smith



THE EVOLUTION OF THE KIDNEY

Michael Moran, MD



Homer W. Smith prior to a lecture on April 26, 1960

U.S. National Library of Medicine

The most important constituents in the body fluid of all vertebrates are water and sodium chloride- ordinary table salt, the primary salt of the sea and of all plants and animals. One cannot, in connection with living organisms, think of water without salt or salt without water. All marine invertebrates are isosmotic with their environment- in other words, their body fluids have the same salt content, and hence the osmotic pressure as the sea water in which they live.

– HOMER W. SMITH

Homer W. Smith, whose 1930s experiments proved that the kidney operated according to physical principles (both as a filter and a secretory organ) wrote "*The kidney is a glandular organ of greater or lesser complexity and highly varied in structure in different animals; it is concerned chiefly with the excretion of such waste products as cannot escape the body by simple diffusion.*"

The embryologic origin of the kidney is from the mesoderm, like the germinal or reproductive structures, not the endoderm like most of the organs. "*It starts out as a segmented structure. From this fact, and from the structure of the adult kidney in the primitive fishes, it is inferred that the kidney of the protovertebrate was also segmented, and that each segment of the body throughout the length of the coelom carried a bilateral pair of nephric tubules.*" Thus a beginning of structure. Smith continues with "*On the interior of the body each of these nephric tubules communicated freely with the coelom by means of an open mouth or coelomostome; on the exterior they drained either through separate vents in the body wall like the scuppers of a ship, or into a common longitudinal groove in the skin.*" These primitive tubules shared functions with the primitive reproductive tracts to carry off eggs and sperm, thus doing

Bowman, like Harvey and Malpighi, studied every type of animal available to him: his classic paper describes the 'corpuscles' and 'tubes' as they appear in the badger, dog, lion, cat, mouse, squirrel, guinea pig, horse, parrot, tortoise, boa, frog, and common eel, as well as man.

– HOMER W. SMITH

Malpighian tubules, indicated with a yellow arrow, protruding from the gut of a dissected Nauphoeta cinerea cockroach. The orange material inside the gut is partially digested carrot. The shiny white tubes are trachea or tracheoles.

Adrian J. Hunter

Wikimedia

Bowman's capsule and Malpighian bodies

Wellcome Library, London

double duty and explaining the close relationship with the urinary tract and the genital apparatus. All one can do with the lack of ancestral kidneys is comparative anatomy. Flatworms have structures called protonephridia that branch throughout the body into bulblike flame cells, or cyrtocytes which were extensively investigated by Goodwin in 1945. The flame cells vary greatly from species to species and actually consist of two cells, one ciliated and the other basilar with interdigitations. They are presumed to act as an ultrafilter. Other invertebrates, particularly the insects, evolved tubules known as metanephridia where NaCl is removed by active cell transport. Insect's metanephridia are called Malpighian tubules and urine is not formed by filtration in these systems. Instead, waste molecules and potassium are secreted into the tubules by active transport with most water and K+ being resorbed in the hindguts to which they drain. It is from the vertebrates that the kidney has evolved into quite interesting complexity. The vertebrate kidney produces a filtrate that enters tubules and is modified to become urine.

This solution has major disadvantages, but the flexibility of the kidney has obviously resulted in natural selection to favor the development of complex kidneys allowing vertebrates to invade many diverse environments and adapt successfully. Homer Smith points to the flawed design of mammalian kidney formation as follows: "*… and it may be accepted that it was with this meager equipment that the protovertebrate tried to enter the brackish lagoons or fresh-water rivers and lakes of the Paleozoic continents.*" The essential feature of the vertebrate kidney would require some complex vascular interactions: "*Consequently the early fresh water invaders had to compensate for this irreducible influx of water by increasing the rate of its excretion. It appears that no better way could be devised to get this water out of the body than to have the heart pump it out; and the simplest way to do this was to install, close to the open mouths of the pre-existing tubules, a filtering device in the form of a tuft of permeable capillaries.*" This capillary tuft is called a glomus and is still encountered embryologically in the pronephros. This adaption was further improved with the migration into the mouth of the tubule to form Bowman's capsule. Now the problem of tying the original kidney to the reproductive tract has obvious implications since they are now competing for a common channel for egress: ovum, sperm, or urine. "*With the evolution of the glomerular nephron, there began a battle between the kidney and the reproductive organs that continued for three hundred and fifty million years.*" The evolution of the vertebrate kidney allowed many further adaptations- the evolution of amphibians with kidneys similar to fresh water teleost fishes, the development of reptiles, birds, and mammals. These tetrapods would further evolve into animals capable of returning to marine environments such as dinosaurs as well as mammals such as cetaceans, seals, manatees, and otters. Perhaps the most extreme adaptation is the desert mice and animals that do not drink any water at all.

Notomys Alexis (Spinifex Hopping Mouse) has the most concentrated urine of any mammal

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THE HISTORY OF MEDICAL ILLUSTRATION OF THE KIDNEY

Sutchin R. Patel, MD

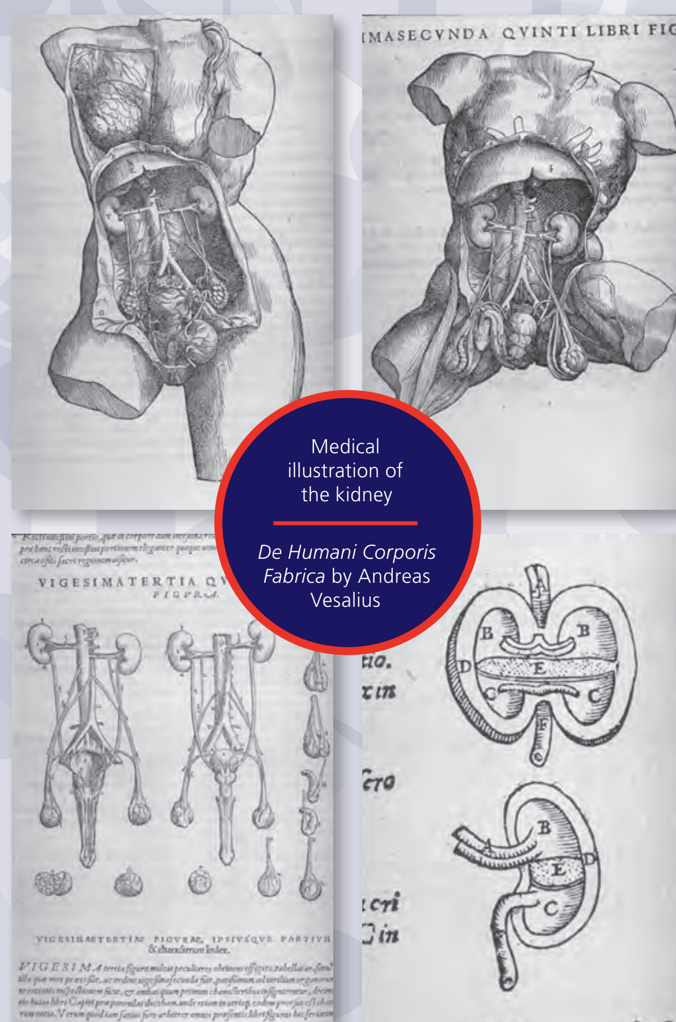
Ancient depiction of the kidney was rare compared to other organs (heart, liver, lung, intestine) which were often taken from sacrificed animals to be offered to the gods. The names for urine and kidney, however, appear in Sumerian writings (3500-3000 BCE). One of the oldest votive offerings of the kidney was a bronze figure found in the Kition temples in Cyprus (13th century BC).

Aristotle (384-322 BCE) referred to the kidney in his two works, *Historia Animalium* and *De Partibus Animalium*, and felt that the kidney had two functions: 1. To separate the surplus liquid from blood and 2. To modify this liquid eliminated through the ureters, bladder and urethra. Galen of Pergamon (130-200 AD) showed in his animal experiments that the kidneys and not the bladder produced urine, though he believed that kidneys did not filter blood but "attracted watery fluid." Illustrations were not used in anatomy during the classical period when the subject was dominated by the descriptive texts of Galen.

Though illustrated medical manuscripts were circulated to a limited extent in medieval times, it was the introduction of the printing press (circa 1450) and movable type which lead to the growth in all types of literature. Illustrations were reproduced initially using woodblocks and then copper engravings by the late 16th century. Leonardo da Vinci (1452-1519) depicted the kidney more accurately than any of his predecessors. Though he did not provide any new information on renal physiology, his drawings, which came from direct observations of human and animal dissections, rendered a high degree of accuracy.

ANDREAS VESALIUS (1514-1564)

Andreas Vesalius established the science of modern anatomy. His firsthand knowledge through dissections of the human body led him to overthrow the Galenic tradition with the publication of his *De Humani Corporis Fabrica* (1543). Jan Steven van Calcar (1499-1546), a pupil of Titian, collaborated with Vesalius to illustrate the *Fabrica*. Even though in book V, figure 22, the human kidney is incorrectly shown higher on the right than the left, Vesalius goes on to refute the long-held idea that the kidney acts as a sieve where blood entered the upper portion of the kidney and was filtered by a sieve such that urine left by the ureter from the lower portion of the kidney.



Medical illustration of the kidney

De Humani Corporis Fabrica by Andreas Vesalius

REALDO COLOMBO (1516-1559)

Realdo Colombo was a pupil of Vesalius and would be his successor as that Chair of Anatomy and surgery at the University of Padua. His work, *De Re Anatomica*, was published after his death in 1559. There he corrects the error by Galen that had been perpetuated for centuries that the right kidney is higher than the left, and he is best known for his description of pulmonary circulation before that of William Harvey. One of his best known patients was Michelangelo, whom he treated for urolithiasis.

BARTOLOMEO EUSTACHIO (1524-1574)

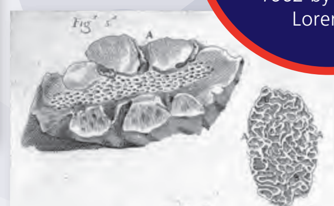
Bartolomeo Eustachio was an anatomy professor at the Collegia della Sapienza in Rome. His work, *Opuscula Anatomica* (1564), had 147 pages devoted to the kidney. His text illustrations were reproduced using copperplate engravings, marking the first time copper was used for anatomical plates. Eustachio was the first to describe the adrenal glands, he described the right kidney to be lower than the left, he accurately illustrated the intrarenal vasculature, he was the first to describe the renal calyceal system in relation to the renal papillae and his correct description of the renal collecting ducts ("certain furrows and small canals") antedated Bellini's observations by 150 years.

Kidney

Opuscula anatomica by Bartholomaeus Eustachius

LORENZO BELLINI (1643-1704)

Lorenzo Bellini was an Italian anatomist and physiologist. In his work, *Exercitatio Anatomica de Structurea et Usu Renum*, he showed that the kidney was not a solid organ but composed of ducts (which bear his name).



Ex typ. sub signo Stellae

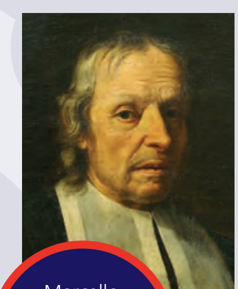
Exercitatio Anatomica de Structura et Usu Renum, 1662 by Bellini, Lorenzo

Giovanni Battista Morgagni

Wikimedia Commons

GIOVANNI BATTISTA MORGAGNI (1682-1771)

Giovanni Morgagni, an Italian anatomist, in his treatise, *De Sedibus et Causis Morborum per anatomen indagatis* (1761), described several renal disorders such as obstructive nephropathy (which he called "urine suppression"), calculi and renal tumors. His work represented the beginning of the science of pathology. Unfortunately, Morgagni did not provide illustrations for his 2,242 page work, a clear case where a picture would have been worth a thousand words.



Marcello Malpighi

Wikipedia

MARCELLO MALPIGHI (1628-1694)

Marcello Malpighi, an Italian biologist and physician, would provide some of the most significant contributions regarding the structure of the kidney. During his time, there was such confusion about the structure of the kidney that in his *De Viscerum Structura* he stated "So varied has been the fate of the kidneys throughout history that they had even been considered superfluous… now, at least, wonderful for their structure and function, they have obtained a place among the most important organs of the body.” Aided by the Galileian lens (later renamed the “microscope” by Cesi), Malpighi, through injection experiments, was able to describe the renal glomerule (in *De Renibus*, 1666), the pattern of renal tubular structures in the renal parenchyma, the direction of blood flow in the kidney and the relationship between glomerules and the excretion of urine. His work helped to lay the groundwork for modern nephrology and, with further improvements in light microscopy, the future contributions of Friedrich Gustav Jacob Henle (1809-1885) and William Bowman (1816-1892).

> *The artist must fully comprehend the subject-matter from every standpoint: anatomical, topographical, histological, pathological, medical and surgical. From this accumulated knowledge grows a mental picture, from which he crystallizes the plan of the future drawing. The planning of the picture, therefore, is the all important thing, not the execution.*
>
> – MAX BRÖDEL

EVOLUTION OF ANATOMIC ILLUSTRATION

In the 19th century, beginning with the Scottish surgeon and anatomist John Bell (1763-1820), in his *Anatomy of the Human Body*, which he self-illustrated, plainness and directness of presentation would replace the classical grandiosity seen in the medical illustrations before his time. Henry Gray (1827-1861), an English anatomist and surgeon, used illustrations in his work focused on depicting anatomic structures free from any artistic styles. Gray’s *Anatomy. Descriptive and Surgical*, with drawings by H. Vandyke Carter, was published in 1858 with the aim of making the text practical in favor of verbal and visual descriptions that would be useful to surgeons and clinicians. This was in stark contrast to the anatomic illustrations from the Renaissance, where there was modeling in light and shade, figures placed in graceful poses and evocative background scenery.

MAX BRÖDEL (1870-1941)

In 1911, Max Brödel became the head of the first Department of Art as Applied to Medicine, establishing the profession of medical illustration. In 1889, Brödel became interested in the vascular anatomy of the kidneys and used a preparation technique for the kidney, where after washing out the renal arteries, veins and the pelvis each was injected with red cinnabar, Prussian blue and arsenic solution of celloidin respectively. The tissue was

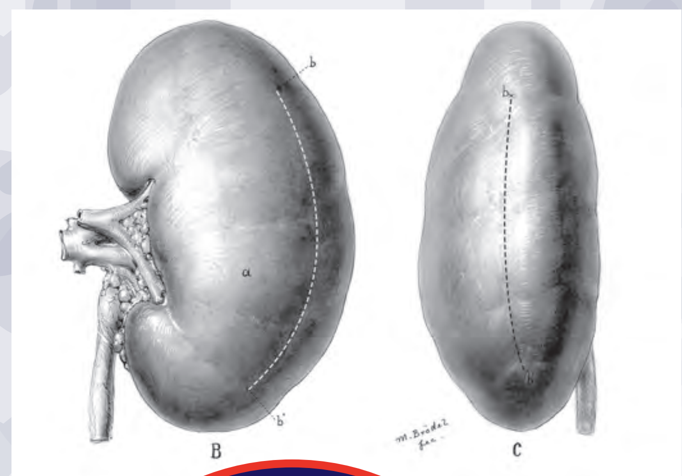
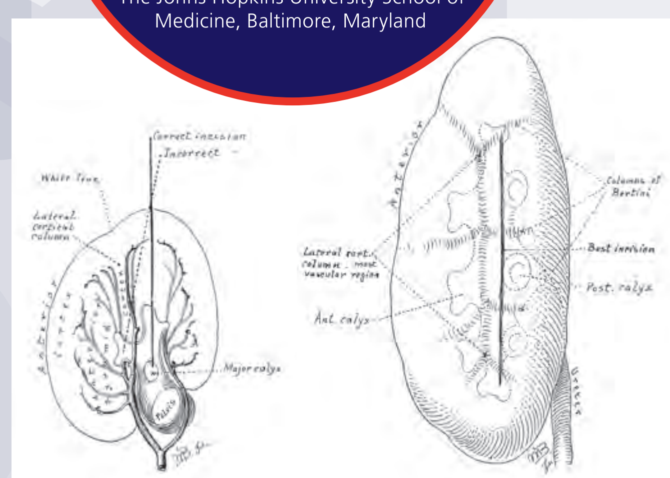


Fig.3 (left): The Surface Appearance of a Normal Kidney (B Anterior view and C Lateral view).

Fig.4 (above right): Section and lateral view of a kidney indicating the method of determining the most advantageous incision.

The British Medical Journal, Feb 1902

Original illustrations from the Women’s Clinic Collection is in the Max Brödel Archives, in the Department of Art as Applied to Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland



then removed via a digestive fluid leaving casts of the injected vessels and pelvis. Drawings of these casts were made by Brödel and by studying 70 kidneys he was able to define the posterior longitudinal white line of the kidney, that bears his name, most suitable for nephrotomy to minimize blood loss.

An article by Howard A. Kelly in the *British Medical Journal (Method of Incising, Searching, and Suturing the Kidney)* first defines "Brödel's White Line:"

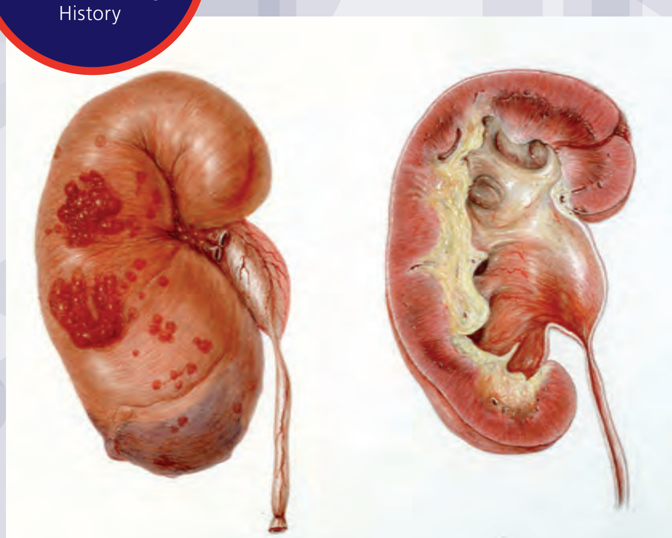
> *The white lines come together in a longitudinal white line on the anterior surface, which I propose to call Brödel's White Line (Fig.3 b-b'). . . . In order, then to make the incision correctly, one must cut parallel to Brödel's line and parallel to the posterior surface of the kidney, leaving about three-fifths of the kidney anterior and two-fifths posterior to the incision (Fig.4, A).*
> – Howard A. Kelly

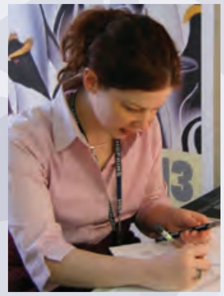
WILLIAM P. DIDUSCH (1895-1981)

In December 1915, Max Brödel recommended William P. Didusch, one of his best students, as artist for the new Brady Urological Institute. Didusch would become the artist for many leading American urologists over the next few decades, developing modern medical illustration in urology. After retiring from active work as an illustrator, Didusch established a collection of his drawings along with historical items for the American Urological Association, eventually leading to the 1972 opening of the William P. Didusch Museum at the AUA headquarters then in Baltimore, where he served as the museum's first curator.

Pyelonephritis

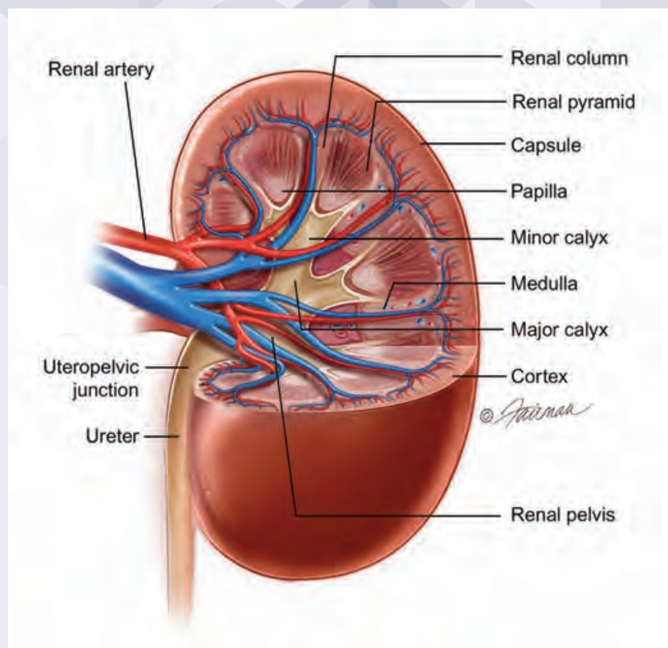
William P. Didusch Center for Urologic History





JENNIFER FAIRMAN

Jennifer Fairman, CMI, FAMI holds a faculty appointment as an Assistant Professor in the Department of Art as Applied to Medicine where she previously received her Master of Arts in Medical and Biological Illustration.



THE HISTORY OF KIDNEY STONES

Johan J. Mattelaer, MD

In contrast with bladder stones, which were described and operated upon since ancient times, the description and treatment of kidney stones was introduced very late in medical history.

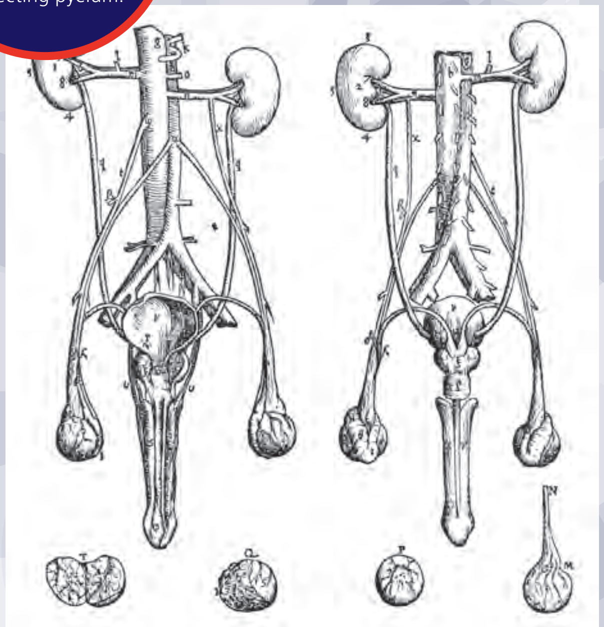
Nephrolithiasis and its consequences for the kidney. Various upper tract stones.

Traité des maladies des reins by P. Rayer, J.B. Ballière, Paris and London, 188

Gravel and smaller stones are described as *renal colics*. But even when doctors were aware that kidneys and stones had something to do with urinary excretion, it was only since the scientific dissection of the human body by Andreas Vesalius (1514-1564) that knowledge of the anatomy of the kidneys progressed. Later on, the renal physiology was brought into medical science by Marcello Malpigi (1628-1694).

In the writings of Arabian medicine, we first meet with surgical advice to incise the kidney for the evacuation of an abscess or the removal of a stone. In the 11th century, Avicenna (1037) along with Rhases (850) and Serapion in Damascus (11th century) took a distinct step backwards, and recommended to inject the rennet of a hare for bleeding from the kidney. Avicenna, however, did not take a favourable view of incision for stone in the kidney, but it is still clear from Avicenna's words there is reason to believe that cutting the kidney was practised in his time. Turner (*Art of Surgery*, London, 1725) says of Avicenna: *There are some who attempt to take the stone out of the kidneys by incision of the ilea, but there is a great danger therein and it is an unreasonable operation.*

Vesalius' view of the internal anatomy of the kidney: outer cortex and the inner sinuses, with the collecting pyelum.



GUY DE CHAULIAC

Guy de Chauliac

Wikipedia

In the 14th century, Guy de Chauliac advocated the advice given by Galen—the administration of drugs to break up the stone—and he regarded stone in the kidney to be beyond the sphere of the surgeon. He says, however, that should medical treatment fail, although it is dangerous, the stone should be cut out of the bladder, but for renal calculus no operation is justifiable.

CARDANUS OF MILAN

Cardanus of Milan (A.D. 1501) complained that the influence of the teaching of Hippocrates had become lost by his time and strongly advised the revival of the methods advocated by that great teacher. Cardanus quotes a case of Albertus, who reported that he saw a woman, who having been long afflicted with the nephritic illness, was operated upon to remove 18 stones of the bigness of a die.

CASPAR BAUHIN

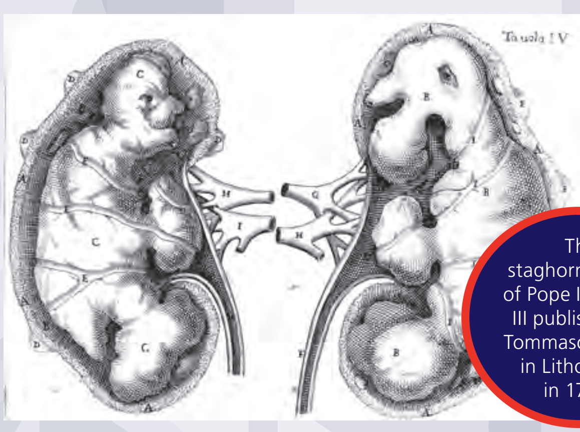
Caspar Bauhin, (1560-1624), copper engraving

Theo de Bry

Courtesy Johan Mattelaer

Caspar Bauhin (1560-1624), according to Turner, makes mention of a young girl born of nephritic parents, who labouring long under suppression of urine, a swelling arose about the loins, which having long waited for suppuration to no purpose and finding only an induration of the part, the surgeon boldly cut through the same and drew forth a couple of stones; after which her water came right as formerly, the wound being healed up. This history, he said, he had from his master Gulielmus Capellus when he was at Paris.

In the 15th century, the most remarkable instance of an operation upon the kidney, and the first case in which nephrotomy is supposed to have been performed for the removal of a renal calculus from a kidney that was not suppurating, is related in the *Chronicles of Jean de Troyes* and quoted by Ambroise Paré (1510-1590). Paré himself discredits this operation, and it is very difficult to know how much importance to attach to it.



The staghorn stones of Pope Innocent III published by Tommaso Alghisi in Lithotomia in 1707.

Gustav Simon, Professor of Surgery at the University of Heidelberg (Germany), pioneer in renal surgery.

One of the first staghorn stones was described at the autopsy of Pope Innocent XI by Tommaso Alghisi in 1707. But the author drew the stones inside out!

In 1873, Ingalls from Boston carried out the first nephrotomy.

Gustav Simon performed the first planned nephrectomy for a fistula in 1869.

The first pyelotomy was performed by Heinecke in 1879, and the first nephrolithotomy was carried out in 1881 by Auguste Le Dentu.

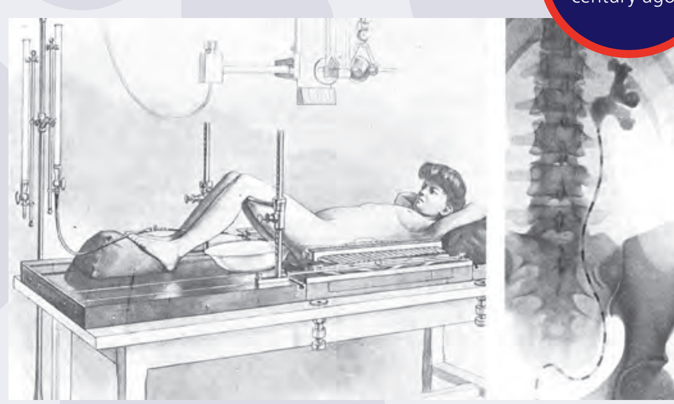
Vincenz Czerny (1842-1916) is credited with being the first to suture a nephrotomy incision in 1887.

Vincenz Czerny in the operating room at the University Clinic in Heidelberg, where he succeeded Gustav Simon.

The discovery of X-rays by Roentgen at the end of the 19th century made it possible to localize a kidney stone within the body. In 1905 the German urologists, Friedrich Völcker (1872-1955) and Alexander von Lichtenberg (1880-1949), were successful in infiltrating the iodine-containing substance collargol into the ureters, and by retrograde pyelography, it became possible for the first time to reliably reproduce images of kidney stones.

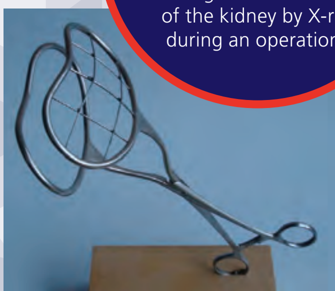
Kummel and Bardenheuer carried out the first partial nephrectomies for stone disease in 1889. Max Brödel described the avascular area of the kidney in 1901. Lower revived interest in pyelolithotomy by suggesting in 1913 that it may be a safer and easier method for removing renal stones than nephrolithotomy.

Another important advance in open renal stone surgery was intrasinusally *extended pyelolithotomy*, pioneered by Gil-Vernet in 1965.



Retrograde pyelography a century ago!

To localize the stone in the kidney during the operation, a lot of useful tools and devices have been developed.

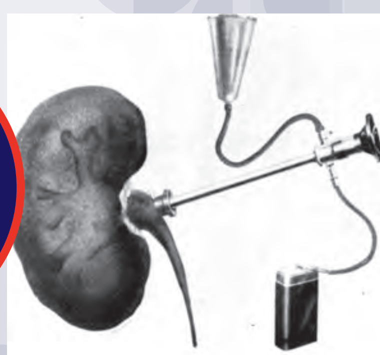


Instrument developed by Gerhard Dijkman and made by the factory of the Ignatius Clinic in Breda, The Netherlands, to localize the stone fragments in the calices of the kidney by X-ray during an operation.

Fitzpatrick et al. from England suggested in 1974 the combination of extended pyelolithotomy with multiple radial nephrotomies for the treatment of large, complex staghorn stones.

Smith and Boyce from USA introduced and popularized anatrophic nephrolithotomy for the treatment of staghorn stones in 1967. This technique has further gained popularity, became treatment of choice for large staghorn stones and is even applied during laparoscopic approaches.

The first investigation of *ultrasound* for the destruction of urinary stones was undertaken by Mulvaney in 1953, and Kurth applied it to renal stones in 1977.



Trattner's pyeloscope from 1948. A metal flange was sewn into the renal pelvis for a watertight connection.

Trattner, *J.Urol*, 60/817, 1948

Improvements in intracorporeal lithotripsy also allowed renal stones to be treated by percutaneous renal surgery. Rupel and Brown removed a stone in 1941 through a nephrostomy tract that had previously been established surgically, and Trattner in 1948 used a cystoscope to examine the renal collecting system at open renal surgery.

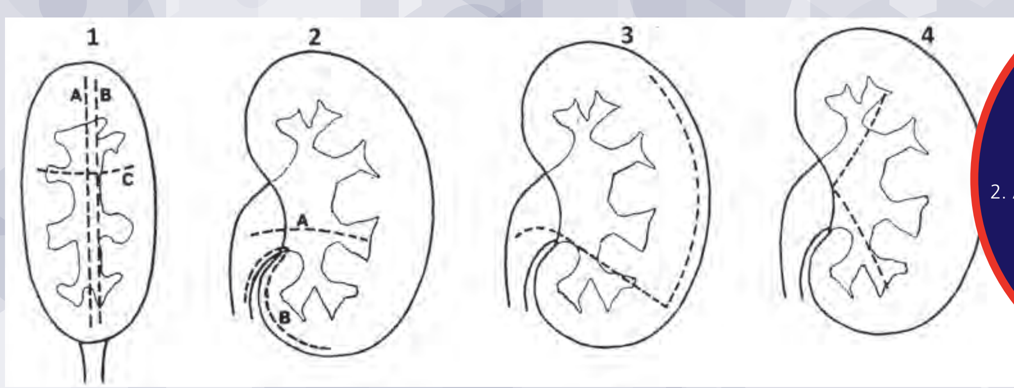
Goodwin et al. were the first to place a nephrostomy tube to a grossly hydronephrotic kidney to provide drainage in 1955, but it was not until 1976 that Fernstrom and Johannson established percutaneous access with specific intention of removing a renal stone.

Dornier HM-3

Courtesy EAU

Advances in endoscopes and other instruments allowed urologists to refine the percutaneous nephrolithotomy technique during 1970s and large series were reported in 1980s.

Finally, with the introduction of the first ESWL machine, Dornier HM-3, in 1980, a dramatic change in stone management was observed. This was probably the outstanding invention in the management of urinary stones. The US Food and Drug Administration approved the use of ESWL machines in 1984, and thereafter it has been used all over the world.

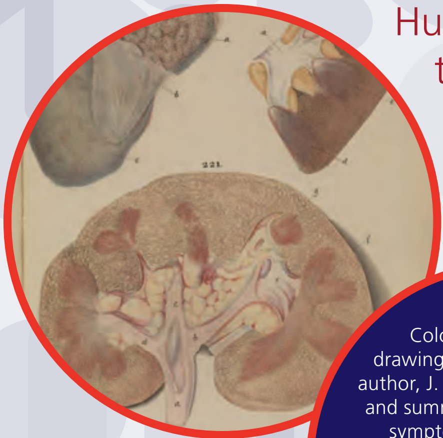


Incisions for nephrolithotomy.
1. A. Midline: after Tuffier (1889) and Morris (1892)
1. B. "bloodless line" after Hyrtl (1882) and Brödel (1902)
1. C. Transverse after Marwedel (1907)
2. A. pyelotomie élargie, after Marion (1922)
2. B. Inferior pyelonephrotomy after Zuckerkandl (1908)
3. Howard Kelly's incision (1909)
4. Prather's nephrolithotomy (1934)

THE KIDNEY — INFECTIONS

Emily Denstedt, BSc DVM
Justin Kwong, MD
John Denstedt, MD FRCSC

Humans have been documenting evidence of urinary tract infections (UTIs) for centuries, dating back as far as the 27th century BC. Before microorganisms were recognized as the underlying cause, and long before the establishment of urology as a specialty in medicine, mankind has suffered from UTIs.



Coloured lithographic drawings from originals by the author, J. Hope, with descriptions and summary allusions to cases, symptoms, and treatment.

Principles and illustrations of morbid anatomy; adapted to the elements of M. Andral, and to the Cyclopaedia of practical medicine, 1834

Wellcome Images

Among the most historic medical texts is the Ebers papyrus, which was written in 1500 BC in Ancient Egypt. This scroll, discovered in 1862 inside a tomb, describes over 900 diseases focusing mainly on therapies. Myrrh and other herbal remedies are cited as the recommended treatment for urine retention and excessive urination. It is apparent in these written documents that the depth of knowledge about kidneys and renal function was limited.

Humans have been documenting evidence of urinary tract infections (UTIs) for centuries, dating back as far as the 27th century BC. Before microorganisms were recognized as the underlying cause, and long before the establishment of urology as a specialty in medicine, mankind has suffered from UTIs. Among the most historic medical texts is the Ebers papyrus, which was written in 1500 BC in Ancient Egypt. This scroll, discovered in 1862 inside a tomb, describes over 900 diseases focusing mainly on therapies. Myrrh and other herbal remedies are cited as the recommended treatment for urine retention and excessive urination. It is apparent in these written documents that the depth of knowledge about kidneys and renal function was limited.

One thousand years after the Ebers papyrus was written, The Hippocrates Collection was developed, laying the foundation for evidence-based medicine. Hippocrates gathered knowledge on four renal diseases, which had been originally classified by the book, *About Inner Sufferings*, believed to be written by either Hippocrates himself or by the Cnidos medical schools of Ancient Greece. The four renal conditions he describes are presumed to be nephrolithiasis, renal vein thrombosis, renal tuberculosis and urinary tract infection (cystitis) with renal involvement in more chronic situations. The cause of the UTI, or cystitis more specifically, is described to be "*caused by bile and phlegm, especially during the summer months; it is also caused by excessive intercourse.*" Hippocrates discusses symptoms of flank pain, dysuria, turbid urine or hematuria. Holding true to the same principle used today, he declares "*what drugs will not cure, the knife will.*"

Greek physicians migrated to Rome, and between 25 BC to 40 AD treatment of kidney disease consisted of warm hip baths and bowel cleansing with enemas. Dietary modifications were also held in high importance and salty, sour, acidic or cold foods were not recommended. Diuretic herbs were common therapeutics as

Several examples of a disease of the kidney whereby the accumulation of urine in the kidney pelvic region results in distention and atrophy.

Colour etching by Oudet for Rayer

well. It was around this time that detailed descriptions of urinary catheterization and a procedure for lithotomy first emerged. During the decline of Hippocratic medical practices, Galen—an important physician during Roman times—developed his own practices influenced by elements from other medical schools. Galen recognized that abscess drainage was a sign of favorable prognosis, while pus accumulation was associated with kidney ulceration and other complications.

Canon Medicae

Wellcome Images

During the 10th century AD, Middle Eastern physician Avicenna replaced the works of Galen with his book *Canon Medicae*. Nearly all kidney disorders were described thoroughly from presenting complaint through their clinical course including nephritis, tuberculosis and abscesses. But even by the 19th century, still no accurate causal pathway had been explored.

After centuries of historic literature focused on symptom description and therapies – a breakthrough! Koch and others in the late 19th century finally speculate that infections in the human body have a microbial etiology. Many years pass, however, before the underlying source of UTIs is linked to bacterial organisms.

Cases of UTIs and pyelonephritis were still treated conservatively with bed rest, herbal remedies and hip baths. Minor interventions, such as bladder injections with tannic or gallic acid, were performed. Surgery to drain the kidney of pus was left as a last resort. The turn of the 20th century brought forth the beginnings of evidence-based urology with the first trials of chemotherapeutic agents using hemaxine, pyridium, hexylresorcinol and mercurochrome. In 1935, shortcomings of the available therapies were captured well by Berglund in an authoritative text, *The Kidney in Health and Disease*, when describing drug therapy: "Although much has been written on the subject the reports of benefit therefrom are most unconvincing." Diagnostics such as urinalysis, nitrite assay and urine culture were developed and

Watercolour drawing of a kidney in a condition of acute interstitial nephritis.

Thomas Godart, 1887

Wellcome Images

Watercolour and ink drawing of a kidney, from a case of chronic interstitial nephritis. The kidney is very small, and its surface was highly granular, whilst the cortex was extremely narrow and contained a few cysts.

Thomas Godart, 1887

The incidence of acute nephritis was very much increased during the Great War, when an epidemic of so-called "war nephritis" constituted a serious medical problem. The exact causation of this war nephritis has never been definitely settled, but a good deal of evidence pointed to the conclusion that it was an insect-borne disease – probably a louse infection.

– MACLEAN, M.D. 1924

refined, but the most important advance of this time was the introduction of antimicrobials.

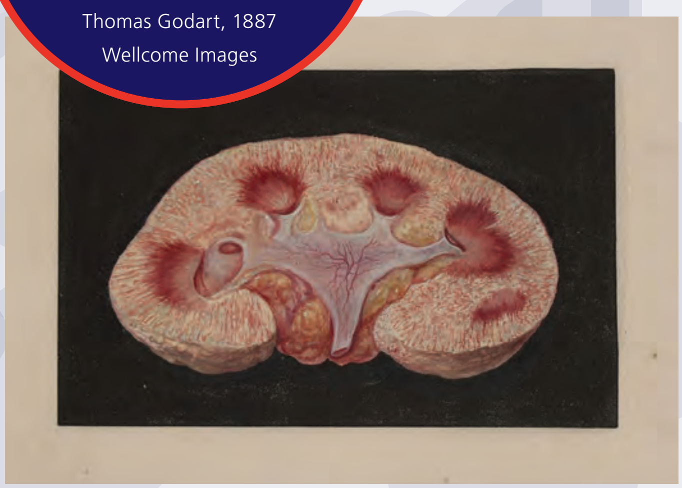
> *Often, in mild cases, the condition is revealed by an examination of the urine, the patient simply feeling somewhat 'out of sorts,' without any other prominent symptom.*
>
> – MACLEAN, M.D. 1924

A bacterial infection of notable importance through history is that of renal tuberculosis. In ancient times, renal TB was described as being due to heavy physical exertion and would first manifest with hematuria. With disease chronicity, the patient developed pyuria and the infected kidney would develop pus and even invade the opposite kidney. The result was death or spontaneous drainage in the rectum, which carried a better prognosis. Treatment at the time included taking restful periods. A century ago, *Berglund* described the experience as "*The symptoms may persist for years with remissions and relapses, the condition gradually growing worse. General symptoms may be absent for long periods of time, but usually there are night-sweats, loss of weight, malaise and afternoon fever.*" When selecting nephrectomy candidates, "*careful examination and good judgment are needed.*"

Watercolour and ink drawing of a kidney, from a case of chronic parenchymatous nephritis. The kidney is large and pale, somewhat granular upon its surface and with an adherent capsule. The cortex is pale and mottled, whilst the pyramids are of a bright pink colour.

Thomas Godart, 1887

Wellcome Images



Cystic kidneys: surgical specimen showing both kidneys, supported by renal and pelvic arteries.

Watercolour by W. Thornton Shiells, 1946

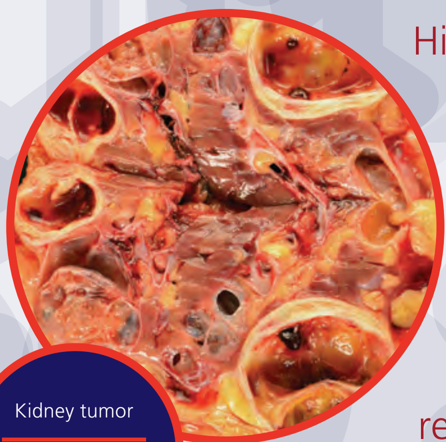
Wellcome Images

In modern times, prevention and treatment of kidney infections has been dramatically altered by the availability of both pharmacologic agents and corrective surgical procedures for anatomic abnormalities predisposing to infection. Certain beta-lactams as well as trimethoprim/sulfamethoxazole were widely used for UTIs upon their introduction with great success, but overuse of these medications led to antimicrobial resistance. Newer antimicrobials, such as fluoroquinolones, are now used for empirical treatment. Prudent use guidelines will be essential in maintaining our ability to fight urinary tract infections with the current antimicrobials we have available.

Today, the emergence of advanced imaging modalities has provided phenomenal direction in treatment planning. Endoscopic advances and minimally invasive surgical techniques have shifted the management of UTIs and kidney infections dramatically. Techniques in emergency supportive care have driven down morbidity and mortality rates associated with urosepsis. And, of course, the introduction of antimicrobials and their use in modern medicine has changed the face of what it means to have a kidney infection, or any other bacterial infection for that matter. Where we are today can be credited to the collaboration of many great minds spanning over 4500 years.

HISTORY IN PROGRESS: THE CLASSIFICATION OF RENAL TUMORS

Jennifer Gordetsky, MD



Kidney tumor

OncoTherapy Network

Historically, renal tumors were first classified based on gross examination. In 1826, the first classification of renal tumors was proposed by König, whereby tumors were divided into fungoid, medullary, scirrhous and steatomatous types. In 1841, Rayer proposed a different classification, which created three categories based on morphology and clinical features. These included encephaloid tumors without renal enlargement or hematuria, calyceal tumors, which were associated with renal pain and hematuria and scirrhous carcinoma, which was associated with hematuria.

By the mid 1800s, attention was turned to tumor histology and the presumed cell of origin of renal tumors. Tumor cells were phenotypically compared to benign renal parenchyma and categories were created. In 1855, Robin proposed that tumors arose from renal tubular cells, which was later confirmed by autopsy studies performed by Waldeyer. However, there was still a misconception from other studies that renal cell carcinoma arose from adrenal rests in the kidney. Thus, the term "hypernephroma" became commonly used in the literature for what we now call renal cell carcinomas. The debate was resolved in 1959 when Oberling and colleagues proved via ultrastructural studies that renal carcinomas arose from renal tubular cells. However, there was still confusion as to the differentiation between benign adenomas and carcinoma. In 1981, the World Health Organization (WHO) proposed a primitive classification for renal parenchymal tumors that grouped adenoma, renal cell carcinoma and "others." This system was expanded upon by Thoenes and colleagues in 1986, which delineated benign and malignant tumors based on histopathologic criteria. Categories included clear cell, chromophil (eosinophil, basophil), chromophobe (typical, eosinophil), collecting duct carcinoma and oncocytoma. This system, known as the *Mainz classification*, became widely accepted as its categories were supported by cytogenetic studies.

By the turn of the 21st century there was a new understanding of the genetic basis of renal tumors. This

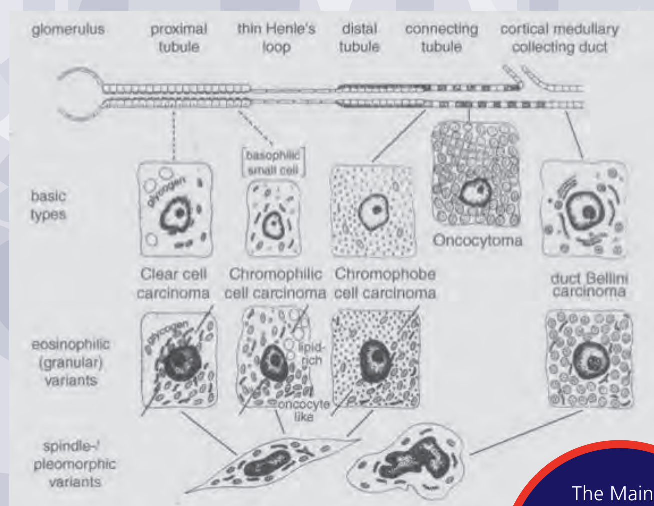
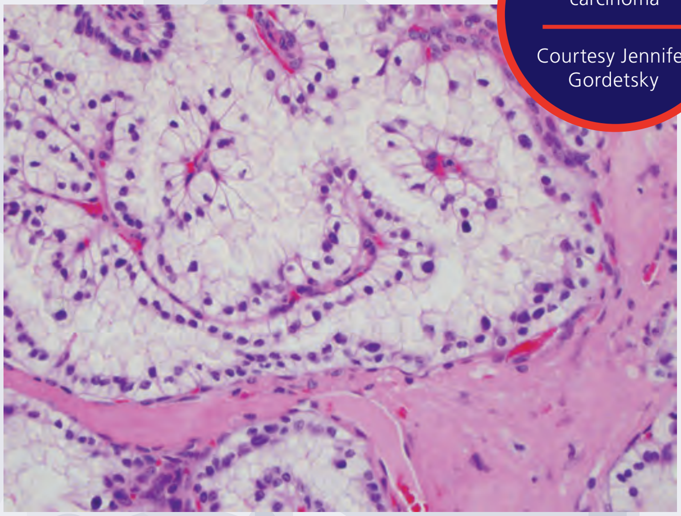


Fig. 6. The Mainz classification of renal tumors.

The Mainz classification of renal tumors.

OncoTherapy Network

allowed for a better classification of renal cell carcinomas, although tumors were still diagnosed based predominantly on histology. In 1997, the consensus conferences on the classification of renal cell tumors held in Heidelberg and Rochester, Minnesota placed approximately 90% of renal cell carcinomas into four subtypes. This included *clear cell renal cell carcinoma*, *papillary renal cell carcinoma*, *chromophobe renal cell carcinoma* and *collecting duct carcinoma*. Renal cell carcinoma, unclassified, was suggested for all other tumors that did not fit into a category either by morphology or genetic analysis. This category came to include some tumors that had overlapping histologic features. For example, if a tumor had both clear cells and papillary areas, there was ambiguity as to how to appropriately classify the lesion. With the development of sophisticated molecular techniques and immunohistochemistry, these "unclassified" lesions began to receive more attention. In 2004, a number of renal tumors were newly recognized in the WHO classification, including *multi-locular clear cell renal cell carcinoma*, *medullary carcinoma*, *Xp11 translocation carcinoma*, *carcinoma associated with neuroblastoma and mucinous tubular* and *spindle cell carcinoma*.



Clear cell papillary renal cell carcinoma

Courtesy Jennifer Gordetsky

In 2013, the International Society of Urological Pathology (ISUP) formally recognized several new renal tumors which have been added to the WHO Tumours of the Urinary System and Male Genital Organs 2016 edition. *Clear cell papillary renal cell carcinoma* is one of the newly added renal tumors. This tumor has perhaps the most appropriate and yet confusing name of the newly described entities. As its name suggests, this tumor is composed of clear cells with variable papillary architecture. The nuclei are low grade and have a characteristic reverse polarity, with a linear arrangement of nuclei away from the basal aspect of cells. Ironically, the clear cell papillary renal cell carcinoma is neither a clear cell renal cell carcinoma nor a papillary renal cell carcinoma. In fact, this tumor may not even be a carcinoma, as it is known to have an indolent clinical course, with no metastases reported in the literature to date. Clear cell papillary renal cell carcinoma shows diffuse positivity for CK 7 and CA IX, which is a unique immunophenotype. CA IX classically shows a membranous distribution with an absence of staining along the luminal borders of the tumor cells, commonly described as a "cup-shaped" appearance. Clear cell papillary renal cell carcinoma also does not show the characteristic VHL gene mutations or losses of chromosomal region 3p25, which are seen in conventional clear cell RCC. It has negative staining for AMACR, and lacks trisomies of chromosomes 7 and 17, which are associated with papillary RCC.

Other recently added renal tumors include *Tubulocystic renal cell carcinoma*, *acquired cystic disease associated renal cell carcinoma*, *MiT family translocation renal cell carcinoma* (including t(6;11) renal cell carcinoma) and *hereditary leiomyomatosis renal cell carcinoma syndrome associated renal cell carcinoma*. Time, technology and research will continue to expand upon the classification of renal tumors.

KIDNEY TUMORS

Michael E. Moran, MD

Renal tumors were originally appreciated as causes of death during post mortem autopsy examinations.

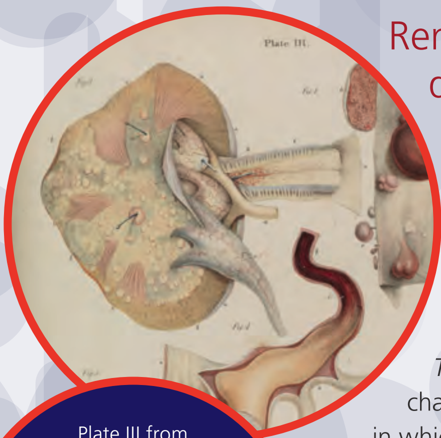


Plate III from Carcinoma chapter.

Fig 3 (top left) Carcinoma of the kidney

Pathological anatomy: illustrations of the elementary forms of disease, 1833

Wellcome Images

Johnson's textbook of 1852, *On the Diseases of the Kidney: Their Pathology, Diagnosis, and Treatment*, has a chapter on renal cancers in which he states that cancer of the kidney is one of the rarest diseases. In this era before x-ray diagnosis, he notes that most cases are not confined to the kidneys but rather have locally-extensive spread to the liver and lungs. He then notes that an "encephaloid" variety predominates in a series of 40 cases reported by Walshe. He believes that most cancers begin in the cortical regions of the kidneys but frequently extend to the medullary cones and sometimes to the walls of the pelvis and ureter. He carefully notes that lymphatic invasion is common and even presents some data on involvement of the renal vein and vena cava with tumor.

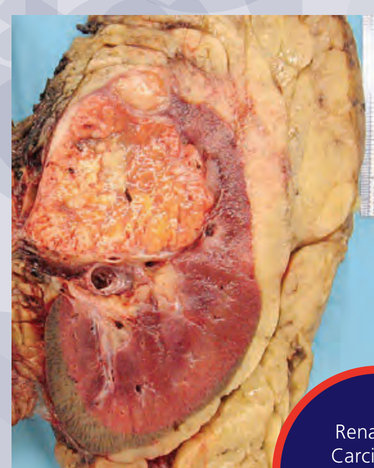
Otto Lubarsch, pathologist at Posen

Medical World by Mansch, Dr. Anton, 1906

Wellcome Images

In 1855, Robin devised a theory that renal carcinoma had its origins in the proliferation of the epithelium of the renal tubules. This investigation was bolstered by Waldeyer's own study in 1867 with similar findings. The name *hypernephroma* was coined by Lubarsch in 1894. Kocher, in 1876 and again in 1877, tried nephrectomy on two patients for carcinoma: neither survived. Grégoire recommended a more radical approach, removing the perirenal fascia, fat, lymphatic glands and the suprarenal gland in cases of suspected malignancy in 1905. Beare and McDonald noted that in a series of nephrectomies for cancer, the capsule of the kidney was breached in 70% of their cases, supporting the philosophy of Grégoire. An early follow-up study by Dickinson in 1882 reported that of 11 patients with cancer of the kidney, only two were alive two years later. A partial nephrectomy for suspected malignancy was performed by Czerny in 1887. A partial nephrectomy for malignancy was also performed on a solitary kidney by Semb in 1954.

Renal carcinoma is now known to be a group of malignancies including clear cell and papillary which arise from the epithelium of the proximal tubule and chromophobe, oncocytoma and collecting duct which come from the epithelium of the collecting tubule. The incidence of RCC has been steadily rising by 2-4% per year and is now the 7th leading cancer type in men in the US. There are about 58,000 new cases and about 13,000 deaths from kidney cancer every year in the US. Thus, compared to 1971 there has been a 5-fold increase in incidence and a 2-fold increase in mortality. Cigarette smoking, obesity, hypertension, diabetes and end stage renal disease all increase the risk of this disease. Only 10% of patients now present with the classic renal triad- hematuria, flank pain, and flank mass. The vast majority of patients now present with an incidental mass, 60%.



Renal Cell Carcinoma

Wikipedia

SURGERY DRIVES SPECIALIZATION

Friedrich Moll, MD
Peter Rathert, MD

Gustav Simon, Professor of Surgery at the University of Heidelberg (Germany), pioneer in renal surgery.

One of the historic landmarks in urology is the first planned nephrectomy performed in 1869 by Gustav Simon of Heidelberg (1824-1877). In the history of medicine the reflections and considerations of the specialized surgeon reveal distinguished analyses of the "case'' and, thus, the beginning of a modern scientific discussion of a patient's quality of life. Analysis of the first German nephrectomy shows the introduction of scientifically-oriented thinking in urology, especially in Germany during the middle of the nineteenth century, and parallels the rise of urology and general surgery.

During the last quarter of the nineteenth century, operative medicine saw a change from the philosophical deductive methods of the Romantic Era to inductive and scientifically-orientated ways of working. The previously limited scope of operative medicine abruptly altered then. Simultaneously, organ-related thinking gained acceptance among surgeons. This became the conceptional prerequisite for modern surgery of the inner organs, which acquired increasing importance as a means of both therapy and diagnosis in clinical internal medicine. As the boundaries of operative expertise expanded, a variety of specialties evolved.

The numerous discoveries made in the emerging medical disciplines (cellular pathology, experimental physiology, microbiology, anesthesia) in turn stimulated far-reaching advances in urology. The development of urology as an independent subject area paralleled the rise of gynecologic and abdominal surgery as well as traumatology. In some modern textbooks of medical history this thesis does not find much acceptance. Although many surgeons were attached to ``universal surgery'' due to their education, the protagonists of the 'new movement'' specialized in the treatment of selected organs (e.g., urologic surgery, traumatology, gynecology).

These radical changes determined the growth and expansion of hospitals, which became a symbol of a city's progress at the end of the nineteenth century. Hospitals, previously seen as the refuge of the sick poor, increasingly became accepted as places of specialized medical care for a wider section of the community. The greater ease and safety of surgery afforded by improved antisepsis and anesthesia permitted surgeons to go into anatomic regions previously unexplored, thus stimulating the beginnings of specialization.

By the mid-nineteenth century, especially Germany had supplanted England and France as the centers of European surgical knowledge. This success was due to the efficient German system of surgical training. Basic sciences with practical clinical teaching were integrated. In the United States, William St. Halstead (1852-1922) incorporated this system into students' education at the famous Johns Hopkins Hospital, Baltimore, in 1889.

Margaretha Kleb, the patient of Gustav Simon's first successful, nephrectomy.

THE KIDNEY IN SURGERY

Michael E. Moran, M.D.

The kidney was immune to the ancient surgeons because of its abundant blood supply, its location tucked away nicely with one third above the 12th rib, protected by large back muscles in three layers and nested in behind the abdominal viscera. None other than Hippocrates himself warned physicians of operating upon the kidney. Thus renal surgery was slow to come into the realm of the surgeon. But all of that changed with the invention of three major enabling technologies: anesthesia, aseptic surgical techniques and radiology. All three converged at the end of the 20th century and the kidney was now a surgeon's playground.

Renal cysts attracted the surgeon, especially in the days before CT scanning was available; there were always a certain degree of rounded renal tumors and cysts looking similar. The great Morgagni described cases in which he believed renal cysts had ruptured causing ascites in 1761. Tuffier performed a partial nephrectomy for a cyst in 1891 and Récamier reported injecting a cyst with silver nitrate trying to scarify the cyst to prevent recurrence. Multiple cyst decortications have been done laparoscopically as well as robotically.

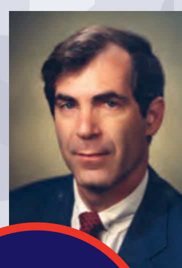
The ureteropelvic junction is also prone to congenital obstruction secondary to either muscular defects or obstruction by crossing vessels and fibrosis. The history of this type of surgery is fascinating with a number of highly innovative methods for repair; Küster (1891), Van Hook (1893), Cramer (1894), Bazy (1896), Fenger (1892), Israel (1896), Sir Henry Morris (1897), Albarran (1888), von Lichtenberg (1921), Schwyzer (1916), Foley (1937), Davis (1943), Stewart (1947), and Anderson-Hynes (1949) which has now almost become the standard of repair, though rarely by open surgery. The open procedure lost some steam at the beginning of the endourology era. Percutaneous endopyelotomies were done using the methods described by Davis to cut open the UPJ almost half a century prior. This passed into the past with the rise of laparoscopic and robotic pyeloplasties, typically of the Anderson-Hynes type.

An almost-forgotten surgical intervention that was popular through the early years of urology as a specialty was the renal surgery for *ptosis*, or *floating kidney*, or *ren mobilis seu migrans*, or *wanderniere*. This was first clinically described by Johannes Mesuë (1777-1837) in Bagdad and was commented upon again in the 16th century by Francesco di Piedimonte. This condition was associated with flank or loin pain, worse with the patient standing and relieved with the patient reclining.

Though Gustav Simon is classically listed as performing the first nephrectomy in 1869 for a benign ureterovaginal fistula, it had been performed in animals at numerous centers prior (Combair 1803, Prevost and Dumas 1823, Spillgelberg 1867, Peaslee 1868, and Wolcott 1886). It was Kocher who performed an anterior, transabdominal nephrectomy in 1878 for renal disease. This was followed by Sir Henry Morris in 1881 who performed a nephrectomy for infection and stones and developed the nephrolithotomy, and nephrostomy. Wells is credited as performing the first partial nephrectomy in 1884 to remove a benign tumor, a fibrolipoma. Berg described the transverse abdominal incision for securing the renal pedicle and facilitation of removal of a vena caval thrombosis in 1913. Vincent Vermooten developed the rationale for the concept of nephron-sparing surgery in 1950. The retroperitoneal flank approach began in the early 1900s. Robson described in 1963 the radical nephrectomy that is often used today. He specifically iterated the notion of early vascular control and ligation to decrease the risk of hematologic spread accompanied by removal of perinephric fat and excision of all regional lymph nodes. Ralph Clayman and his team at Washington University, St. Louis performed the first laparoscopic nephrectomy in 1990. In 1993 the first laparoscopic partial nephrectomy was performed and since then surgical robotic systems have been increasingly utilized to facilitate these surgical methods. Now even less-invasive nephrectomies have been reported via single-site and miniaturized video systems.

Vincent Vermooten

National Library of Medicine



Ralph Clayman

William P. Didusch Center for Urologic History

JÓZEF DIETL, THE STORY BEHIND 'DIETL'S CRISIS', AND HIS DESCRIPTION OF THE SYMPTOMS OF URETEROPELVIC JUNCTION OBSTRUCTION

Helen L. Bernie, William C. Hulbert, Jimena Cubillos,
Egils Veverbrants, Friedrich Moll, and Ronald Rabinowitz

Józef Dietl, while best known for his description of "Dietl's Crisis", was one of the greatest European physicians of the 19th century. During a time when primitive and frequently harmful therapeutic methods existed, he was progressive and rational. Here, we explore the life and contributions of Jozef Dietl.

Józef Dietl

Wikipedia

Józef Dietl was born in 1804 in a small village in the Austro-Hungarian-Empire-annexed area of Galicia. Initially wanting to go into the military, after his mother's discouragement he decided upon a career in medicine. In 1829, Józef Dietl graduated with his Doctor of Medicine from the University of Lviv in Vienna. His dissertation was titled "Some words about the credibility of health science especially worth remembering, for non-physicians." His thesis was unconventional in that a 25-year-old medical graduate was addressing himself mainly to non-medical readers, and his thesis indicated that society criticized physicians because their attempted treatments often produced no results. Dietl explained that recovery from illness depended largely on the forces of nature and the role of the physician was not to produce miracles, but rather to stimulate the natural forces of the body. He argued that many of the treatments used by physicians were actually harmful. Dietl explained that recovery from illness depended largely on the forces of nature and the role of the physician was not to produce miracles, but rather to stimulate the natural forces of the body. He argued that many of the treatments used by physicians were actually harmful.

In 1841 Dietl became a chief physician and director of a new hospital in Vienna, where he met Karl von Rokitansky and Josef Škoda. These three became the co-founders of the *New Vienna School of Medicine*, which sought to move medicine along the lines of rational and scientific study, creating evidence-based research prior to undertaking therapies. From here, Dietl's prolific research career took off. In 1849, he published in German (and then translated into Polish) one of his most significant works, entitled (in English) *On bloodletting in Pneumonia from a Clinical and Physiological Point of View*. Using evidence-based medicine, Dietl cited statistical data

17th century Delft bleeding bowl

William P. Didusch Center for Urologic History

showing greater mortality in those treated with bloodletting, a therapy in use since the time of Hippocrates. Dietl became widely known in Europe.

Main Assembly Hall, Jagiellonian University

Wikimedia

In 1851, he became head of the medical department of the Jagiellonian University in Krakow. Here, he emphasized physical examination of patients and held special classes on percussion and auscultation. He also produced the first work on hospital hygiene ever published in Germany, which remains highly valued by experts in the field today. During this time, Dietl eradicated the general belief in the benefits of the kołtun, a Polish term for a mass of tangled hair. People used to have matted hair hanging halfway down their backs and sometimes to the waist, creating a repulsive odor and crawling with vermin.

Kołtun

Wikipedia

In Poland it was believed the kołtun would rid one of many chronic diseases, and that people who shaved it off, were opening themselves to the dangers of convulsions, paralysis, blindness, mental disturbances, and even death.

Józef Dietl

Wikipedia

In 1864, Dietl wrote about "nephroptosis and observation of floating kidney incarceration". It was here that he described the symptoms of hydronephrosis and intermittent uretero-pelvic junction obstruction. Following are his descriptions of 5 of his 9 patients, wherein he described the symptoms attributable to a kink in the ureter or renal vessels when a mobile kidney descended, resulting in sudden attacks of abdominal pain, nausea, and vomiting, known by the eponym as "Dietl's Crisis."

55 year old day laborer – "…his sense of wellbeing was disturbed by frequent occurrences of loin pain, nausea and vomiting…"

37 year old washer woman – "…simultaneous occurrence of vomiting, an unease…caused the patient to spend several days in bed. The patient noted a fist sized swelling under her right ribcage which caused pulling pain."

47 year old washer woman in very reduced circumstances – "…one year history of painful swelling, under her right costal arch, accompanied by nausea and vomiting….:

43 year old peasant woman – "…sudden very sever painunder her right costal arch, nausea, vomiting."

30 year old wife of a civil servant – "…of delicate constitution, with severe pain under the right costal arch with simultaneous nausea, vomiting, and unease."

While initially used to describe a "wandering or floating kidney" that caused symptoms when it turned upon its pedicle, creating a partial incarceration, nowadays the term "Dietl's Crisis" is used to describe the symptoms of uretero-pelvic junction obstruction.

For treatment, Dietl promoted conservative approaches of abdominal support using corsets, abdominal belts, and placing gentle pressure on the lower pole of the kidney to slide it posteriorly towards the lumbar region for relief of prolonged pain.

In 1866 Dietl switched careers from medicine to politics and became the mayor of Krakow. During his eight years as mayor, he brought order to the neglected city in the sectors of hygiene, technical infrastructure, fire safety, and municipal finances. He developed schools that promoted educational reform and encouraged secondary schools for women, and the protection of historical relics. He died in 1878, but to this day he is still regarded as one of the best mayors of all time and a statue in Krakow and a Polish postage stamp remain in his honor.

Józef Dietl was one of the most influential European physicians of the 19th century, playing significant roles in improving hospital hygiene, using evidence-based medicine, stopping bloodletting in treating pneumonia, and promoting the concept of therapeutic nihilism to allow the body to heal itself. He published 138 works and books. He also had political interests, serving as mayor of Krakow, during which time he reformed the educational system, protected city relics, and built the city infrastructure. Despite all of these outstanding and progressive accomplishments, he remains best known for his contribution to urology in describing the symptoms of hydronephrosis and intermittent uretero-pelvic junction obstruction, known as "Dietl's Crisis."

Józef Dietl Statue

Wikipedia

PATENT MEDICINES FOR KIDNEY DISEASES

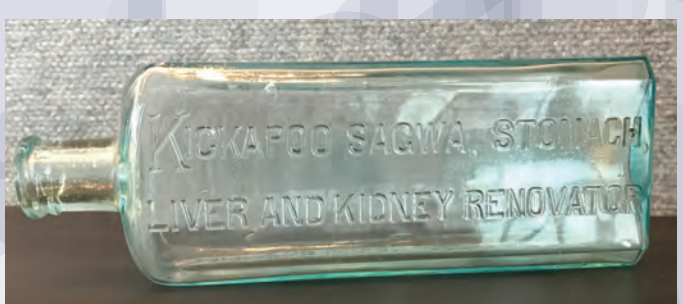
Ron Rabinowitz, MD

The United States Patent Office was established in 1790; six years later the first medical patent was issued to Samuel Lee of Connecticut for 'Bilious Pills" (soap, aloe, potassium nitrate, and gamboge, an eastern Asian tree resin). Patent medicines had existed since ancient times when they were called 'nostrum remedium' ('our remedy' in Latin).

Existing long before patent laws, these nostrums were essentially over-the-counter medicines used to treat various diseases and often contained exotic ingredients such as swamp root, snake oil, and Kickapoo Indian Sagwa. Many others contained opium, cannabis, and alcohol. These medications were advertised in publications such as Harper's Weekly, postcards, trade cards, and at traveling medicine shows. Because some of these salesmen promoted snake oil nostrums, the term 'snake oil salesman' became synonymous for 'charlatan'. While most patent medicines did not successfully treat conditions that they were advertised to treat, some ingredients were clearly hazardous. A few in the late 18th century led to fatal radiation poisoning. Additional hazards occurred with ingestion of morphine, opium, cocaine, alcohol, and various other toxic chemicals, including organophosphates.

Many nostrums were sold to treat kidney disease and diabetes, because diabetes was thought to be a kidney disease. Many of these patent medicines have survived in the form of bottles, trade cards, and pill packages.

Analysis of Doan's Kidney Pills, manufactured in Buffalo, New York in the 1830s by Foster-Milburn Company, showed these pills to contain oil of Juniper, potassium nitrate, powdered fenugreek, corn starch, wheat flour and hemlock pitch. Testimonials for Doan's Pills appeared in local newspapers. The Blackwell Oklahoma News of 24 August, 1911, contained

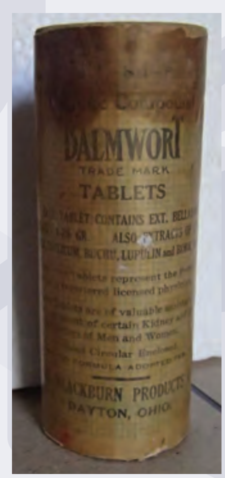


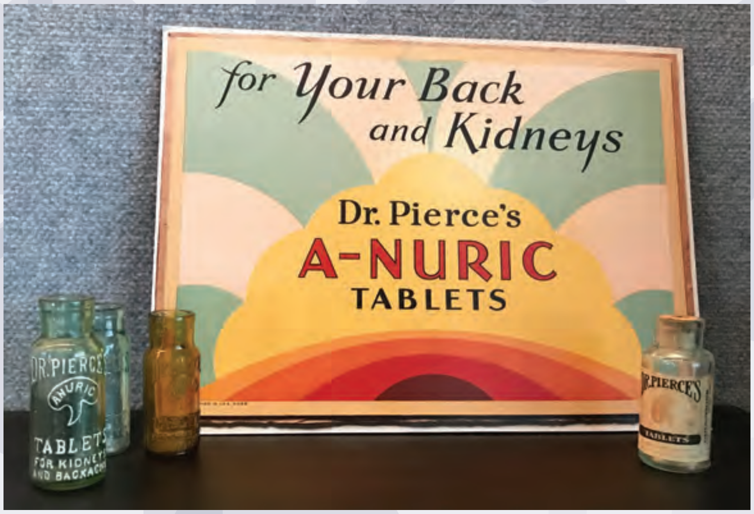
Doan's Pills

Courtesy Ronald Rabinowitz

the testimonial of kidney sufferer Mrs. Charles Boucher, who said, "it really seemed marvelous how promptly they brought me relief." However, Mrs. Boucher had died of kidney disease two months earlier. A newspaper clipping from 17 October, 1918, contained testimony from Nettie Woodrow recommending Doan's pills "to my friends whenever they have complained of headache or kidney disorders…." Her death notice was on the same page!

"Compound Fluid Balmwort" sold by Blackburn Products Company of Dayton, Ohio, was recommended "for kidney disease." The company also sold Balmwort tablets. The indications were listed: *If too much urine is secreted or if not sufficient is secreted; if the urine is passed too frequently or not frequently enough; and when the urine has too much color and when it has too little.*





An American physician of the late nineteenth century, with his doctor's bag and horse and buggy.

Colour lithograph by E.C. Pease, 1910

Wellcome Images

Kilmer Swamp Root

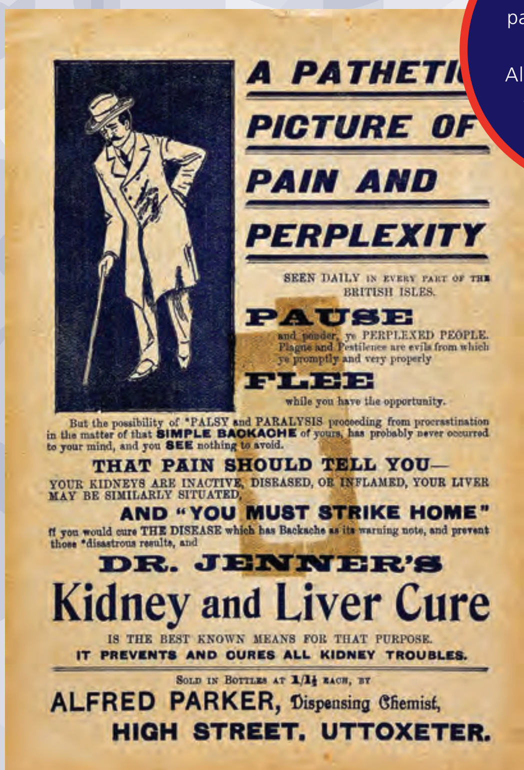
William P. Didusch Center for Urologic History

> *Many patent-medicine frauds escape the law because of their inconspicuousness. Some more important nostrums evade the law by the skill of lawyers, the amiable interpretations of the courts, or their own finesse in discovering loopholes. One triumphantly overrides the law. That one is swamp root. It is the greatest, the most profitable, the most widely exploited, and, on the whole, the most profoundly and dangerously fraudulent of all the quack nostrums now conspicuously before the public.*
>
> – SAMUEL H. ADAMS, 1912, *COLLIER'S MAGAZINE*, *"GREAT AMERICAN FRAUD"*

Balmwort was advertised in newspapers under a section entitled "The Doctor's Advice." A (so-called) Dr. Lewis Baker answered inquiries about various ailments, and each answer recommended a patent medicine sold by Blackburn Products Company. Compound fluid Balmwort contained 16% alcohol and the recommended treatment was to mix 1 ounce of Balmwort with 2 ounces of syrup of Sarsaparilla and 2 ounces of Gin. Thus, there was a significant amount of alcohol, though in the recommendations, people were advised to avoid alcohol.

In early 20th century, Dr. R. V. Pierce (1865 graduate of Eclectic Medical Institute, Cincinnati), sold *Dr. Pierce's A-Nuric Tablets, The Newest Discovery in Chemistry*, in a box containing 50 kidney-shaped red pills. Pierce's A-Nuric tablets were recommended to treat Bright's disease, pyelitis, nephrolithiasis and perinephric abscess. Analysis of the tablets revealed acetate, carbonate, iodide, chloride, phosphate, salicylate, calcium, iron, ammonia, potassium, sodium, emodin, quinine, aloin, hexamethylenamin, Canadian hemp, Queen of the meadow and sugar. A statement from the *Journal of the American Medical Association*, 15 September, 1917 concluded, "Not only are A-Nuric tablets foisted on the public under false and misleading claims, but, as alleged cures for diseases that should never be self-treated, they are fundamentally and essentially vicious."

S.A. Kilmer, MD, of Binghamton, New York, a general practitioner and graduate of Jefferson, Bellevue, and Albany, developed *Swamproot, The Great Kidney Specific Kidney, Liver, and Bladder Cure*. When analyzed, it was found to contain alcohol, sugar, water and flavoring with a laxative.



A pathetic picture of pain and perplexity....

Alfred Parker, [1900s] Wellcome Images

Swamproot was still being sold in 1960!

H. H, Warner of Rochester, New York, became a millionaire selling fireproof safes in the1870s. He supposedly developed Bright's Disease and improved after taking a patent medicine. He sold his safe business and bought a patent medicine business, promoting his medicines as 'Safe" cures with a drawing or outline of a safe on the bottles. He became the foremost patent medicine maker with more than 20 *Warner's Safe Cures*. His most successful was "Warner's Safe Kidney and Liver Cure" made of alcohol, water, glycerin, potassium nitrate, extract of wintergreen, extract of liverwort and extract of lycopus virginiana. Testimonials from Thomas Edison, Mark Twain, Oliver Wendell Holmes, Henry Wadsworth Longfellow, and Presidents Garfield, Hayes and McKinley helped to sell Warner's medicines.

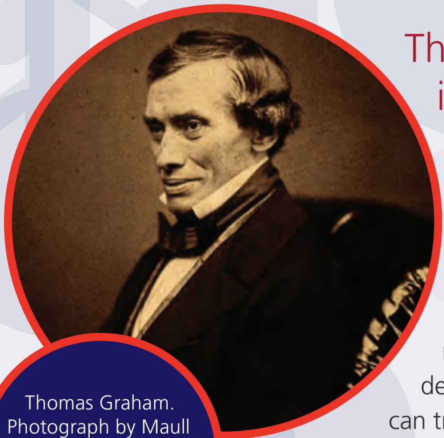
Warner's Safe Kidney & Liver Cure

Courtesy Ronald Rabinowitz

A BRIEF HISTORY OF HEMODIALYSIS

Douglas Silverstein, MD (FDA)

The word dialysis is defined as "the separation of particles in a liquid on the basis of differences in their ability to pass through a membrane." Evidence suggests that the term was first described by Professor Thomas Graham in 1861.

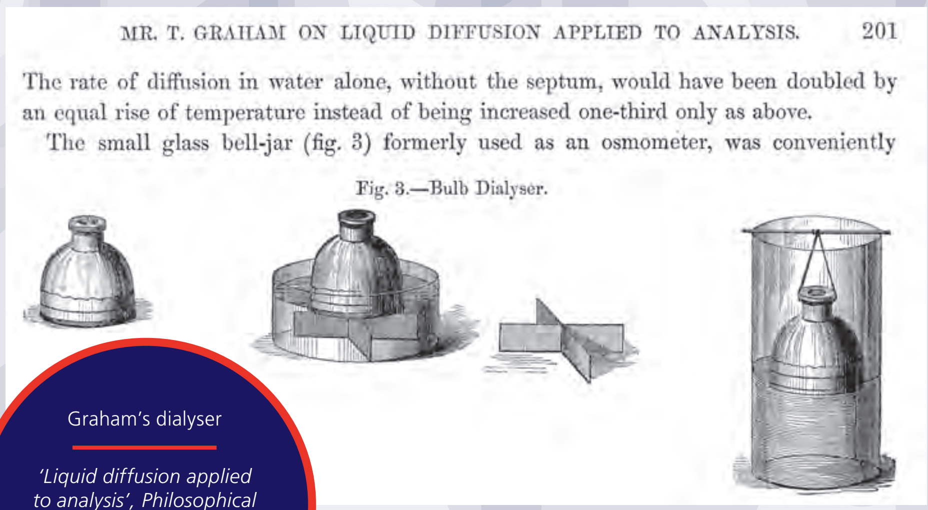


Thomas Graham. Photograph by Maull & Polyblank.

Wellcome Images

By Graham's mechanistic definition, one actually can trace the origins of modern-day dialysis back to ancient times in which the Egyptians and Romans attempted to cure disease by bloodletting to eradicate toxins. The Romans advocated using steam baths to induce the "diffusion" of particles and toxins from the body. Leeching, a form of bloodletting, continued well into the nineteenth century. Among the many faults and limitations of bloodletting is the safety of removing large amounts of blood which may contain small concentrations of impurities. That realization prompted scientists in the early twentieth century to develop devices that removed volumes of blood from diseased subjects and circulate the blood through tubes surrounded by saline for the purpose of removing toxins.

The first "dialyzer" was developed by Graham in the mid-1800s. Graham's inventive tool was a bulb (bell-shaped) dialyzer which was a primitive membrane—but nevertheless a semi-permeable membrane—that could separate substances. Adolf Fick expanded on Graham's device by using collodion membranes to separate small molecular weight solutes from blood, thereby establishing that dialysis membranes could perform diffusion. John Abel developed the first artificial kidney for animals in 1913. He experimented with separating large molecules from other substances by using a vegetable parchment coated with albumin as a membrane. It is widely believed that the first hemodialysis treatment of a human was performed by George Haas in Germany in 1924 using a dialyzer made of collodion that was immersed in dialysate solution. Haas demonstrated that some toxins could be removed from the blood and into the dialysate.



MR. T. GRAHAM ON LIQUID DIFFUSION APPLIED TO ANALYSIS. 201

The rate of diffusion in water alone, without the septum, would have been doubled by an equal rise of temperature instead of being increased one-third only as above.

The small glass bell-jar (fig. 3) formerly used as an osmometer, was conveniently

Fig. 3.—Bulb Dialyser.

Graham's dialyser

'Liquid diffusion applied to analysis', Philosophical Transactions by Thomas Graham

Published: 1861

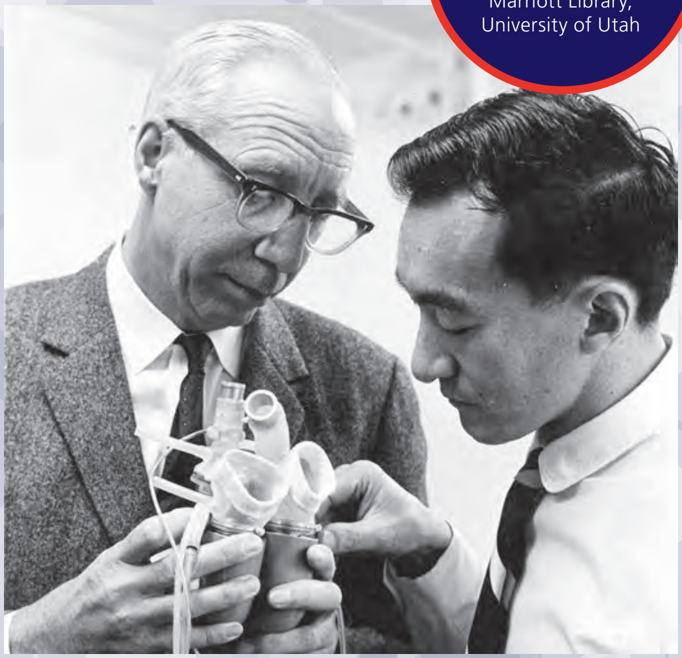
Wellcome Images

Diagram of Graham's Osmometer (to study osmosis)

Wellcome Images

By 1933, heparin was considered safe for infusion to prevent coagulation of blood in an extracorporeal circuit. Further iterations of the dialyzer were made in the next two decades. Nils Alwall developed a device consisting of a vertical drum kidney bathed in dialysis fluid. Finally, Fred Kiil of Norway developed the first plate dialyzer comprised of multiple polypropylene boards that supported flattened cellulose membranes.

The development of a dialysis machine by Dutch scientists in 1943 heralded the first real attempt to perform what we now recognize as hemodialysis. Willem Kolff, considered the father of dialysis, constructed a dialyzer in 1943 using various available household items including sausage skins, orange juice cans and washing machines! His crude membrane was used to treat 16 patients who had developed acute kidney injury (AKI), but this effort was initially unsuccessful. However, he did achieve success two years later by reviving a woman from a coma due to AKI. While there was only modest advancement in his device, his work inspired others worldwide to develop better devices. Unfortunately, there were minimal advances for about ten years. Then, in the mid-1950s, researchers (including George Thorn at the Peter Bent Brigham Hospital in Boston) iterated Kolff's dialyzer and developed the stainless steel Kolff-Brigham dialyzer. This period also saw the development of the first plate dialyzer and twin coil machine.



Dr. Kolff with Dr. Clifford Kwan-Gett

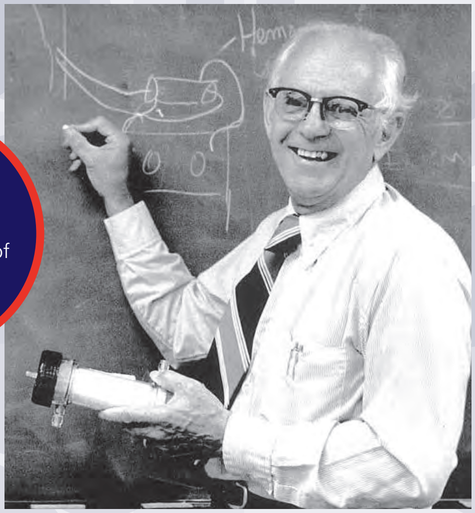
1941/43, J. Willard Marriott Library, University of Utah

Nurse Maria ter Welle modeling 1st artificial kidney in Netherlands

1941/43, J. Willard Marriott Library, University of Utah

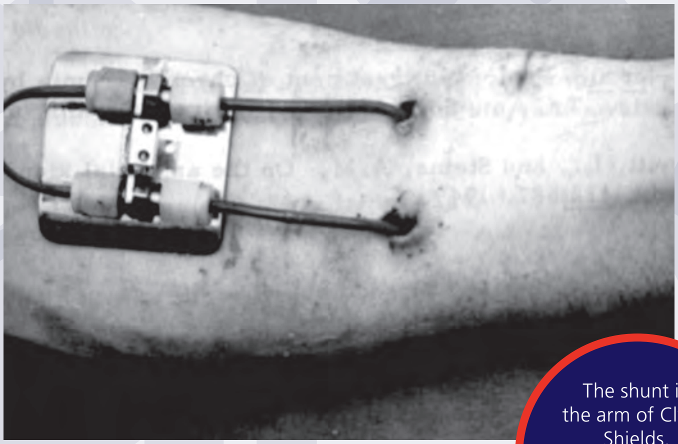
While the plausibility of hemodialysis for AKI was beginning to take shape, maintenance hemodialysis for patients with end stage renal disease (ESRD) was limited by the paucity of reusable vascular access options. This all changed with the

While technological advances were proceeding, it was necessary for sociological, financial and regulatory progress to develop simultaneously. Indeed, the necessity for dialysis for AKI and ESRD existed long before the 1960s. A key question was who was most eligible to receive chronic hemodialysis. Those decisions were assigned to community committees consisting of local residents and physicians.



Belding Scribner

American Society of Nephrology



The shunt in the arm of Clyde Shields.

American Society of Nephrology

advent of the Scribner shunt, developed by Belding Scribner. Scribner's device was actually not the first such type device. Indeed, Nils Alwall developed the first cannula for blood access in the 1940s, but Scribner's device revolutionized hemodialysis blood access. While the device was originally developed from available tubing and plumbing supplies, it eventually was comprised of Teflon. This device permitted one to repeatedly connect and disconnect patients to a hemodialysis circuit without requiring new incisions for each treatment.

Scribner went on to develop a small, portable dialysis machine that could be operated by family members. The portable unit allowed people to undergo dialysis in their own homes, making it easier to maintain their daily routines and freeing up machines in dialysis centers.

The first chronic dialysis center in the world, originally named the Seattle Artificial Kidney Center and later the Northwest Kidney Center (NKC), began treatments in January 1962. At that time, patients were required to pay for the procedures themselves. Not until the early 1970s did legislation address the payment issues regarding chronic dialysis. Finally, in 1973 Congress passed a bill to establish the Medicare End-Stage Renal Disease (ESRD) Program that permitted payment for the treatment for most patients requiring chronic dialysis in the United States.

Throughout the late twentieth century and early twenty-first century, hemodialysis machines continued to develop and provide enhanced safety for patients. This included more efficient alarms and enhanced usability to assess a patient's vital signs and hemodynamic status during a treatment. Simultaneously, dialyzers were iterated to permit, via diffusion and convection, larger toxins that accumulate in renal disease. Finally, better and safer access of the patient's bloodstream was achieved with sophisticated techniques and devices such as arteriovenous fistulas and grafts, and central venous catheters.

The foundation for hemodialysis was initially developed thousands of years ago, but the significant technological, sociologic and economic advances over the past 150 years have permitted the rapid development of modern hemodialysis. Exciting and innovative devices are being developed today that will create a new transformation in hemodialysis technology.

TIMELINE: THE FIRST HUMAN RENAL TRANSPLANTS

John M. Barry, MD

1933 UKRAINE

The first human renal allograft was performed by Yu Yu Voronoy into a 26-year-old woman. The donor was a 66-year-old man whose kidney was removed six hours after death. The recipient died two days later. Although the vascular anastomoses to the femoral vessels and the cutaneous ureterostomy were technically successful, the procedure was doomed because of prolonged warm ischemia time and ABO blood group incompatibility.

1945 BOSTON

Landsteiner, Hufnagel and Hume transplanted a human deceased donor kidney onto the brachial artery and cephalic vein of a young woman with acute renal failure at the Peter Bent Brigham Hospital. The woman's own kidneys recovered a few hours later and the allograft was removed without demonstration of significant function.

Charles A. Hufnagel (left) and David M. Hume (right)

U.S. National Library of Medicine

1950 CHICAGO

The first intra-abdominal human renal transplant was done by a team led by Richard Lawler. After removal of the recipient's left polycystic kidney, a deceased donor kidney's

Richard H. Lawler, M.D.

U.S. National Library of Medicine

vessels were anastomosed to her renal vessels, and a stented uretero-ureterostomy was done. An indigo carmine test showed excretion from the allograft and from the remaining native kidney. Seven months later, transplant function had ceased.

1951 PARIS

René Küss (1913-2006)

Bull. Acad. Natle Med., 2008, 192, no 3, 469-482

The principles of renal transplantation surgery into the iliac fossa were established. Three human kidney transplants were performed by three separate teams in January. Rene Kuss went on to perform four more transplants that year. The kidneys were transplanted by an extraperitoneal approach into the contralateral iliac fossa onto the iliac vessels, and a cutaneous ureterostomy was done to monitor renal function. Kidneys were obtained from decapitated criminals and from living donor kidneys with moderate abnormalities. They were transplanted into ABO blood group compatible recipients, no immunosuppression was used, and all kidneys failed within weeks of implantation.

1954 BOSTON

The first long-term success with human kidney transplantation in which the patient survived for more than a year occurred on December 23. A kidney from one 24-year-old twin was transplanted into the other twin, who had end stage renal disease. Monozygosity was confirmed by the successful exchange of full thickness skin grafts between the twins. The left kidney was

Dr. Joseph E. Murray, center, and his team perform the first successful kidney transplant operation in 1954.

Brigham and Women's Hospital

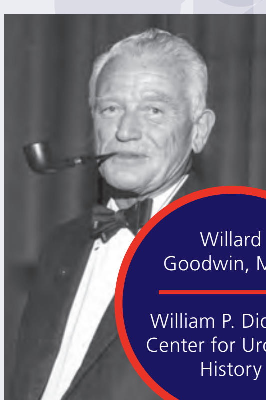
transplanted into the right iliac fossa, and a transvesical ureteroneocystostomy with a submucosal tunnel was done. Joseph Murray, 1990 Nobel Laureate, led the recipient's surgical team and J. Hartwell Harrison led the donor's team. The recipient had good kidney function until cardiac death eight years later.

1959
BOSTON AND PARIS

There were two long-term successful kidney transplants from donors who were not identical twins of the recipients. Both recipients had been prepared with total body irradiation, and both survived for more than a decade.

1960
PARIS

The first successful use of pharmacological immunosuppression in a human kidney transplant recipient occurred. A 26-year-old woman underwent kidney transplantation from her brother-in-law by Kuss' team. A rejection crisis was confirmed by biopsy, and daily 6-mercaptopurine and hydrocortisone were prescribed along with graft irradiation and additional total body irradiation. The transplant eventually failed, and she died of renal failure 16 months after transplantation.



Willard Goodwin, M.D.

William P. Didusch Center for Urologic History

1960
LOS ANGELES

Willard Goodwin successfully used glucocorticoids to reverse a kidney transplant rejection in a patient immunosuppressed with cyclophosphamide.

1961
BOSTON

Peter Bent Brigham Hospital, front view

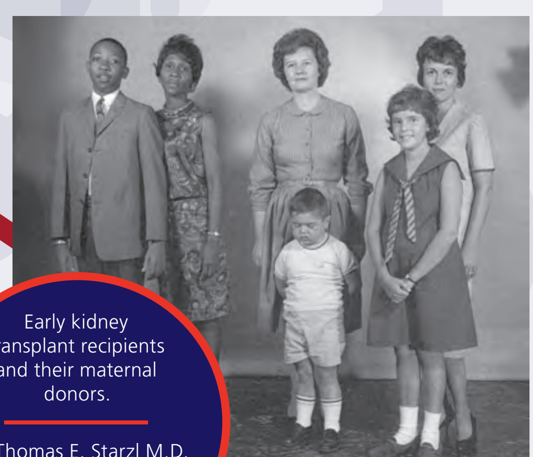
U.S. National Library of Medicine

Azathioprine was used clinically at the Peter Bent Brigham Hospital, and the first long-term successful cadaver kidney transplant was performed in 1962.

1963
BELGIUM

This was probably the first kidney transplant from a brain-dead donor. It was transplanted into a patient with uremia who experienced immediate renal function but died of sepsis three months later.

1966
DENVER



Early kidney transplant recipients and their maternal donors.

Dr. Thomas E. Starzl M.D. Papers, Archives Service Center, University of Pittsburgh

Thomas E.Starzl's team used antilymphocyte globulin clinically. Antilymphocyte antibody induction followed by azathioprine plus glucocorticoid maintenance therapy, and high dose glucocorticoid administration with or without graft irradiation for kidney transplant rejection became common in kidney transplant immunosuppression protocols.

1966
LOS ANGELES

The direct cross-match between donor lymphocytes and recipient serum was introduced. This nearly eliminated hyper-acute renal transplant rejection due to preformed anti-donor antibodies in kidney transplant recipients.

1967, 1969
SAN FRANCISCO AND LOS ANGELES

Human renal preservation over 24 hours became possible with either pulsatile machine perfusion or simple cold storage after an ice-cold intracellular electrolyte flush.

1973
WASHINGTON, DC

Medicare co-insurance for patients with end stage renal disease was instituted.

1970s
MULTIPLE COUNTRIES

Brain-death laws were passed. This allowed organ retrieval from beating heart deceased donors and improved the quality of deceased donor kidney transplants.

Kidney donor cards like this one were introduced in the United Kingdom in 1971.

Science Museum, London
Wellcome Images

1978
CAMBRIDGE

Successful use of cyclosporine as an immunosuppresssant.

1981
BOSTON

Successful use of a monoclonal antibody to treat kidney transplant rejection.

1984
WASHINGTON, DC

The National Transplant Act was passed. This paved the way to a national organ-sharing system, mandatory transplant registries, mandatory center-specific transplant outcome reports and codification of the interdisciplinary management of patients with end stage organ disease.

1995

Surgeons performing a live donor kidney transplant through laparoscopy

ETMC Transplant Center, Texas

Laparoscopic living donor nephrectomy was introduced.

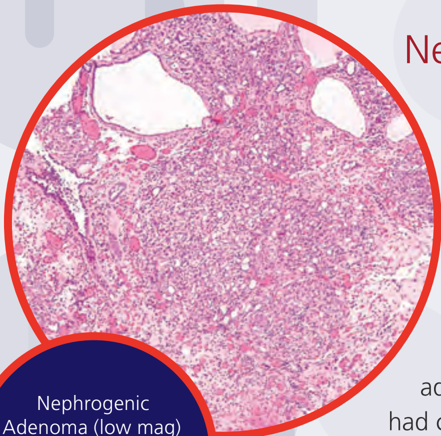
2015
USA

17,878 kidney transplants were performed; 12,250 were from deceased donors. One-year kidney transplant survivals are reported to be 92% for primary kidney transplants and 90% for repeat kidney transplants, results only dreamed of two generations ago!

DISCOVERING THE ORIGIN OF THE NEPHROGENIC ADENOMA: IS THAT A KIDNEY IN YOUR BLADDER?

Jennifer Gordetsky, MD

Nephrogenic adenoma is an uncommon benign lesion with no ability for malignant transformation or metastasis. Nephrogenic adenomas are found predominantly in the bladder, with less common occurrences in the urethra and upper urinary tract.



Nephrogenic Adenoma (low mag)

Wikimedia Commons

This entity was first recognized in adult patients who had chronic irritation of the urinary tract, such as urolithiasis, recurrent urinary tract infection or previous genitourinary surgery. However, some cases of nephrogenic adenoma are asymptomatic and are discovered incidentally. Since its discovery in 1949, nephrogenic adenomas have been recognized in all age groups and have an especially high incidence in renal transplant patients. Although benign, nephrogenic adenomas can be large masses and are known to recur, causing hematuria and obstruction in some cases. Nephrogenic adenoma can also be diagnostically challenging as it can both clinically and histologically mimic malignancy. This tumor has several histologic patterns including tubular, tubulocystic, polypoid, papillary, fibromyxoid and flat. Due to its morphologic variability, this benign lesion can mimic papillary urothelial carcinoma, metastatic tumors and clear cell adenocarcinoma. To add to the complexity, nephrogenic adenoma is found in association with other urothelial lesions in about one-third of cases, including urothelial carcinoma and urothelial papilloma. Most of these tumors can be treated with transurethral resection, although larger lesions may require more invasive surgery.

Nephrogenic adenoma was first described in 1949 by Thomas A. Davis, MD, who reported the lesion in a 40-year-old male treated at the V.A. Center in Wadsworth, Kansas. The patient presented with a urinary tract infection and hematuria. Cystoscopic examination revealed two 3-4 mm masses at the dome of the bladder. The diagnosis provided was "peculiar type of papillary filiform papilloma of the bladder (hamartoma)." Davis believed that "these growths should be classified as hamartomas" due to certain "microscopic features and embryologic factors". An article published a year later by Nathan B. Friedman, MD and Hartwig Kuhlenbeck, MD from the Armed Forces Institute of Pathology in Washington, DC, described the same lesion in eight patients and noted the close resemblance to renal tubules. The authors felt these lesions should be "interpreted as nephrogenic adenoma." Subsequently, the terminology of nephrogenic adenoma came to be preferred over bladder hamartoma. Many speculated that nephrogenic adenomas developed as a metaplastic process of urothelial cells in response to chronic injury. However, others questioned whether these tumors might be of renal origin. In 1985, Marie-Lydie Pierre-Louis, MD and colleagues questioned the pathogenesis of nephrogenic adenoma. They demonstrated the similarity of

Nephrogenic Adenoma (intermediate mag)

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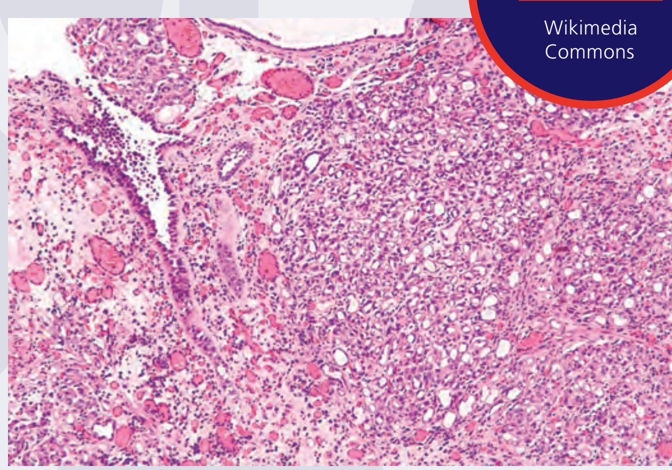

the tubules seen in nephrogenic adenoma to the tubules found in the distal segments of the nephron both on electron microscopy and immunohistochemistry. The ultrastructural similarity of both renal epithelium and nephrogenic adenoma cells seemed to favor a non-metaplastic process.

Nephrogenic Adenoma (high mag)

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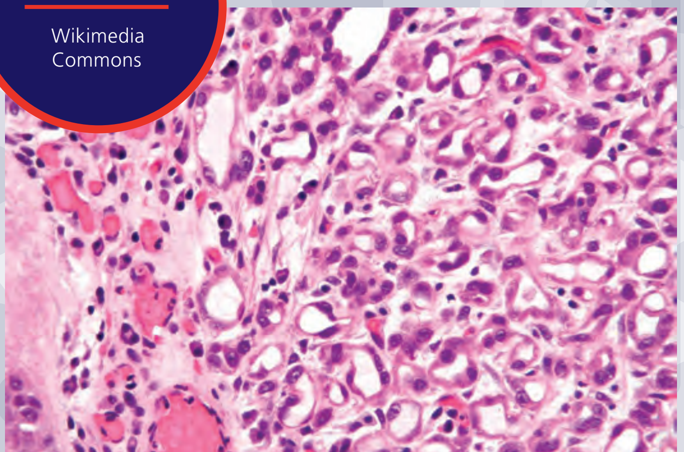


Definitive evidence of the pathogenesis was discovered in 2002 by Peter R. Mazal, MD and colleagues. They noted that nephrogenic adenoma was not uncommon in renal transplant recipients. They took tissue samples from 24 patients who had received a transplant kidney from a donor of the opposite gender. Nephrogenic adenomas in these patients were evaluated utilizing fluorescence in situ hybridization to analyze sex chromosomes as well as immunohistochemical detection of antigens to nephrons. All nephrogenic adenomas in recipients of transplants from a donor of the opposite gender showed the same sex-chromosome status as the donor kidney. In addition, immunohistochemistry identified antigens specific to a renal tubular origin. This study proved that nephrogenic adenoma is a tumor from the proliferation of exfoliated and implanted renal tubular cells and not a metaplastic proliferation of the urothelium. The findings were published in the *New England Journal of Medicine*.

THE FUTURE OF KIDNEY TREATMENT

Anthony Atala, MD, and Karen Richardson, Sr. Communications Manager,
Wake Forest Institute for Regenerative Medicine and Urology

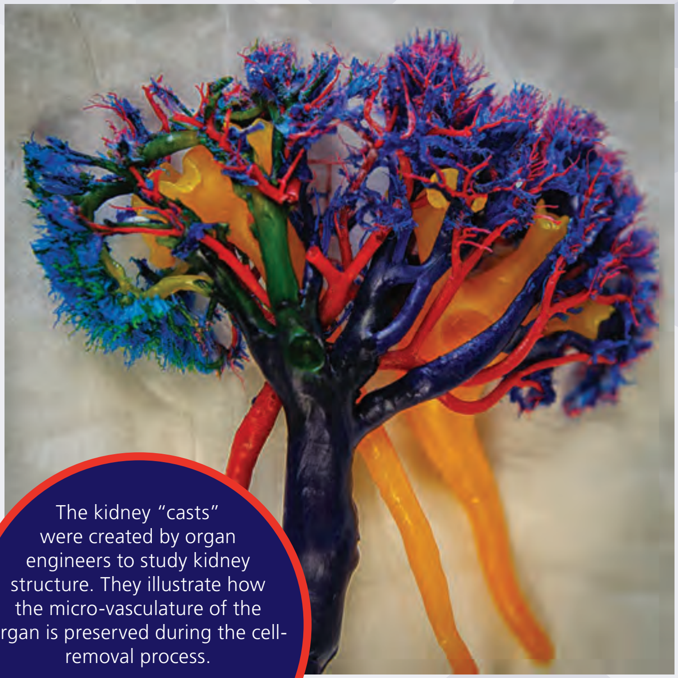
While kidney transplantation is currently the most effective therapy for end stage renal disease, scientists around the world are looking for better options due to the shortage of donor organs and the side effects of immunosuppression. The field of regenerative medicine, which aims to harness the body's innate healing abilities, offers several promising strategies.

ENGINEERING REPLACEMENT KIDNEYS

Will it be possible to one day build a replacement kidney in the lab? Engineered muscle, bladders, cartilage, urine tubes and vaginas have already been successfully implanted in patients. However, the "holy grail" of the urology field is solid organs—such as the kidney.

When implanted in an animal, this structure (made up of biomaterials and kidney cells) was able to filter blood and produce diluted urine.

Courtesy Wake Forest Institute



The kidney "casts" were created by organ engineers to study kidney structure. They illustrate how the micro-vasculature of the organ is preserved during the cell-removal process.

Courtesy Wake Forest Institute

Kidneys undergoing the decellularization process.

Courtesy Wake Forest Institute

There is precedent for the idea of a fabricated kidney. Scientists have created miniature kidney scaffolds using biomaterials and cells that experimentally were shown to be functional, in that they were able to filter blood and produce dilute urine.

"RECYCLING" DISCARDED ORGANS

Several options for creating implantable scaffolds are being explored. One strategy is to use discarded donor organs from humans, or kidneys from pigs, as a platform for organ engineering. The process starts by removing all cells from the organ, creating a scaffold that could hold a patient's own cells.

A 3D bioprinter at work on a kidney structure.

Courtesy Wake Forest Institute

THE QUEST TO BIOPRINT REPLACEMENT KIDNEYS

Another strategy is to print replacement organs using a 3D bioprinter. Scientists have successfully bioprinted muscle, bone and cartilage that, when implanted in animals, developed a system of nerves and blood vessels. They are currently working on more complex structures.

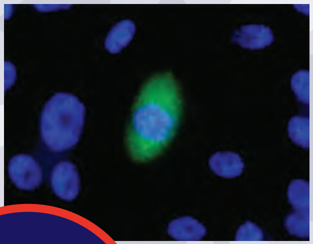
A 3D printed kidney structure.

Courtesy Wake Forest Institute

CELL THERAPY

The ability to expand renal cells in the lab offers the potential not only for organ engineering, but for cell therapy. A phase 2 clinical trial is using selected renal cells obtained from patients during a standard medical biopsy. The cells are combined with a gelatin hydrodrel and implanted into the patient's diseased kidneys. The intent of the therapy is to prevent or delay dialysis and transplantation by increasing renal function. A small, phase 1 trial has been completed.

Recent in vitro research has shown the potential to use autologous renal cells from diseased kidneys for the treatment of renal failure.



Cloned kidney cells.

Courtesy Wake Forest Institute

THE KIDNEY AS FOOD

Jonathan Goddard, Consultant Urological Surgeon

Animal kidneys, along with other edible organs, form part of the attractively named food group, offal, and are eaten in regional dishes all over the world.

The American diet was introduced to offal in the 1940s when meat was scarce because the US government shipped much of the nation's domestic meat supply to WWII soldiers. Kidney had become a staple at dinner and continued to stay that way for many years after the war.

The Swedes are known for their *Hökarpanna*, a Swedish pork and kidney stew. The Spanish eat *Riñones al Jerez* (kidneys in sherry), and one of the great classic British dishes is *Steak and Kidney Pie*, or even more traditionally, *Steak and Kidney Pudding*.

Copper pots in the kitchen of Beaumesnil Castle in France

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THE BRITISH STEAK AND KIDNEY PUDDING

Steak and kidney pudding is a savoury pudding of chopped beef steak and lamb or pig kidney pieces in a gravy contained within a suet pastry.

The suet pudding became extremely popular in the eighteenth century and could be sweet or savoury. One reason for its popularity may be that the pudding could be left unattended to boil away in a pan or copper for hours while the housewife got on with her other chores. The introduction of the muslin pudding cloth in the seventeenth century possibly went some way to popularise this type

MRS BEETON'S BEEF-STEAK AND KIDNEY PUDDING

2 lbs. of rump-steak

2 kidneys

Seasoning to taste of salt and black pepper

Suet crust made with milk, in the proportion of 6 oz. of suet to each 1 lb. of flour

Procure some tender rump steak (that which has been hung a little time), and divide it into pieces about an inch square, and cut each kidney into 8 pieces. Line the dish with crust made with suet and flour in the above proportion, leaving a small piece of crust to overlap the edge. Then cover the bottom with a portion of the steak and a few pieces of kidney; season with salt and pepper (some add a little flour to thicken the gravy, but it is not necessary), and then add another layer of steak, kidney, and seasoning. Proceed in this manner till the dish is full, then pour in sufficient water to come within 2 inches of the top of the basin. Moisten the edges of the crust, cover the pudding over, press the two crusts together, that the gravy may not escape, and turn up the overhanging paste. Wring out a cloth in hot water, flour it, and tie up the pudding; put it into boiling water, and let it boil for at least 4 hours. If the water diminishes, always replenish with some, hot in a jug, as the pudding should be kept covered all the time, and not allowed to stop boiling. When the cloth is removed, cut out a round piece in the top of the crust, to prevent the pudding bursting, and send it to table in the basin, either in an ornamental dish, or with a napkin pinned round it. Serve quickly.

For a pudding with 2 lbs. of steak and 2 kidneys allow 4 hours to cook.

Sufficient for 6 persons.

of food. Prior to this, puddings were cooked in cases made from animal intestine or omentum (like Scottish Haggis).

Continuing the kidney theme, suet is the fat used to make the firm pastry which holds the Steak and Kidney pudding together; suet is the grated fat from around an animal's kidneys: the perinephric fat.

The first Steak and Kidney pudding description in print appears to be recipe 605 in Mrs Beeton's Book of Household Management, the famous cookery book published in October 1861.

KIDNEYS FOR BREAKFAST

Devilled Kidneys were a popular breakfast staple for Victorian and Edwardian English gentleman. The kidneys were cooked in fiery spices (as hot as the Devil!) and served on toasted bread. The devilling of food was mentioned in the eighteenth century; James Boswell (1740 – 1795) wrote of his love of Devilled Bones (probably spiced ribs) in his 1791 biography. Spiced food was popular in England following the Crusades when the knights brought exotic spices from the East back to England's chilly shores. The English developed a love of curried food in the next century as Army officers and diplomats brought back the taste from British India.

James Joyce

By Djuna Barnes Originally published 1922 *Vanity Fair*

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BREAKFAST WITH MR. BLOOM

In his classic 1922 novel *Ulysses*, James Joyce's (1882 – 1941) hero Leopold Bloom enjoys the taste of grilled kidneys for breakfast.

Mr. Leopold Bloom ate with relish the inner organs of beasts and fowls. He liked thick giblet soup, nutty gizzards, a stuffed roast heart, liver slices fried with crustcrumbs, fried hencods' roes. Most of all, he liked grilled mutton kidneys which gave to his palate a fine tang of faintly scented urine.

DEVILLED KIDNEYS

(Serves 2)

- 4 very fresh lambs' kidneys
- 2 tbsp flour mixed with a good pinch of salt and black pepper
- 25g soft butter
- 1/2 tsp cayenne pepper
- 1/2 tsp mustard powder
- 1 tsp Worcestershire sauce
- 1 tsp anchovy sauce or puree, or 2 anchovies, mashed
- 2 thick pieces of bread

Remove the suet from around the kidneys if necessary, along with the thin membrane that might still encase them. Slice in half laterally, so they retain their kidney shape, and use a good pair of scissors or a sharp knife to snip away the membranes that attach the white fatty core to the meat, and remove. Dust in the seasoned flour.

Mash the butter with the other ingredients, and adjust to taste.

Get a small frying pan hot, then add the butter and turn down the heat to medium. Shake off the excess flour, then cook the kidneys for two and a half minutes on each side. Meanwhile, toast the bread. Scoop the kidneys on to the toast, along with the butter from the pan, and serve.

BOSTON'S MEDICAL FIRSTS

In a city known for many "firsts", Boston is heralded for the first public library (Boston Public Library), the first American newspaper (Publick Occurences), the first dog bred in America (The Boston Terrier), and even the first safety razor (Gillette). However and maybe more importantly, Boston is also credited with many medical firsts. It is to these scientific milestones that we turn our attention.

The first demonstration of surgical anesthesia, Boston, 16th October 1846: Dr W. T. G. Morton is administering the anesthetic, ether, at Massachusetts General Hospital

An eye-witness account of the discovery of anesthesia

Wellcome Images

BRIEF HISTORY

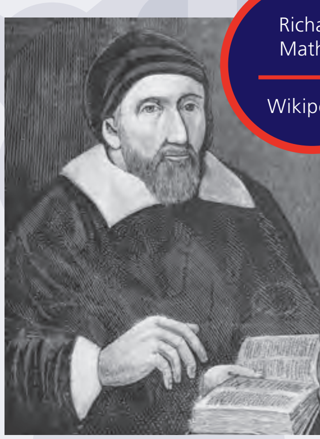
Clearly, it is not by chance that Boston has so many medical firsts. It is a city rich in history of medicine, home to some of the most prestigious hospitals and medical schools, physicians and medical scientists in the world. As the healthcare landscape has changed over the centuries, Boston's commitment to quality medical care and research continues to be innovative—improving patients' lives from the first inoculation in 1721 to the first American penile transplant in 2016. Today, Boston ranks as a preeminent center for healthcare and research. Let's learn more about some of its medical firsts…

FIRST INOCULATION IN AMERICA

On June 26, 1721, after much research with Reverend Cotton Mather, the first inoculation in American history was completed by Dr. Zabdiel Boylston at Boston. This first

Mezzotint portrait of Cotton Mather (1663 - 1728), American Puritan clergyman.

Wikipedia



Richard Mather

Wikipedia

Cow-Pock, or, the Wonderful Effects of the New Inoculation

James Gillray, 1802

Harvard University Library

inoculation in Boston is historic for two reasons: Religious faith opposed experimentation on the human body at that time, and the medical profession had not yet even conceived the use of laboratory analysis to treat diseases back then.

FIRST USE OF ETHER FOR SURGERY

On October 16, 1846 a crowd of doctors and students gathered in the surgical amphitheater at Massachusetts General Hospital to watch as a dentist named William T.G. Morton instructed a patient to inhale the fumes from an ether-soaked sponge. After the patient was sufficiently sedated, a surgeon removed a tumor from his neck. When the patient awoke from his ether-induced stupor, the surgeon asked how he felt, to which he reportedly replied, "feels as if my neck's been scratched."

FIRST ORGAN TRANSPLANT

On December 23, 1954, Doctors Joseph Murray and David Hume completed the first living-related organ transplant when they transplanted a kidney from Ron Herrick into his twin brother, Richard, at Boston's Peter Bent Brigham Hospital (now Brigham and Women's). Eight years later, Murray and Hume completed the same surgery, but this time utilizing the kidney of a deceased donor. In 1990, Murray was awarded the Nobel Prize in Physiology or Medicine for his work in the transplantation field.

FIRST SUCCESSFUL IN-UTERO CARDIAC IMPLANT

Boston was the site of yet another medical breakthrough in 2006, when a team of 16 specialists performed heart surgery on Grace VanDerwerken—while she was a fetus still in utero. Their job was to thread a lifesaving stent, which they completed successfully at Children's Hospital Boston.

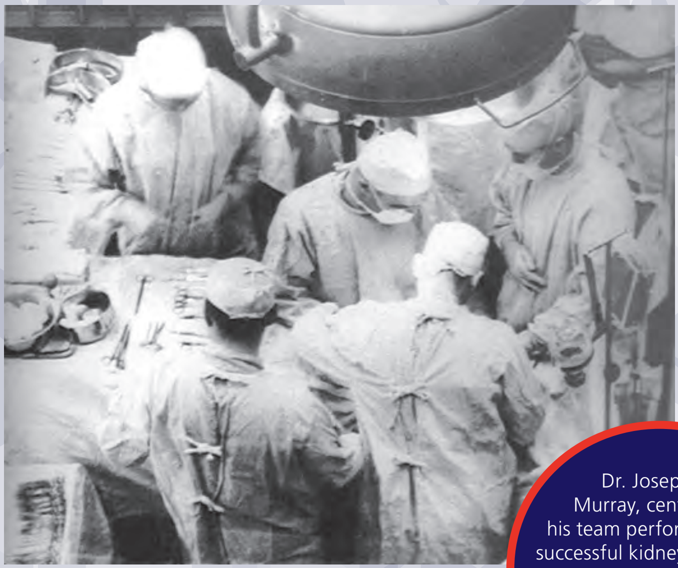
> *Whether a Christian may not employ this Medicine (let the matter of it be what it will) and humbly give Thanks to God's good Providence in discovering of it to a miserable World.*
>
> – REV. COTTON MATHER

FIRST FULL FACE TRANSPLANT

In 2008, construction worker Dallas Wiens suffered severe burns to his head when a piece of machinery he was operating crashed into a power line. Three years later, following 22 surgeries to smooth out his skin and prepare for surgery, the 25-year-old became the first person to successfully undergo a full face transplant in America, which took place at Boston's Brigham and Women's Burn Center.

FIRST PENILE TRANSPLANT IN AMERICA

In May, 2016, the first penis transplant in the U.S. was performed on a cancer survivor in Boston. Surgeons at Massachusetts General Hospital performed the 15-hour transplant operation, using an organ that came from a deceased donor. The surgery, part of a research program, has the goal of helping combat veterans with severe pelvic injuries, as well as cancer patients and accident victims.



Dr. Joseph E. Murray, center, and his team perform the first successful kidney transplant operation in 1954.

Brigham and Women's Hospital

Penile transplant patient Tom Manning hopes to be a role model for others considering the surgery.

© Michael Warren

Dr. Murray, top left, and his team of surgeons with identical twins Richard, bottom left, and Ronald Herrick, bottom right, after the first successful kidney transplant surgery in 1954. Richard received his brother's healthy kidney.

Brigham and Women's Hospital

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