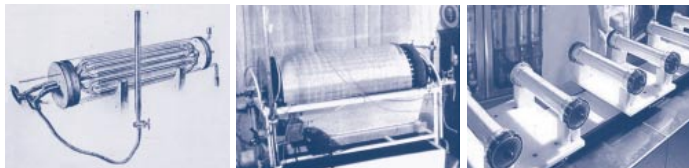




DIALYSIS COMPACT

The invention, development and success of the artificial kidney



Fresenius Medical Care

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Hemodialysis – now and then

The first signs of uremia within the human body are an indication that the kidneys are no longer performing or are unable to completely fulfill their vital function. The Greek origin of the word shows that knowledge of the condition is much older than the ability to treat this life-threatening problem.

It was not until the 1940s that researchers finally established a scientific basis advanced enough to support the first therapeutic trials. The discoveries and inventions of dedicated doctors and scientists are to thank for the advances that have cleared the way for continuous technological improvement over the decades.

On the following pages we document the captivating history of hemodialysis and the artificial kidney (dialyzer) – inventions that help secure the life and quality of life of more than 1.2 million hemodialysis patients worldwide.

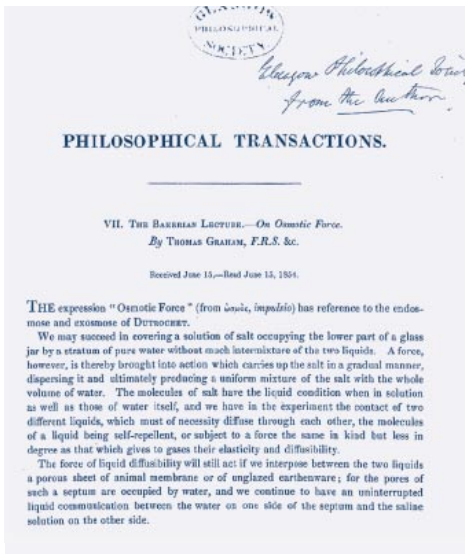
Historical basis of hemodialysis

Acute and chronic kidney failure, which can lead to death if untreated for several days or weeks, is an illness that is as old as humanity itself. In early Rome and later in the Middle Ages, treatments for uremia (Greek for urine poisoning, or literally, “urine in the blood”) included the use of hot baths, sweating therapies, blood letting and enemas.

Current procedures for the treatment of kidney failure include physical processes such as osmosis and diffusion, which are widespread in nature and assist in the transport of water and dissolved substances.

The first scientific descriptions of these procedures came from the Scottish chemist Thomas Graham, who became known as the “Father of Dialysis”. At first, osmosis and dialysis became popular as methods used in chemical laboratories that allowed the separation of dissolved substances or the removal of water from solutions through semipermeable membranes. Far ahead of his time, Graham indicated in his work the potential uses of these procedures in medicine.

In 1855 the German physiologist Adolf Fick published a quantitative description of the diffusion process. But it was not until 50 years later that someone gave a solid basis for the process – and that someone was Albert Einstein. He derived those empirically defined diffusion laws thermodynamically accurately from the theory of Brownian molecular motion. With that, Einstein established a solid scientific basis. Still, Graham and Fick had discovered the underlying principle which led to the current forms of treatment for kidney failure.



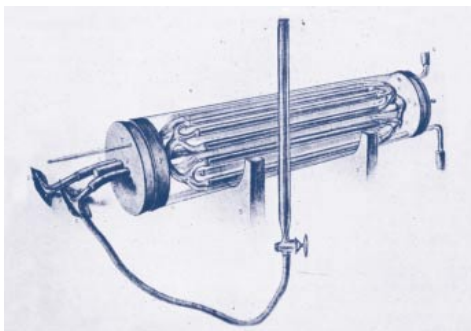
Manuscript of Thomas Graham's „Bakerian Lecture“ about osmotic force at the Royal Society in London in 1854. Hand-written note: Glasgow Philosophical Society from the author.

Today, the term “hemodialysis” describes an extracorporeal procedure, or procedure outside the body, for filtering uremic substances from the blood of patients suffering from kidney disease. The actual purifying process, which requires the use of a semipermeable membrane, is based on the above-described works of Graham, Fick and others.

The early days of dialysis: John J. Abel and Georg Haas

The first historical description of this type of procedure was published in 1913. Abel, Rowntree and Turner “dialyzed” anesthetized animals by directing their blood outside the body and through tubes with semipermeable membranes. The membranes were made from Collodion, a material based on cellulose. It remains unclear if Abel and his colleagues originally intended to use the procedure, known as vividiffusion, to treat kidney failure or rather, as is sometimes believed, later adopted it for this use. Still, dialysis treatment today continues to use major elements of Abel’s vividiffusion machine.

Before Abel could route the animals’ blood through the “dialyzer”, the blood’s ability to clot or coagulate had to be at least temporarily restricted. Abel and his colleagues used a substance known as Hirudin.



Vividiffusion machine from Abel and colleagues, 1913

Hirudin was first identified in 1880 by the British physiologist Haycraft, and is the anticoagulant element in the saliva of leeches.



Dr. Georg Haas performing dialysis on a patient at the University of Giessen

A German doctor by the name of Georg Haas, from the town of Giessen near Frankfurt am Main, performed the first dialysis treatments involving humans. It is believed that Haas dialyzed the first patients with kidney failure in the summer of 1924 after performing preparatory experiments. By 1928, Haas had dialyzed an additional six patients, none of which survived, likely because of the critical condition of the patients and the insufficient effectiveness of the dialysis treatment. The Haas Dialyzer, which also used a Collodion membrane, was built in a variety of models and sizes.

When and how much Haas learned about the efforts of the Abel research group has been discussed in great detail, but a precise answer to the question is not known. Haas most likely completed much of his preparatory experiments beginning in 1914, and without knowledge of Abel's experiences because of the confusion

surrounding the war. But following this interruption, he was likely informed of the efforts of the Abel team.

Haas, like Abel, also used Hirudin as the anticoagulant in his first dialysis. However, Hirudin often led to massive complications arising from allergic reactions since the substance was insufficiently purified and originated in a species very distant from humans. In the end, Haas used a substance known as Heparin in his seventh and final experiment. Heparin is the universal anticoagulant in mammals and was first isolated in dog livers by an American named MacLean, in 1916. This substance caused substantially fewer complications than Hirudin – even when it was insufficiently purified – and could be produced in much larger amounts. Heparin became – and remains – the anticoagulant of choice, with the development of better purification methods in 1937.

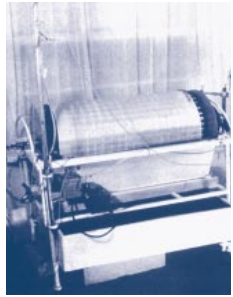
The first successful dialysis treatment: Willem Kolff

Willem Kolff, of the Netherlands, was able to secure a success in Kampen in 1945 that remained elusive to Haas. Kolff used a rotating drum kidney to treat a 67-year-old patient that had been admitted to the hospital with acute kidney failure. The week-long treatment with the device, which Kolff had developed in the years before, allowed the patient to later be released with normal kidney function. She died at the age of 73 from an illness unrelated to the kidney failure. Kolff had unsuccessfully treated 16 previous patients in a series of experiments, but this success became the first major breakthrough in the treatment of patients with kidney disease and proved the usefulness of the concepts developed by Abel and Haas.

The success was partially due to the technical improvements in the actual equipment used for the treatment. Kolff's rotating drum



Willem Kolff



Kolff rotating drum kidney (1943)

kidney used membranous tubes made from a new material known as cellophane that was actually used in the packaging of food. During the treatment, the blood-filled tubes were wrapped around a wooden drum that rotated through an electrolyte solution known as "dialysate". As the membranous tubes passed through the bath, the uremic toxins would pass into this rinsing-liquid using the above-mentioned physical principles.

Passing the practical test: the Kolff-Brigham rotating drum kidney

Examples of the Kolff rotating drum kidney crossed the Atlantic after the Second World War and landed at the Peter Brent Brigham Hospital in Boston, where they underwent a significant technical improvement. The modified machines became known as the Kolff-Brigham kidney, and between 1954 and 1962 were shipped from Boston to 22 other hospitals worldwide.



Paul Teschan performing acute dialysis during the Korean War (1952)

The Kolff-Brigham kidney had passed its practical test under extreme conditions during the Korean War. At that time, eight of ten injured soldiers with post-traumatic kidney failure died. Major Paul Teschan, a military doctor with the U.S. Army, was familiar with the work at the Peter Brent Brigham Hospital and took one of the machines from the Walter Reed Army Hospital to a MASH (Mobile Army Surgical Hospital) unit in Korea where he used 72 treatments to dialyze 31 patients. Under the most extreme conditions, the use of dialysis was able to significantly increase the average survival rate of the severely ill patients and win time for additional medical procedures.

Dialysis and ultrafiltration: Nils Alwall

One of the most important functions of the natural kidney, in addition to the filtering of uremic toxins, is the removal of excess water from the body. When the kidneys fail, this function must be taken over by the artificial kidney, which is also known as a dialyzer. This procedure is termed “ultrafiltration” and squeezes plasma water from the patient through the dialyzer membrane using pressure.

In 1947, the Swede Nils Alwall published a scientific work describing a modified dialyzer developed between 1942 and 1947 that could better combine the necessary processes of dialysis and ultrafiltration than the traditional Kolff kidney. The cellophane membranes used in this dialyzer could withstand higher pressure because of their positioning between two protective metal grates. All of the



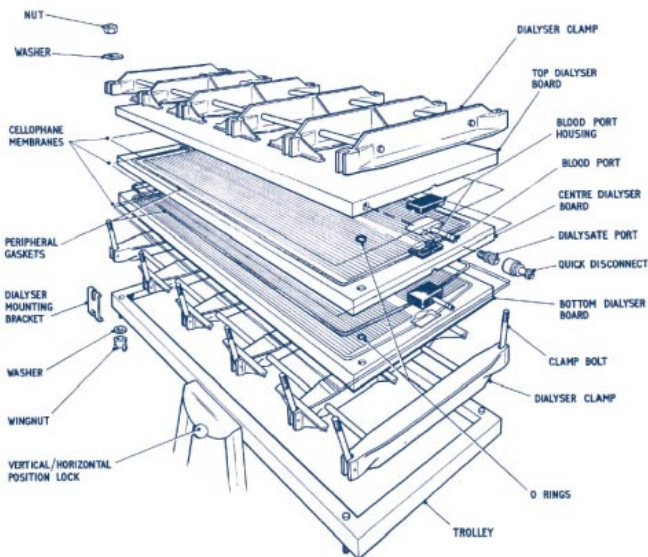
Alwall dialyzer

membranes were in a tightly closed cylinder so that the necessary pressure did not have to come along with the blood but could rather be achieved using lower pressure in the dialysate.

Further developments

By proving that uremic patients could be successfully treated using artificial kidneys, Kolff sparked a flurry of activity around the world to develop improved and more effective dialyzers. The “Parallel Plate Dialyzer” evolved as the most significant development of this period. And rather than pumping the blood through membranous tubes, it directed the flow of dialysis solution and blood through alternating layers of membranous material. This development began with the first Skegg-Leonards dialyzer in 1948, and reached its technological peak in 1960 with the presentation of the Kiil dialyzer from the Norwegian doctor Fredrik Kiil. These dialyzers were the predecessors of the current plate dialyzers. Kiil dialyzers were in use in some clinics until the end of the 1990s.

Scientific discoveries in the transport of substances across membranes accompanied the technological refinement of dialyzers and began to include dialysis-specific research. These efforts made a quantitative description of dialysis possible and allowed the development of dialyzers with clearly defined characteristics.



Schematic construction of a Kiil dialyzer according to the original English drawings

Vascular access and chronic dialysis

Despite widespread technological advances, gaining access to an appropriate amount of the patient's blood for treatment presented a significant problem in the early years of dialysis. Typically, a glass cannula or tube would be surgically placed in a blood vessel to allow

access. Unfortunately, the complex nature of the surgery coupled with the fact the cannula could not remain in place for a significant period of time meant it was impossible to provide the type of dialysis treatment necessary to save the lives of patients with chronic renal failure (so-called uremics).



Quinton, Dillard and Scribner's vascular access

Quinton, Dillard and Scribner made a breakthrough in this field in 1960 in the United States with the development of an access that would later become known as the Scribner Shunt. The access could remain in place for about two months, gave relatively simple access to a patient's circulatory system, and for the first time made it possible to offer dialysis treatment to uremics. The shunt was on a small plate that would be attached to the body, for example on the arm. One cannula from the then-newly discovered material Teflon was placed in a vein and another in an artery. Outside the body, the tubes were joined in a circulatory short-circuit – hence the name “shunt”. During dialysis, the shunt would be opened and attached to the dialyzer. Further development brought the introduction in 1962 of shunts made entirely from flexible material that extended life spans anywhere from several months to several years.

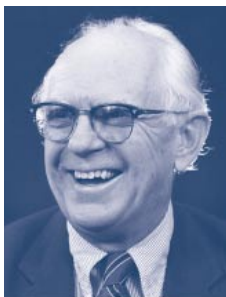
Still, the most decisive breakthrough in the field of vascular access came in 1966 from Brescia, Cimino and their colleagues. Their work remains of basic importance to dialysis today. Using surgery, Brescia and his colleagues joined an artery in the arm with a nearby vein. The vein is normally not exposed to high arterial blood pressure, so the operation “arterialized” the vein and caused it to swell. Needles could then be more easily placed in this vein, which lay beneath the skin, to allow repeated access. This technique lowered the risk of infection in the vascular access and permitted dialysis treatment over a period of years. The so-called Arteriovenous (AV) Fistula remains the access of choice for dialysis patients, and some AV fistula implanted more than 30 years ago are still in use today.

The developments that began with the Scribner Shunt allowed the long-term treatment of patients with chronic kidney failure. In the spring of 1960, Belding Scribner implanted a shunt in the American Clyde Shields, in Seattle. Shields became the first chronic hemodialysis patient, and the dialysis treatments allowed him to live an additional eleven years before dying of cardiac disease in 1971.

These initial successes provided a fertile basis for the first-ever chronic hemodialysis program, which was established in Seattle in the following years. Over the years, Belding Scribner and his team consciously refrained from seeking patent protection for many of their inventions and innovations to ensure swift distribution of their life-saving techniques for dialysis patients. The lifelong efforts of Belding Scribner were recognized in 2002 when he and Willem Kolff were awarded the distinguished “Albert Lasker Award for Clinical Medical Research”. Scribner died in 2003 at the age of 82.



Clyde Shields
(1921 – 1971)



Belding H. Scribner
(1921 – 2003)

Modern hemodialysis: the first hollow-fiber dialyzers

Hemodialysis established itself as the treatment of choice worldwide for chronic and acute kidney failure after the early successes in Seattle. Membranes, dialyzers and dialysis machines were continually improved and produced industrially in ever-increasing numbers. A major step forward was the development of the hollow-fiber dialyzer by the American Richard Stewart in 1964. This technology replaced the until-then traditional membranous tubes and flat membranes with a number of capillary-sized hollow membranes.

This procedure allows for the production of dialyzers with a surface area large enough to fulfill the demands of efficient dialysis treatment.

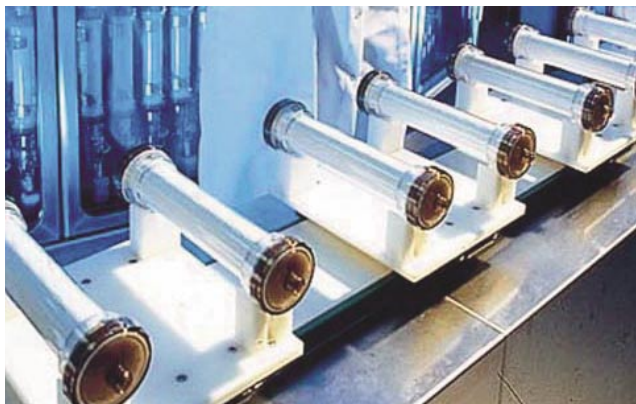
The development of the related industrial manufacturing technology was completed by Dow Chemical between 1964 and 1967, with Dr. Ben Lipps, current Chairman of the Management Board of Fresenius Medical Care, playing a significant role. This new technology allowed the production in subsequent years of large numbers of dialyzers at a reasonable price. The typical hollow-fiber dialyzers of today – which are equipped with a more effective and better-tolerated membrane made primarily from synthetic polymers – are still based on these concepts.



The first family of hollow-fiber dialyzers (C-DAK, “Cordis Dow Artificial Kidney”)

As the clinical use of hemodialysis became increasingly widespread, scientists were better able to investigate the unique attributes of patients with chronic kidney disease. In contrast to the early years of dialysis presented here, the lack of adequate treatment methods or technologies is no longer a challenge in the treatment of renal patients. The present challenges are multifold and come from the sheer number of patients requiring dialysis treatment, the

complications resulting from years of dialysis treatment, and a growing population of patients that presents demographic as well as medical challenges; a population that would be without help were it not for the innovative researchers presented here.



The current generation of dialyzers produced by Fresenius Medical Care



This publication is the second in a series of publications covering the topic of dialysis. Last year we presented the “Dialysis Compact – The function, diseases and treatment of the human kidney” to offer a glimpse into how the kidneys function, the causes of chronic kidney failure, treatment alternatives and an insight into how dialysis functions. This publication is available from Fresenius Medical Care AG, Investor Relations.

Fresenius Medical Care is the world’s largest provider of products and services for patients with chronic kidney failure, a disease that affected more than 1.3 million people in 2004. More than 124,400 patients were treated with renal replacement therapy in our network of clinics in the United States, Europe, Asia and Latin America at the end of 2004. In addition, we are the leading provider of dialysis products such as hemodialysis machines, dialyzers and related disposable products.

Further information about our company and the history of dialysis can be found at www.fmc-ag.com

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