HISTORY AND EVOLUTION OF DIALYSIS

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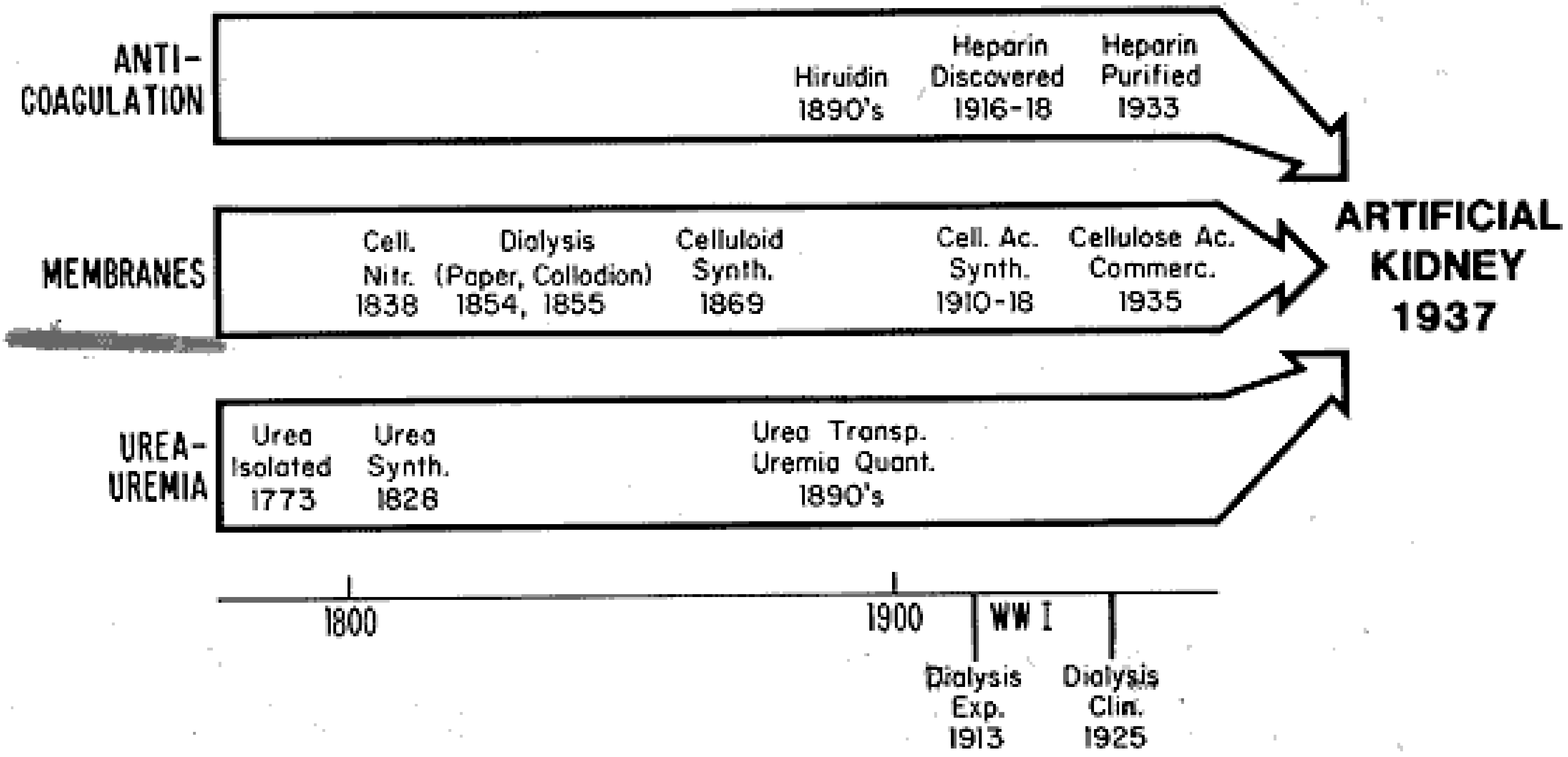
WHAT IS NEEDED FOR DIALYSIS

- ANTICOAGULATION
- SEMIPERMEABLE MRMBRANES
- KNOW WHAT TO REMOVE AND HOW MUCH

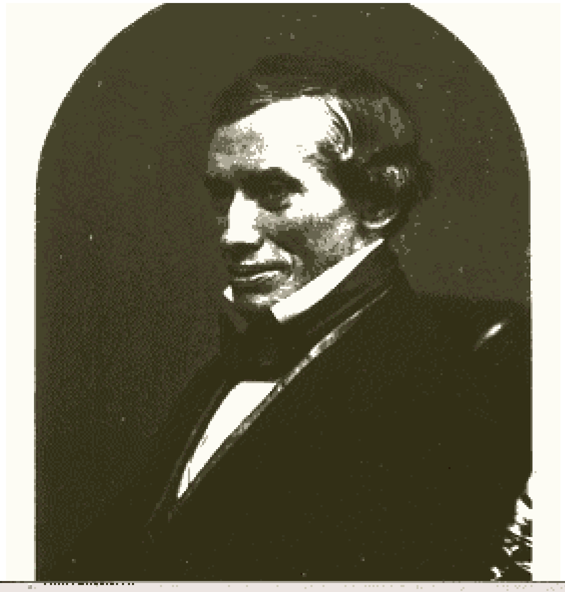
Dr. Carl Magnus Kjellstrand **History of Dialysis. Men and Ideas** Nordic Nephrology Days, University of Lund, May, 1997. Selected Symposia
http://www.hdcn.com/symp/lund/kjel.htm

TIMELINE, HISTORY OF DIALYSIS



THOMAS GRAHAM (1805–1869).

- His first major article on osmosis appeared in 1854.
- After examining the diffusion of 1 liquid into another, he divided particles into 2 classes—crystalloids, such as common salt, having high diffusibility, and colloids, such as gum arabic, starch, albumin, and gelatin, having low diffusibility. He devised ‘‘dialysis,’’ a method for separating colloids from crystalloids.



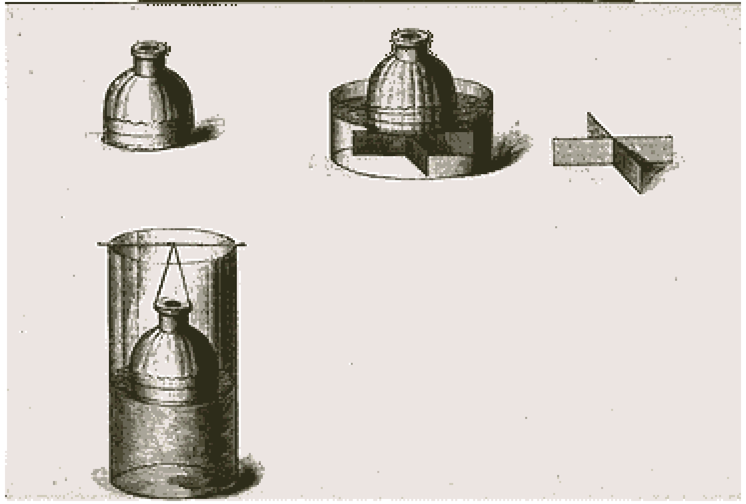
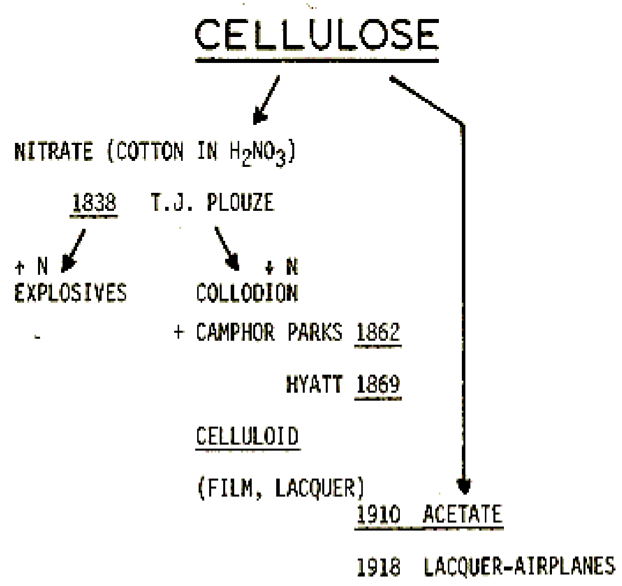


TABLE XII.—Dialysis through Parchment-paper during twenty-four hours, at 10° to 15°.

Ten per cent. solutions.	Diffusate, in grammes.	Relative diffusate.	Osmose, in grammes of water.	Relative osmose.
Gum-arabic,	0·029	·004	5·0	·263
Starch-sugar,	2·000	·266	17·0	·894
Cane-sugar,	1·607	·214	15·3	·805
Milk-sugar,	1·387	·185	15·0	·789
Mannite,	2·621	·349	17·6	·926
Glycerine,	3·300	·440	17·6	·926
Alcohol,	3·570	·476	7·6	·400
Starch-sugar (second experiment),	2·130	·284	16·8	·884
Chloride of sodium,	7·500	1	19·0	1

MEMBRANE DEVELOPMENT

- **Membrane technology is spinoff of military technology.**
- Plouzé, discovered that balancing the amount of cotton and nitric acid, you can either get a solution that exploded or a solution that made a very strong membrane, then he was able to make a very strong solution, collodion, but using less nitric acid and more cotton. Parks in turn added camphor to that to make billiard balls, which were getting in scarce supply at that particular time. That was finally even bettered by Hyatt.
- At that time, somebody invented, that if you solve in acetate instead, it didn't burn and was equally strong. So there you have both the cellulose nitrous membrane cellophane and the cellulose acetate.
- Cuprophane is cellophane manufactured using the cuprammonium process. Cellulose is dissolved in [Cu(NH3)4](OH)2 solution and then regenerated when extruded into sulfuric acid. The Cuprophane is stronger than cellophane and has greaterporosity. It was initially used in packaging and in the sausageindustry.



UNDERSTANDING OF UREMIA

- **Urea is isolated from the urine:** starting point is 1773--220 years ago, when Hillaire Nurepuel. He said: There is something in urine that comes out of the body. It's a poison. He called it **urea** after **urine**, and we use the word **uremia.**(Urine boiling experiment)

German chemist, Wöhler
synthesized urea and describes its molecular structure. Only God can make the organic life-containing substances. Wöhler overnight killed that philosophical school by taking ammonia, carbon dioxide, and combining them -- two inorganic substances -- into urea, an organic substance.

UNDERSTANDING OF UREMIA

Sept. 1, 1888.]

THE BRADSHAWE LECTURE

ON

URÆMIA.

Delivered before the Royal College of Physicians, August, 1888.

By WILLIAM CARTER, M.D., B.Sc., LL.B.Lond., F.R.C.P.Lond.,

Physician to the Royal Southern Hospital, Liverpool; Professor of Materia Medica and Therapeutics, in University College, Liverpool.

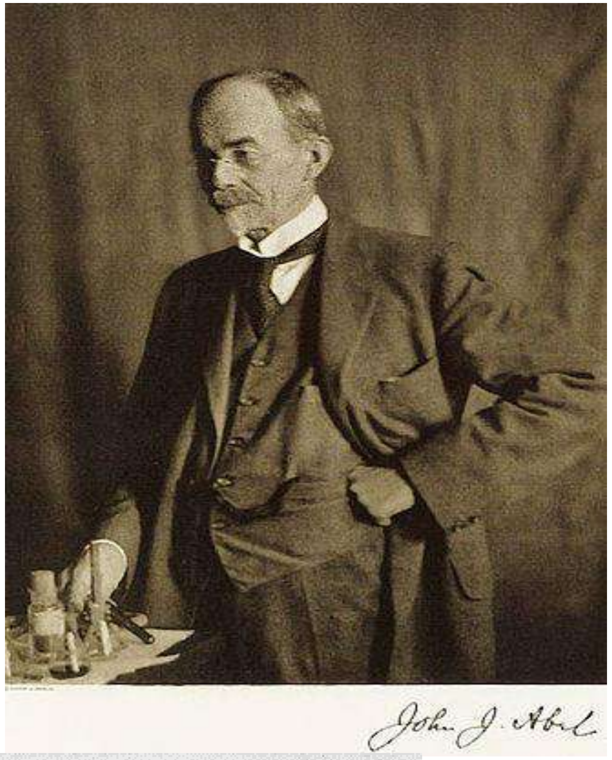
This is a lecture on uremia given in 1888 in London.

Table 1 Evolution of discoveries enabling development of hemodialysis for renal failure in the 20th century

Author(s)	Year	Discovery	Comment
Egyptian tomb[30]	ca 1500 BC	Blood sucked by leeches does not coagulate	First remark about anticoagulation
Leucippus of Miletus Democritus of Abdera[17,18]	ca 440 BC	Concept of the atom	Atoms are separated by a void and can move—basis for diffusion
Erasistratus of Ceos[3,4]	ca 270 BC	Kidneys may be the source of urine	Work cited by Galen
Galen[3,4]	ca 150	Kidneys are the source of urine	
Gassendi[19]	1659	Union of atoms forms *moleculae* or *corpuscula*	Reviver of atomism by separating the belief in atomism from atheism
Nollet[22]	ca 1750	Discovery of osmotic pressure	Pressure in a solution separated from a solvent by a semipermeable membrane
Fourcroy and Vauquelin[8–11]	1797–1808	Urine contains large amount of urea, which may be toxic if not excreted in the urine	Discovery of urea in the urine
Dalton[21]	1803	Refinement of molecular theory	Atoms can combine to form compounds
Ségalas and Vauquelin[12]	1822	Infusion of urea into blood of animals caused diuresis but not toxicity	Urea may not be a toxic constituent of urine
Dutrochet[22]	1828	Osmometer	First measurement of osmotic pressure
Schönbein[25]	1846	Nitrocellulose dissolved in ether and ethyl alcohol creating collodion	First good semipermeable membrane
Fick[27]	1855	Laws of diffusion based on analogy to flow of heat	Used collodion as a semipermeable membrane
Graham[24]	1861	Diffusion, dialysis, crystalloids, colloids	Major work on diffusion and dialysis. Did not use collodion, but cotton calico painted with steam-coagulated egg albumen
Feltz and Ritter[14]	1881	Most toxic constituent in urine is potassium	Low or no toxicity of other urine constituents
Haycraft[31]	1883	Leech saliva contains anticoagulant	Basis for later isolation of hirudin
Bodong and Jacobj[32]	1904	Isolation of hirudin	First isolated anticoagulant

1913: **Abel, Rowntree, and Turner**

- The first apparatus for dialysis or ''vivi-diffusion'' in animal experiments was designed by Abel, Rowntree, and Turner from the Pharmacology Laboratory of the Johns Hopkins Medical School in Baltimore, MD, U.S.A. The preliminary report was presented before the Association of American Physicians in Washington on May 6, 1913. The method was then presented by Abel in London, UK, on August 11, 1913, and later in Groningen, the Netherlands. The Times of London published a short article reporting that the presentation was greeted with rounds of applause: ''Professor Abel has constructed what is practically n artificial kidney.'' Thus, the term ''artificial kidney'' was coined, not by authors of the paper, but by an anonymous reporter.



V. THE PREPARATION OF THE LEECH EXTRACT

As already stated, an extract obtained from the medicinal leech is employed in our method of vividiffusion to render the blood incoagulable. In consequence of the high price[13] of hirudin, the anticoagulative principle of the leech, we now prepare for ourselves an active extract of this principle, basing our method on the work of Jacobj[14] and his pupils, Franz, Hayashi and Bo-

[13] Hirudin costs $27.50 a gram. We have used more than half a gram in a single experiment of long duration on a large dog. Good medicinal leeches from France can be bought in lots of one hundred or more from cupping barbers at the rate of $6 a hundred. Hynson, Westcott & Co., of Baltimore, inform us that they hope to be able to furnish the best leeches at $20 to $25 a thousand. As a single leech may yield 8 mgm. of active hirudin to extraction with water, the saving that results from making the extract is considerable.

[14] Arch f. Exp. Pathol. u. Pharm. 49, p. 342.

REMOVAL OF DIFFUSIBLE SUBSTANCES BY DIALYSIS 303

dong,[15] investigators who have given us many valuable data in regard to this singular substance.

We have usually prepared our extract from two hundred leeches though lately we have used a larger number at a time. Only the head and the immediately adjoining segments are used. The head is seized with a pair of forceps and the body is cut through at the tenth or twelfth ring. The head portions are then ground up as fine as possible, with or without the use of sand as the case may be. 150 cc. of distilled water (i.e., 0.75 cc. per head) and enough thymol in substance to ensure asepsis are added and the mixture set aside in the ice-chest for twenty-four hours. The mass is then transferred to a Buchner funnel and filtered under pressure and washed with just enough water to give 150 cc. of filtrate. The filtrate is brought rapidly to a tem-

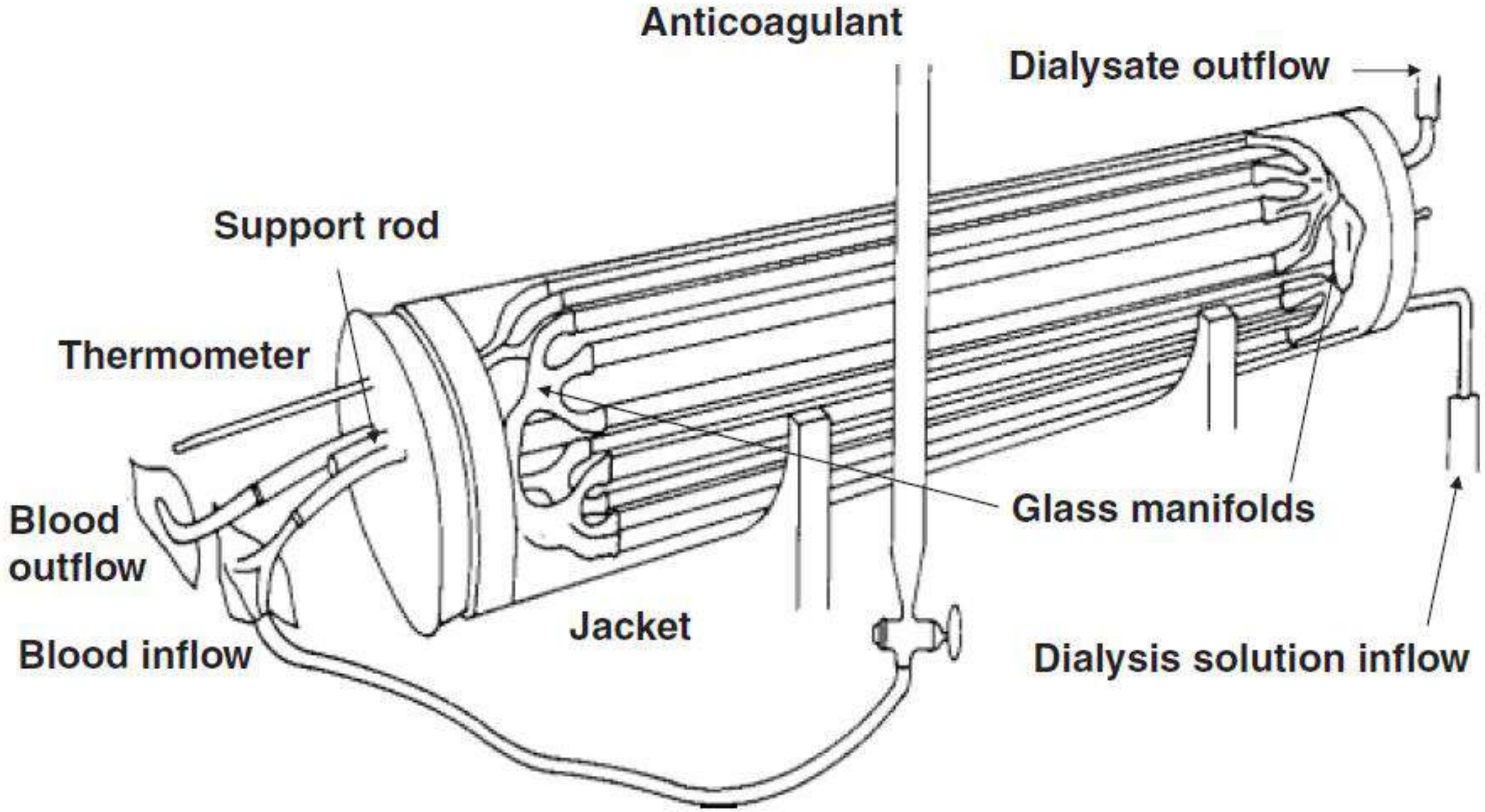


Figure 1 Celloidin dialyzer of Abel, Rowntree, and Turner (modified from Abel et al.[35]).

ANTICOAGULATION

- Jay McLean, a young medical student from Boston came to John Hopkins Hospital in Baltimore in the summer of 1915 to do research. He was asked to take dog's livers, grind them up, and extract out of them a substance that promoted clotting.
- But he said, "I found something opposite to what I was set to do. I found a substance here that will markedly inhibit the coagulation. Isn't that interesting? I'm going to study it.“
- Two years later, two professors from Johns Hopkins, Howell and Holt, publish "Two new factors in blood coagulation: heparin and pro-antithrombin", where they rediscover Jay McLean's story here.

The Discovery of Heparin

By JAY MCLEAN, M.D.

THE THROMBOPLASTIC ACTION OF CEPHALIN

JAY McLEAN

From the Physiological Laboratory of the Johns Hopkins University

Received for publication, June 15, 1916

The heparphosphatid on the other hand when purified by many precipitations in alcohol at 60° has no thromboplastic action and in fact shows a marked power to inhibit the coagulation. The anticoagulating action of this phosphatid is being studied and will be reported upon later. Cuorin and heparphosphatid when dry have no odor, but when moist with warm alcohol have a characteristic odor common to both. It is possible that on further purification the heparphosphatid may be shown to be identical with cuorin.

TWO NEW FACTORS IN BLOOD COAGULATION—HEPARIN AND PRO-ANTITHROMBIN

W. H. HOWELL AND EMMETT HOLT

From the Physiological Laboratory of the Johns Hopkins University

Received for publication October 17, 1918

1926: GEORGE HAAS GERMANY

- He had a device exactly like the one made by Abel and Roundtree. Each of these here contains collodion, two collodion tubes joined with a U tube here. Blood comes from the patient, is pumped by blood pumps through a clot filter and then it flows back and forth through these many tubes here. Then it returns to another clot pad and back to the patient. The patient was anticoagulated with hirudin.

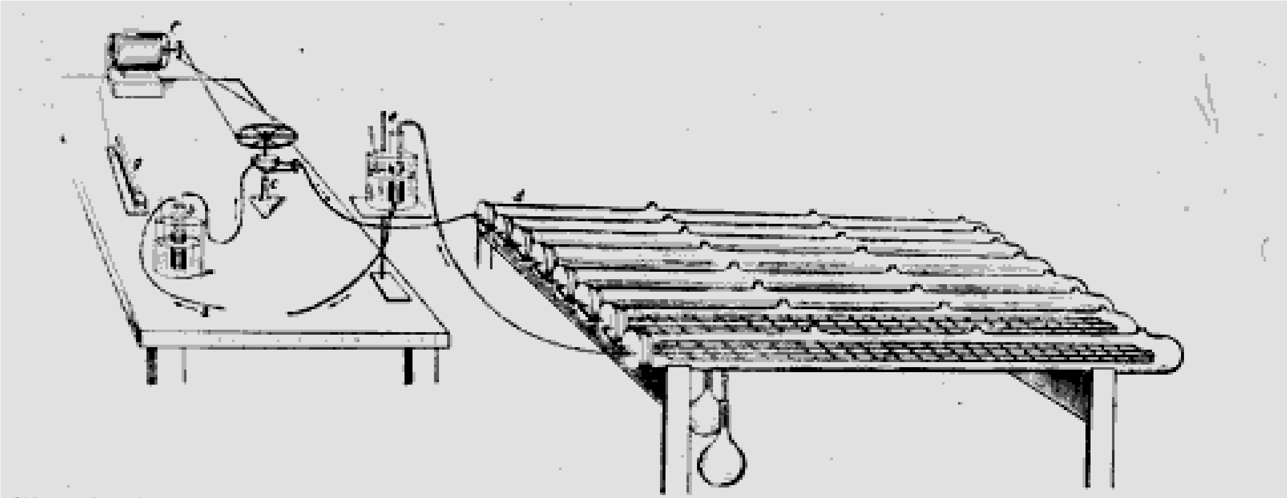
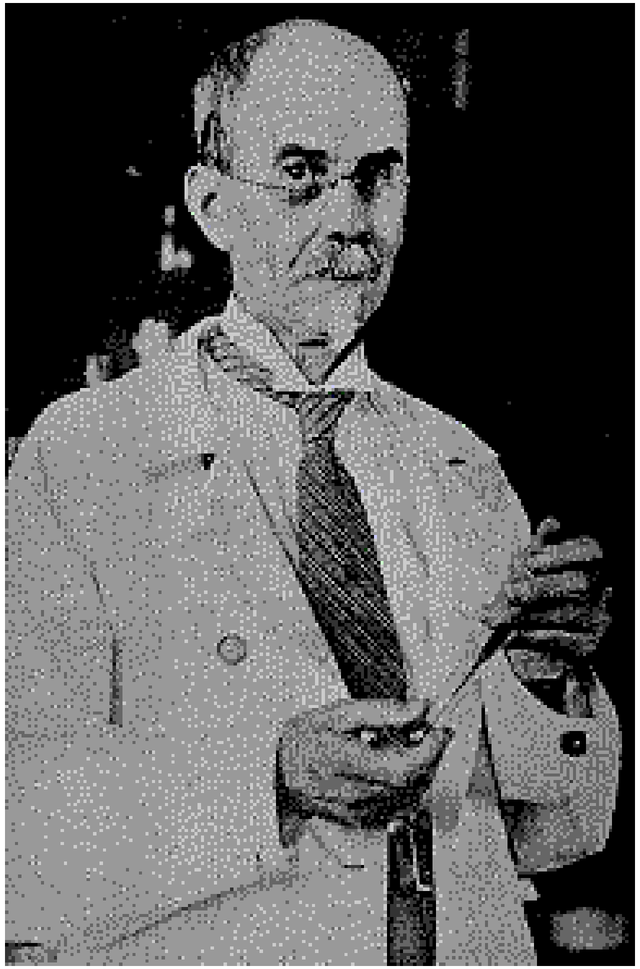


Fig. 412. Methodische Neuanordnung der Blutdialyse nach *Haas* (Kabinensystem). a = arterieller Zustrom nach dem ersten Glasgefäß; b = erstes Glasgefäß, von hier wird das Blut mit Hilfe des *Beck*schen Apparates zu den Dialysierschläuchen gepumpt; c = *Beck*scher Apparat; d = Dialysiersystem (Kabinensystem); e = zweites Glasgefäß, welches das Blut nach Durchströmen der Dialysierschläuche aufnimmt; von hier fließt das Blut infolge der Schwerkraft zurück in die Vene; f = Elektromotor; g = Widerstand.

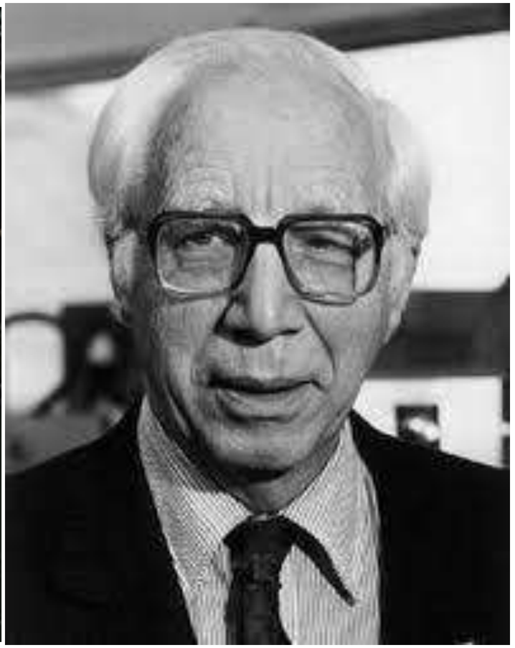


1960:KIIL DIALYSERS

- Frederic Kiil, a urologist from the Ulleva´ l Hospital, Oslo, Norway,104 modified the sheet dialyzer of Skeggs and Leonards by replacing rubber pads with plastic boards made of an epoxy resin compound with talcum as a filler substance. Cellophane sheets were replaced with more permeable cuprophane (Cuprophans Bemberg PT 150, Wuppertal, Germany).

Willem Johan "Pim" Kolff (February 14, 1911 – February 11, 2009)

Pioneer of hemodialysis, artificial heart, as well as in the entire field of artificial organs. Willem was a member of the Kolff family, an old Dutch patrician family. He made his major discoveries in the field of dialysis for kidney failure during the Second World War. He emigrated in 1950 to the United States, where he obtained US citizenship in 1955, and received a number of awards and widespread recognition for his work.



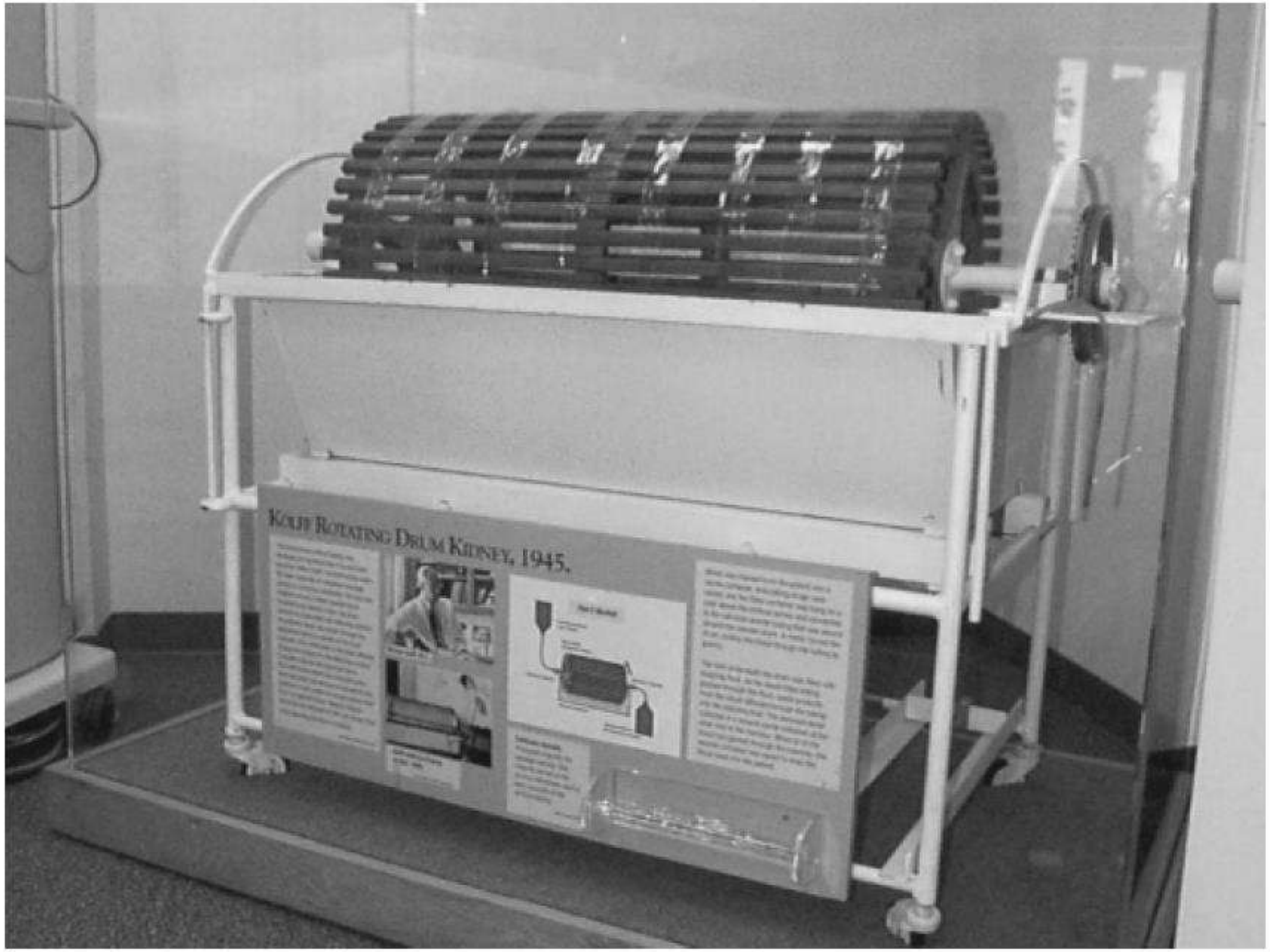
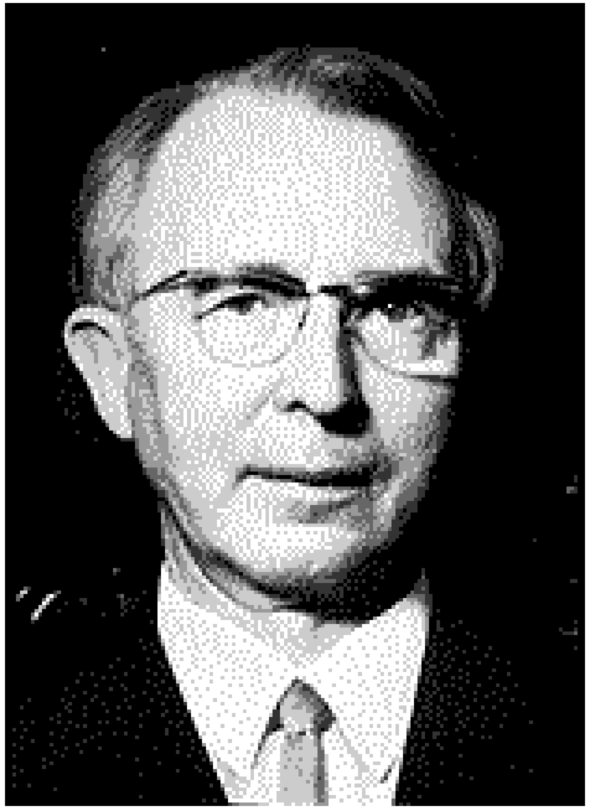


Figure 2 Kolff rotating drum dialyzer made of wooden lathes. Picture taken by the author at the exhibition of Baxter Museum during the Annual Dialysis Conference in Tampa, Florida, in February 2005.

PROF. NILS ALWALL



- Nils Alwall, a Swedish professor at Lund University, Sweden, was a pioneer in hemodialysis and the inventor of one of the first practical dialysis machines. Alwall pioneered the technique of ultrafiltration and introduced the principle of hemofiltration.
- THE ARTIFICIAL KIDNEY AND GAMBRO: **Department of Internal Medicine Lund Hospital 3- 4 September 1946**

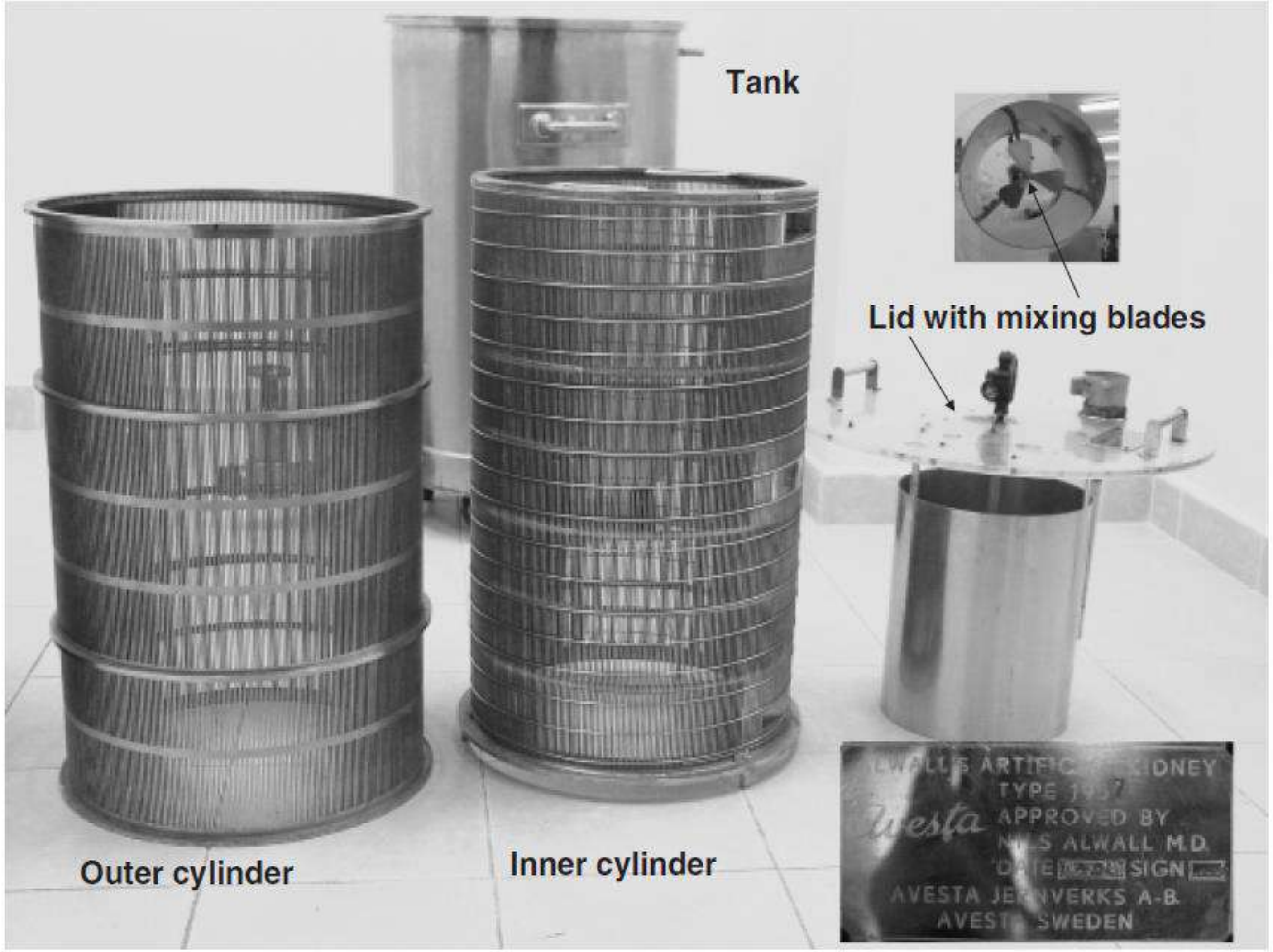
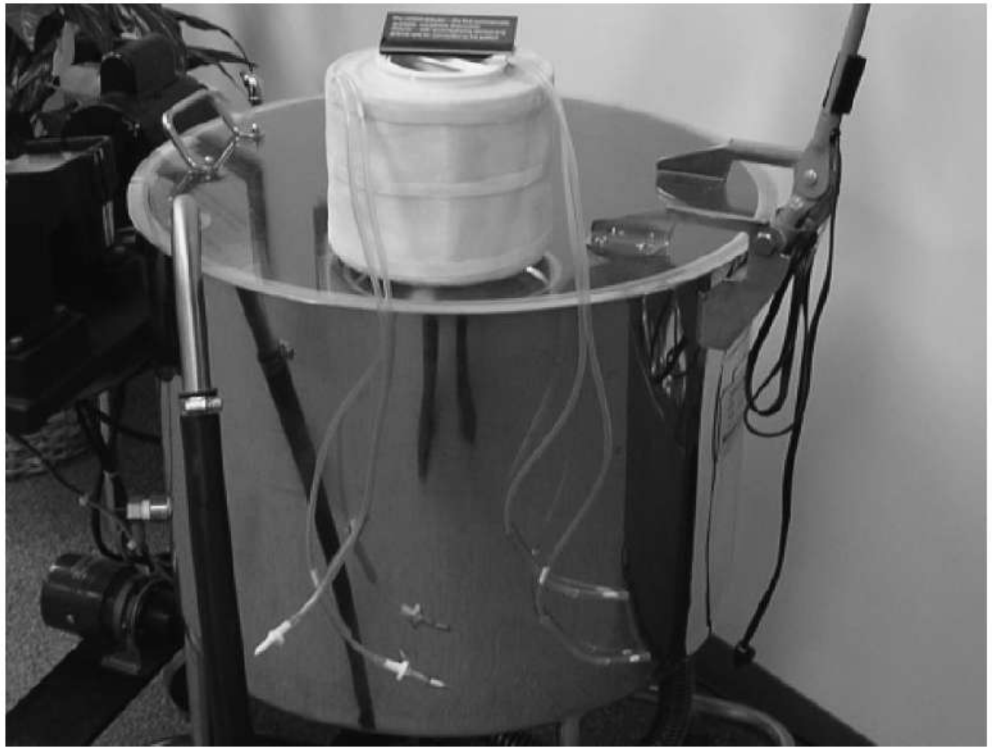


Figure 3 Alwall's dialyzer. Picture taken by the author at the Museum in the Department of Nephrology, Collegium Medicum, Jagiellonian University in Cracow, Poland, in 2002. In the right lower corner is a product label (Alwall's Artificial Kidney Model 1957; Approved by Nils Alwall, MD, Date 1958, Avesta Jernverks A-B, Avesta, Sweden). This artificial kidney was used for the first time in this Department on June 15, 1962.

COIL DIALYSERS

- The first twin coil dialyzer based on the Kolff-Watschinger design was the U-200 Coil Kidney manufactured by Baxter Laboratories, Morton Grove, IL, U.S.A.
- New coil dialyzers were soon developed in many places. Hillenbrand, Hoeltzenbein, and Schmand from the Universita¨t Mu¨ nster/Westfalen designed a coil dialyzer made of cellophane tubing (Nojax 36/32, Visking Corp.) with a 1.5m2 surface area, in a closed Plexiglas containerand connected with silicone rubber blood lines.



CAPILLARY DIALYSER

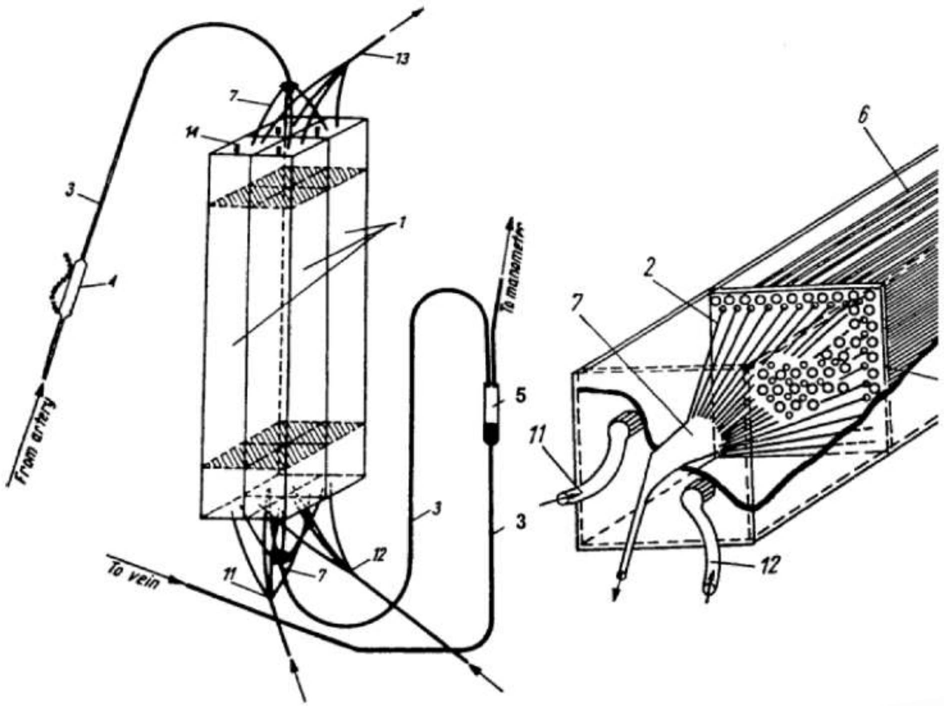
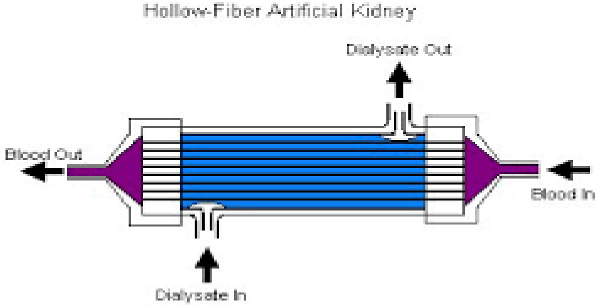


Figure 7 Capillary artificial kidney. Four dialyzing units on the left, details of single dialyzi... ings
adapted from Twardowski Z. Sztuczna nerka kapilarna [Capillary artifici... 11,
1964. Polish Patent Nr 49 137, Granted February 19, 1965. ... nd



Fx8 dialyser

Richard D. Stewart and Joseph C. Cerny from the Section of Urology, Department of Surgery, University of Michigan, Ann Arbor, MI, U.S.A., joined Henry I. Mahon to pursue of the idea of a hollow fiber dialyzer.

The first dialysis apparatus consisted of a bundle of 800 capillaries, each of which was 10 cm long had an inside diameter of 55 mm, and a wall thickness of 14 µm. The capillary ends were sealed in phenolic tubing with Silastic RTV 601 (Dow Corning Corporation, Midland, MI, U.S.A.). This dialyzer, with an internal surface area of 138 cm2 and a volume of 0.19 mL, had a urea extraction ratio of 51% at a blood flow of 9.0 mL/min.

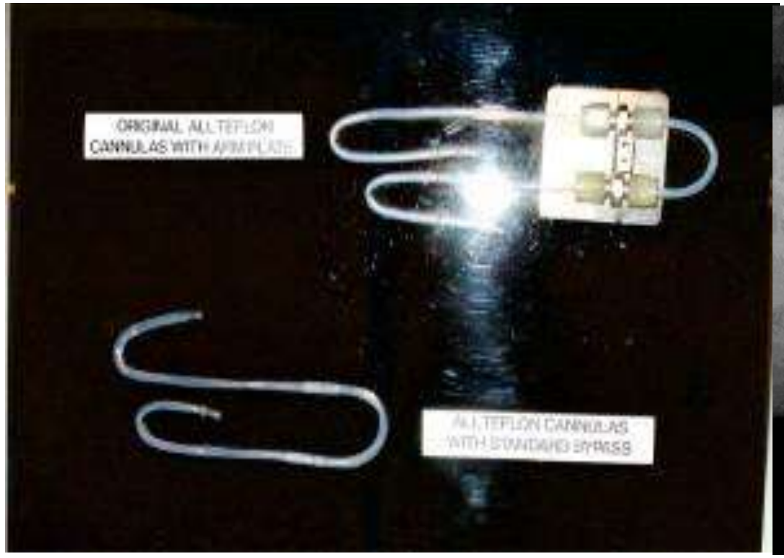
Richard D. Stewart, Edward D. Baretta, Walter R. Piering, Ben J. Lipps, John A. Sargent and Donald A. Roth.

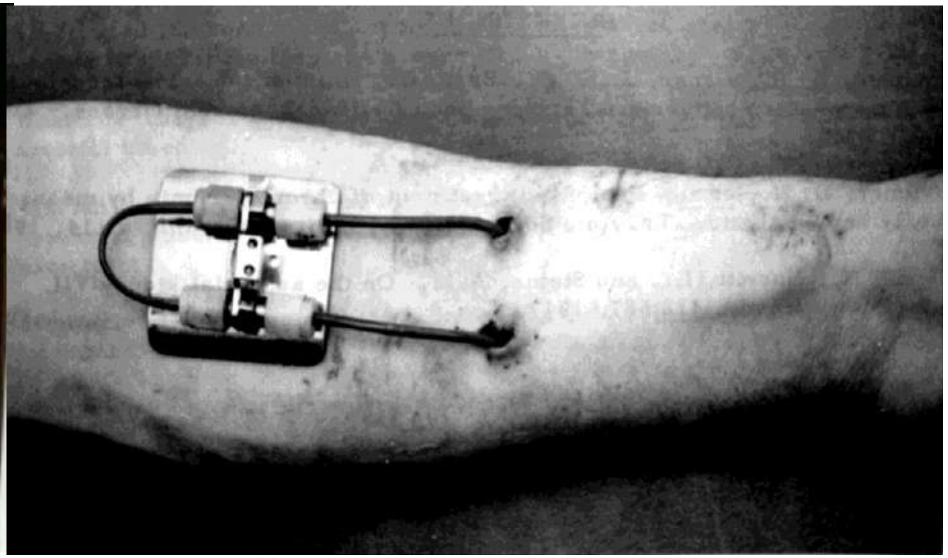
In 1968, they reported the initial results with the first capillary artificial kidney or the ‘‘hollow fiber artificial kidney’’ (HFAK), used for treatment of a patient with chronic renal failure

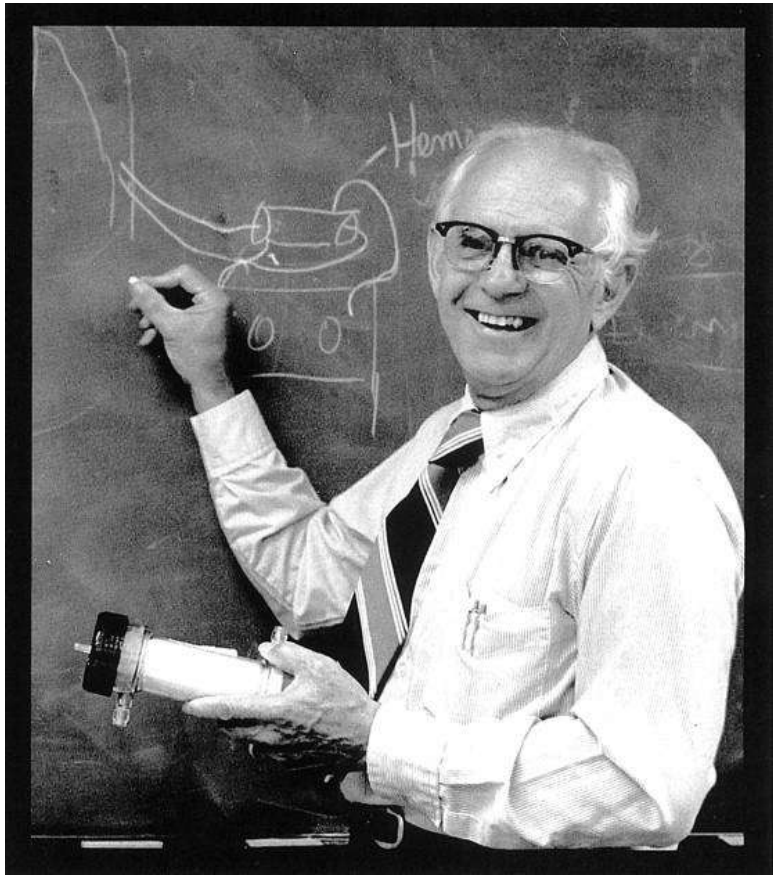
Milestones in the development of hemodialyzers

Alwall[79–81]	1947–1949	Spiral dialyzer with flattened cellophane tube	Good efficiency of dialysis; hydrostatic ultrafiltration possible
von Garrelts[132]	1947	First coil dialyzer for dialysis and ultrafiltration	Small dimensions; high internal resistance
Malinow and Korzon[77]	1947	Parallel tubes flattened between nylon tapes	Ultrafilter, no dialysis solution used
McNeill, Doyle, Anthone, Anthone[86,87]	1948–1962	Parallel tubes flattened between nylon mesh with space for dialysis solution	Similar to Malinow and Korzon but dialysis possible, low internal resistance
Skeggs and Leonards[94]	1948	Single sheets between grooved pads creating pseudocapillary spaces for blood and dialysate	First pseudocapillary dialyzer
Skeggs and Leonards[95]	1949	Double sheets between grooved rubber pads; low capacity, and low internal resistance; countercurrent direction of blood and dialysis solution flows	First sheet dialyzer with good efficiency of dialysis and ultrafiltration; used by Scribner for initial chronic hemodialysis patients. No blood pump needed (Scribner[98])
Kolff and Watchinger[135]	1956	Twin coil dialyzer with fiberglass screen	Lower internal resistance than in single coils
Kiil[104]	1960	Double sheets of cuprophane membrane between grooved plastic boards	Easier to assemble than Skeggs-Leonards; higher efficiency, lower capacity—used by Scribner when became available (Scribner[98])
Bluemle, Dickson, Mitchell, Podolnik[111]	1960	Multipoint membrane support in McNeill-Collins dialyzer	Increased dialysis efficiency due to increased unobstructed surface area for diffusion
Twardowski[150,151]	1963–1964	Capillary dialyzer: high surface area to capacity ratio, low internal resistance, low wall tension at high internal pressure	Theoretical considerations of the optimal dialyzer and ultrafilter; provided formulas for calculating desired parameters; not reduced to practice
Mahon, Stewart, Cerny, Lipps, Baretta, Piering, Roth, Sargent[152,153]	1964–1968	Capillary (hollow fiber) dialyzer made from saponified cellulose triacetate	First capillary dialyzer used in clinical practice
Hoeltzenbein[118,140]	1966	Knotless polyethylene mesh for coil dialyzers	Excellent recovery of blood after dialysis
Funck-Brentano, Sausse, Man, Granger, Rondon-Nucete, Zingraff, Jungers[124]	1973	Disposable plate (sheet) dialyzer with polyacrylonitrile membrane used with RP-6 recirculation system	Higher permeability of the membrane to bigger molecules. Direct measurement of ultrafiltration in closed recirculation system
Streicher , Schreiner, Strathmann, von Mylius, Heilmann, Nederlof [162]	1985	Hollow fiber dialyzers with polysulfone membrane	Absolute domination of hollow fiber dialyzers; final demise of other designs

Quinton Scribner A V Shunt.







ARTERIO VENOUS FISTULAT FOR HEMODIALYSIS

James E Cimino was awarded the prestigious 2009 Belding H. Scribner Award in the field of nephrology

Lundberg M, Erlanson P, Larsson R. Quinton-Scribner arteriovenous shunts for hemodialysis. A review of 6.5 years' experience. Scand J Urol Nephrol. 1977;11(1):47-51. doi: 10.3109/00365597709179691. PMID: 66743.

Kenneth C Apell, James E Cimino, Michael Brescia

Singh D, Harita C. A tribute to the inventor of arteriovenous fistula for hemodialysis:
James E Cimino. Indian J Vasc Endovasc Surg 2019;6:127-8

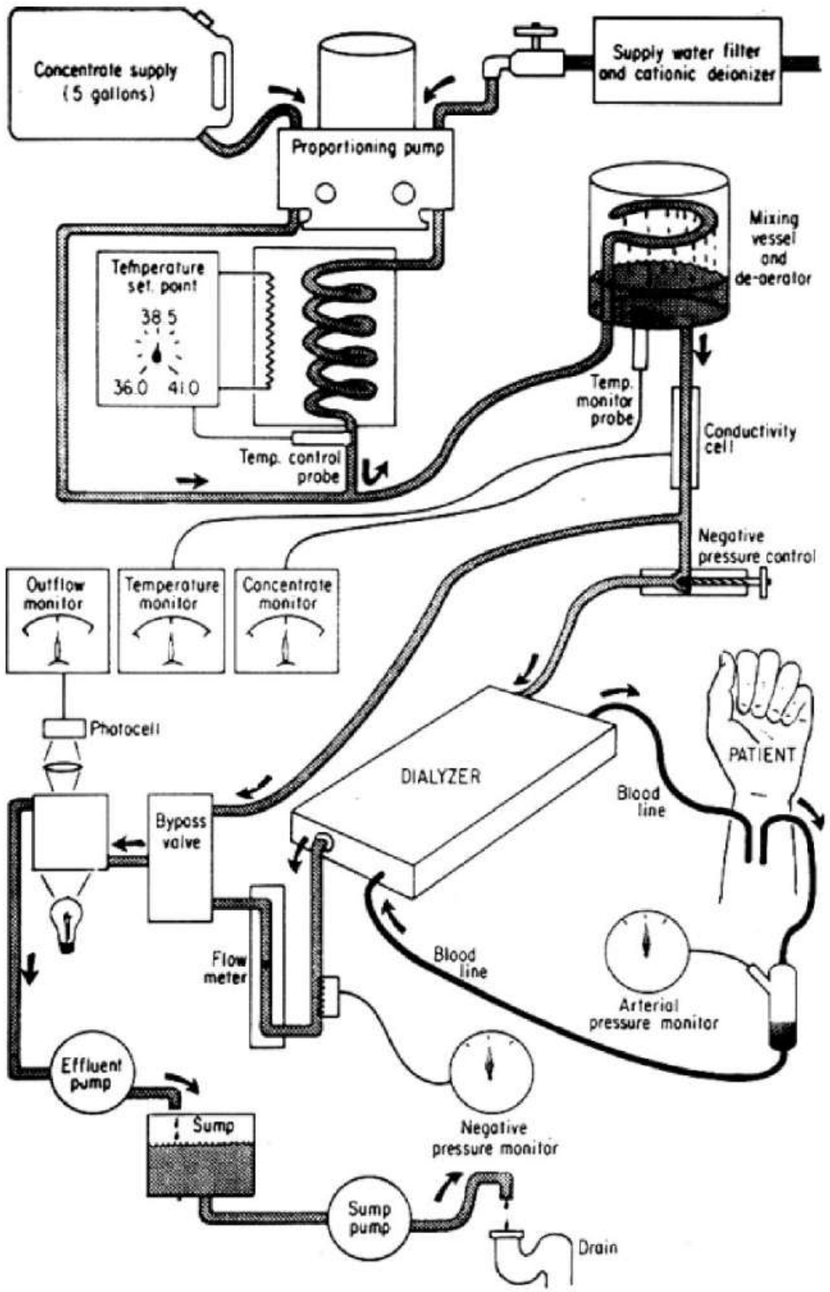


Figure 4 A diagram of Mini-II. It shows 2 pumps for concentrate and water, heater, mixing and deaerating vessel, multiple controls, solenoid bypass valve, hemoglobin detector, and other safety devices (Reprinted with permission from Twardowski, *Laudatio*: Albert Leslie Babb, PhD, PE. *Hemodial Int*. 2003; 7:269–277).

Table 3 Evolution of dialysis solution delivery systems

Author(s)	Year	Design or method	Comment
Abel, Rowntree, Turner[34,35,37]	1913	Dialysis solution in tank	Tank of batch system dominating in early hemodialysis
von Garrelts[132,133]	1947–1956	Dialysis solution, mixed with air, moving transversely to the blood flow, was propelled by a pump	First attempt of dialysis solution flow
McNeill, Doyle, Anthone, Anthone[86,87]	1948–1962	Concurrent direction of blood and dialysis solution flows	Dialysate flowing in the dialysate compartment then returned to the tank
Skeggs and Leonards[94,95]	1949	Countercurrent direction of blood and dialysis solution flows	Countercurrent flow direction maximizes dialysis efficiency
Babb[97,109,110]	1963–1964	Single pass proportioning system for dialysis solution delivery to the dialyzer	Decreased bacterial growth in dialysate, decreased pyrogen reactions in patients
Blaney, Lindan, Sparks, Twiss, Paulsen[164,165]	1966	Regeneration of dialysate by adsorption of uremic toxins on activated charcoal	First mention of wearable artificial kidney; poor adsorption of urea
Gordon, Popovtzer, Greenbaum, Marantz, McArthur, De Palma, Maxwell, Gral[164–168]	1968–1971	Urease and zirconium in addition to activated charcoal; complete sorbent regenerative dialysis system	Reduction of dialysis solution volume to portable size
Twardowski, Kenley[180–184,186]	1991–2007	Personal hemodialysis system (PHD) combining 4 machines in 1: a dialysis machine, a reuse apparatus, a water treatment appliance, and a device manufacturing infusion quality solution	Intended for quotidian (frequent) hemodialysis at home; saved time of patient or helper and has potential to save money
Clark, Turk[187]	2004	NxStage System; uses pre-manufactured dialysis solutions, delivered to the home or dialysis unit	No need to make dialysis solution, but high transportation cost and large storage space required; mobile size

Twardowski ZJ. History of hemodialyzers' designs. Hemodial Int. 2008 Apr;12(2):173-210. doi: 10.1111/j.1542-4758.2008.00253.x. PMID: 18394051.

HISTORY OF DIALYSIS IN INDIA

- The first Kolff twin-coil artificial kidney dialysis machine arrived in India in 1961, donated to the Christian Medical College (CMC), Vellore, as a gift from the Christian Mission of USA.
- The first patient to receive dialysis in May 1961 was His Excellency Shri Gopeshwar Prasad Sahi, the erstwhile Maharaja of Hathwa, in the old state of Bihar, who had developed “chronic uremia.”
- The first few sessions were supervised by Dr Satoru Nakamoto,who had been sent by Dr. Willem Kolff. Dr Nakamoto trained Dr Phillip Koshy, then Professor of Medicine at the CMC, about the technique of dialysis.
- That same year, an Alwall hemodialysis machine was acquired by the King Edward Memorial Hospital (KEM),Mumbai.
- Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh,Punjab, in January of 1963, and our Kolff twin-coil machine arrived in March of that year. The first dialysis treatment was performed on July 3, 1963, on a patient with acute renal failure of obstetrical origin, who recovered.

Chugh KS. Five decades of Indian nephrology: a personal journey. Am J Kidney Dis. 2009 Oct;54(4):753-63. doi: 10.1053/j.ajkd.2009.06.027. Epub 2009 Sep 2. PMID: 19726117.

WITH MY 1ST HD MACHINE, MY GURU AND EARLY COWORKERS

DIALYSIS MACHINE MPUH

1970 TO 1986

1987 TO 1995

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