FOR THE HISTORY OF DIALYSIS

The prehistory of haemodialysis as a treatment for uraemia

J. Stewart Cameron

Emeritus Professor of Renal Medicine. Department of Nephrology and Transplantation, Guy's Campus, King's College, London

Address correspondence to: J. Stewart Cameron; Elm Bank, Melmerby Cumbria CA10 1HB United Kingdom; Tel:+44 (0)1768 881804 e-mail: jstewart.cameron2@btopenworld.com

Abstract

Less is generally known about the ideas, events and personalities which drove developments permitting the evolution of haemodialysis as a clinically useful form of palliation and treatment, than its subsequent success and failures. This "pre-history" of haemodialysis is summarized here. One must remember that with hindsight we can now discern connections between ideas and developments which were not perceptible in their time, and that progress towards any new idea, material or piece of hardware was usually random and undirected, and outcomes uncertain. We must also remember the many blind alleys we can now safely ignore, to give a spurious continuity to the development of ideas. The prehistory of dialysis begins with study of the diffusion of solute and solvent in osmosis in living systems and experimental settings, and the retention of potentially toxic substances in kidney failure, during the 18th and early 19th centuries. These two areas came together in work in the mid-19th century on diffusion of gases and liquids, and showed that natural and synthetic membranes could selectively hinder different solutes. This explained osmosis and allowed semi-permeable membranes to be used and designed. These ideas underpinned the subsequent history of both dialysis using body cavities such as the peritoneum (not discussed here) and ex vivo dialysis of blood. To perform this, new membranes and anticoagulants were needed. These led to the first attempts in animals in 1912-3, and human patients in 1924-8, but only the purification and synthesis of newer materials such as cellulose and heparin allowed practical and successful haemodialysis to evolve in the 1940s.

Key words: Anticoagulation, Artificial kidney, Diffusion, haemodialysis, History of nephrology, Semi-permeable membranes

Today close on 3 million people are alive thanks to dialysis, four fifths receiving extracorporeal haemodialysis in one form or another. This is an amazing transformation for a previously fatal condition of chronic renal failure in its final stages, all achieved since 1960. In Japan as many as 1:400 of the total population are receiving this treatment, in the USA 1:600 and the United Kingdom 1:1000. However a huge tranche of humanity in poorer countries have no prospect of this treatment, as costs vary around $40 000 (€35 000, £30 000) per year. And we must never forget that dialysis only palliates uraemia, failing to correct some aspects of the state, and making some even worse.

Long term treatment of uraemia emerge when technical problems of repeated access were overcome, at least in part, in 1960. The first successful dialyses in the 1940s was inpatients with temporary renal injury, at that time mainly arising from mismatched transfusions, abortions or complications of pregnancy.

But my subject in this article is not these familiar events in the 55 years since 1945 or 1960, but those which made clinical dialysis possible for the first time for acute reversible renal injury in the 1940s, the "prehistory" which led to the reality of this successful but incomplete palliative treatment. This prehistory is much less well known than the spread and rise of haemodialysis. I have written about this in the past [1] which can be consulted for detailed references, and others have covered similar ground [2] but many new data emerge in this article, much of which appears in a recent multi-author book on dialysis [3].

We must remember that this type of retrospective analysis is dangerous, as it can lead to the error of supposing there was any linear relation between events leading to "progress". All we can do is to pick out those ideas, materials and apparatus which were *necessary predecessors* to the events under consideration. With this in mind we can begin our story - in France, in the 18th century.

Osmosis: Nollet and Dutrochet

Dialysis depends upon diffusion, and the first aspect of diffusion to be studied was osmosis (much later identified as the solvent transfer down concentration gradients) across semipermeable membranes (see below). In 1748 the French scientist Jean Antoine Nollet (1700-1770) (usually known as Abbé Nollet) [4] (Figure 1, left) who was amongst many other skills a botanist, noted [5]"et *que me parut d'abord...singulier*" – that when a vial of alcohol was separated by a pig bladder epithelium from water, the volume of the alcohol increased and pricking the membrane resulted in a jet under pressure. He studied also aqueous glucose solutions together with parchment membranes, and noted a similar phenomenon. He is little known outside France, but played a major role in establishing experimental science as a form of enquiry in that country. His main interest was not biology or diffusion, but the new discovery of electricity. In one experiment, often described, he made a circle of monks (or of guards from the king's retinue in other accounts, 20 or 200) holding hands, and got two to grasp the terminals of a voltaic cell (Leyden jar), whereupon they all jumped into the air simultane-

Figure 1.
Two French scientists who first studied the phenomenon of osmosis in plant and then animal tissue. Left: Abbé Jean Antoine Nollet (1700-1770) (Courtesy Wikimedia Commons), Right: Henri Dutrochet (1747-1847) (Courtesy Wellcome Foundation).

ously. Nollet commented that electricity must travel very rapidly.

Nollet had no vocabulary to describe his observations on "osmosis"; this was supplied 80 years later by (René Joachim) Henri Dutrochet (1776-1847) [6] (Figure 1, right), who after a period in the French royalist army became a rural physician near Vendôme in Touraine, but was a corresponding member of the Académie de Sciences. He was an admirer of Spallanzani and a firm opponent of vitalism. Dutrochet had wide interests. Amongst these he studied the generation and movement of sap in botanic tissues, in the course of which he came to the idea that tissues were made of "globules" corresponding to the cells later described by Schleiden and Schwann [7]: "*Les végétaux sont composés de véscicules agglomérés. Ces véscicules ou cellules forment alors que l'on appelle le tissue cellulaire.....Or, l'observation microscopique*[(1)] *apprend que tous les organs des animaux sont ainsi composés de véscicules agglomérés.... ainsi les conditions fondamentales de l'endosmose existent chez les animaux".*

Dutrochet's "endosmose" (from Greek *ώσμοσ*- impulse, force) was the rapid transfer of solvent water in tissues, his "exosmose" the slower transfer of solute in the opposite direction. He demonstrated that these transfers operated in animal tissues by using a segment of chicken caecum, which he filled variously with albumin (presumably from eggs) and gum Arabic, then placed the caecum in rainwater as the purest he could obtain. The caecum increased in weight within the water over some hours, then the weight stabilised, and finally fell somewhat.

Dutrochet designed the first osmometer [8], which he is seen holding in the damaged portrait (Figure 1, right) shown to me by Gabriel Richet (courtesy the Wellcome Foundation). It consists of a membrane separating two compartments, the lower and open dish of pure water and the upper a vertical tube containing the liquid to be tested. Later Graham used an identical instrument. Dutrochet also proposed that the glomerulus operated as a filter, 14 years before Carl Ludwig's description, in which he cited Dutrochet's prior work. Dutrochet deserves greater recognition in the world of science than he enjoys today.

[(1)]*One wonders (he does not say) whether Dutrochet had access to one of Gabriel Amici's new achromatic microscopes, so much superior to the blurred images previously obtained? Amici was selling these in Paris from 1820 onwards. Similar microscopes were developed by Joseph Lister in London about the same time, and revolutionized microscopy.*

Thomas Graham: diffusion dialysis and semipermeable membranes

Graham also quoted Dutrochet's prior work. Thomas Graham (1805-1869) [9] (Figure 2) is probably the most important single figure in the prehistory of dialysis. He was born into a relatively wealthy family in Glasgow, Scotland, the son of a merchant who had a country estate. His father wished Thomas to enter the Church like his grandfather, but Thomas was seduced into science by a charismatic chemistry teacher at Glasgow University on his general MA

course, Thomas Thomson, and in secret set up a lab in Edinburgh whilst pretending to study theology. Inevitably his father found out, and destroyed his lab and cut him off from all financial and emotional support in 1828. Meanwhile however Thomas' mother secretly helped him, with the aid of his elder sister Margaret. He obtained lectureships in Glasgow to support himself after MA graduation in 1824, and meanwhile studied diffusion of gases into liquids which led to his early publications. He obtained a degree by thesis in Glasgow in 1829, and studied diffusion further which led in 1831, still aged only 26, to what became known as "Graham's laws of diffusion". By 1837 he had studied various other chemical topics, been awarded a Fellowship of the Royal Society of London, and moved to London at University College as Professor. He never returned to Scotland, even when he inherited his father's country estate in 1842. In London he did his important work on diffusion, osmosis - and dialysis, a term he resurrected and reframed.

The results of this work were published in three papers in the *Transactions* of the Royal Society in 1846 [10], 1849 [11] and - most important of all - the Bakerian lecture of 1851 [12]. In this paper he repeated and expanded upon Dutrochet's experiments, using a simple apparatus similar to Dutrochet's osmometer, with a perforated metal plate to support the membrane under study. In his summary he wrote:

"*Chemical osmose seems to be particularly well adapted to take part in the animal economy*"

And described the osmotic force, which he renamed "*osmotic pressure*", as:

Figure 2.
Thomas Graham (1805-1869). (Courtesy Science Museum)

"*The conversion of chemical affinity into mechanical power*"

The striking feature of Graham's work was the use of simple materials (glass jars, dishes and tubing, sheets of parchment and paper (Figure 3), plaster of Paris, perforated metal plates, graphite, clay, water and other liquids and gases) in elegantly-designed experiments, clearly explained in a few economical papers.

This work was uninterrupted as he left University College for the Royal Mint, as Master of the Mint - since 1842 he had been advising the government on scientific aspects of policy in a huge variety of areas. He continued to work on diffusion as well as topics to do with the work of the mint, publishing his final paper of interest to us in 1861 "*Liquid diffusion applied to analysis*" [13]. Here he distinguished materials into two classes, soluble ***crystalloids*** which could be purified by crystallisation of salts, were generally of a low molecular size, and diffused readily through membranes; and ***colloids*** (from Greek κωλλα, glue) which were general of large molecular size, did not crystalize and penetrated though membranes poorly. He also characterized membranes as "***semipermeable***" if they permitted crystalloids but not colloids to pass through them.

In this paper also he made an observation which must have encouraged workers in the treatment of renal failure forever after

"*half a litre of urine, dialyzed for 24 hours, gave its crystalloid constituents to the external water. The latter, evaporated in a water-bath, yielded a white saline mass. From this mass, urea was extracted by alcohol in so pure a condition as to appear in crystalline tufts upon the evaporation of the alcohol*"

As a man Graham had in him "*a deep tinge of melancholy*"; he was a "loner", never marrying and keeping to himself. All his papers were authored just by himself, although in some later work he was given "*valuable assistance*" by a future star of metallurgy, WC Roberts. He had poor health, especially in later

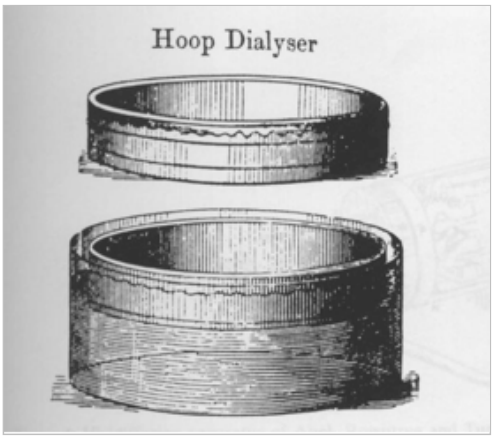

Figure 3.
Graham's hoop dialyser. From such simple apparatus of wood and sized paper he constructed the theories of dialysis and diffusion. From reference [13].

life, which led to some withdrawal from public life before his death in 1869.

Graham was of course not alone in working on dialysis and diffusion in the mid- 19th century. He met his exact contemporary Justus von Liebig (1803-1873) in 1837 on a visit to the UK by the latter, and they remained firm friends by correspondence thereafter. Adolf Fick (1829-1901) was also working in the area in Germany, and did early mathematical work to expand Graham's laws of diffusion. Also in 1858 he obtained new material which Graham never worked with – collodion). This had been first synthesised from wood cellulose in 1833 by chemist and pharmacist Henri Branconnot (1787-1855) in France. It was brittle, and difficult to make, but served as an excellent semi-permeable membrane, and was used extensively for recording photographic images.

Then in 1848 another contemporary of Graham's working in Bern, the Schwabian Carl Friedrich Schoenbein (1799-1868) synthesised both cellulose-dinitrate and -trintitrate. The latter became the explosive in gun-cotton, but the former formed useful membranes which were used for dressings on wounds, and up until 1930 or so for movie films. It also formed a useful membrane for dialysis, collodion, which was widely used in laboratories for this purpose in the following half century.

Bench dialysis was a useful tool, especially in purification of many substances for laboratory use. Zott in 1886 compared 15 different dialysis membranes for laboratory use [14], and concluded that carefully prepared peritoneum was the best, but in 1907 in another "best buy" comparison, Bigelow and Gemberling [15], although agreeing with Zott, suggested that collodion was however generally the most convenient in practice. Ironically although cellulose acetate (cellophane) was already available from 1895, it was not known to the laboratory world as it was used in sheets only for wrapping at this time.

One other membrane is worth mentioning for several reasons, and that is Philippson's used of carefully-prepared reeds in 1908 in Strassburg [16]. First, this confirmed Metchnikoff's suggestion that a tubular format was suitable for dialysis rather than the bags normally used - an idea which would recur later in dialysis machines. Second, because hirudin was purified of its major potassium contamination using this technique and third, Phillipson was able to dialyse whole anticoagulated blood using this new material, instead of defibrinating it by agitation.

Renal failure and uraemia

But should one think of or want to apply dialysis to patients in kidney failure? The idea arose as understanding of how kidney failure killed those suffering from it. As early as the Belgian Joseph Nicolas Comhaire (1778-1837) (Figure 4) who repeated in 1803 [17] earlier experiments of Albrecht von Haller (1708-1777), it had been known that removal of kidneys led to death with no urine in the bladder – but death only after an interval, known to be shorter in dogs than in humans who suffered renal disasters. Comhaire even suggested the delay presented an opportunity for treatment! The uriniferous smell of his dogs and those dying after renal loss recorded by Haller and to Hermann Boerhaave (1668-1738), and familiar to all doctors until the use of dialysis was introduced as treatment, suggested retention of urine constituents. Later this led the great Robert Christison (1798-1889) of Edinburgh to propose in 1839 that such retention, plus a failure to generate enough red cells, accounted for the toxicity of renal failure [18]. Pierre Adolphe Piorry (1794-1879) first gave the description of "uraemia" in 1856 [19]. It should have been "urinaemia", but urea had been identified by Rouelle le Cadet (1718-1779) in 1778, then purified by the end of the 18th century by pharmacist Nicolas Vauquelin (1763-1829) and physician Antoine Fourcroy (1755-1809), again in Paris, who named it "urée". They observed [20].

"*it is extremely probable that when urea is not separated from the blood, the overload of these substances, and above all urea, is capable of causing diseases*"

Urea could be measured fairly easily, and was known to be the bulk substance dissolved in urine. In 1821 pharmacist Jean Louis Prévost (1790-1850) and physician Jean Baptiste Dumas (1800-1884) (Figure 5) of Geneva repeated the work on nephrectomy of dogs [21], but also measured blood urea, whose concentration rose steadily after the nephrectomy. Finally, Graham had shown urea could be dialysed through semi-permeable membranes.

Therefore, despite its demonstrated relative lack of toxicity beginning in work by both Vauquelin and

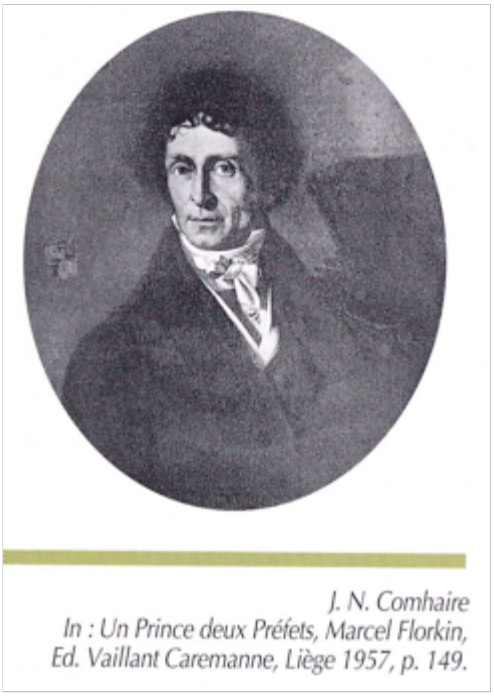

Figure 4.
Joseph Nicholas Comhaire (1778-1837). From Richet G. (1993) Les binéphrectomies expérimentales: premier exemple de'une pathologie humorale. Néphrologie D'hier et d'Aujourd'hui 1: 16-9. He noted the delay of several days before death in nephrectomised animals, and their urinous smell.

Fourcroy and Prévost and Dumas, it was the prototype marker and remains so to today, still inhibiting rational thought about uraemia. But other dialyzable substances such as potassium were long known to accumulate when kidneys failed, and also diminished in the urine, as Bright and Bostock had shown in the 1820s. Potassium had also been shown to be dialyzable. Thus removal of the burden of accumulated "urinary substances" seemed a rational goal, and dialysis looked to be one possible route to it. Other manoeuvres of "epuration" such as sweating in saunas and hot baths, or diuretics to increase output, or even induction of diarrhoea, were tried repeatedly right until the 1950s, alone or as adjuncts to dialysis, but failed to have much effect and even though of historical interest, lie outside the scope of this essay.

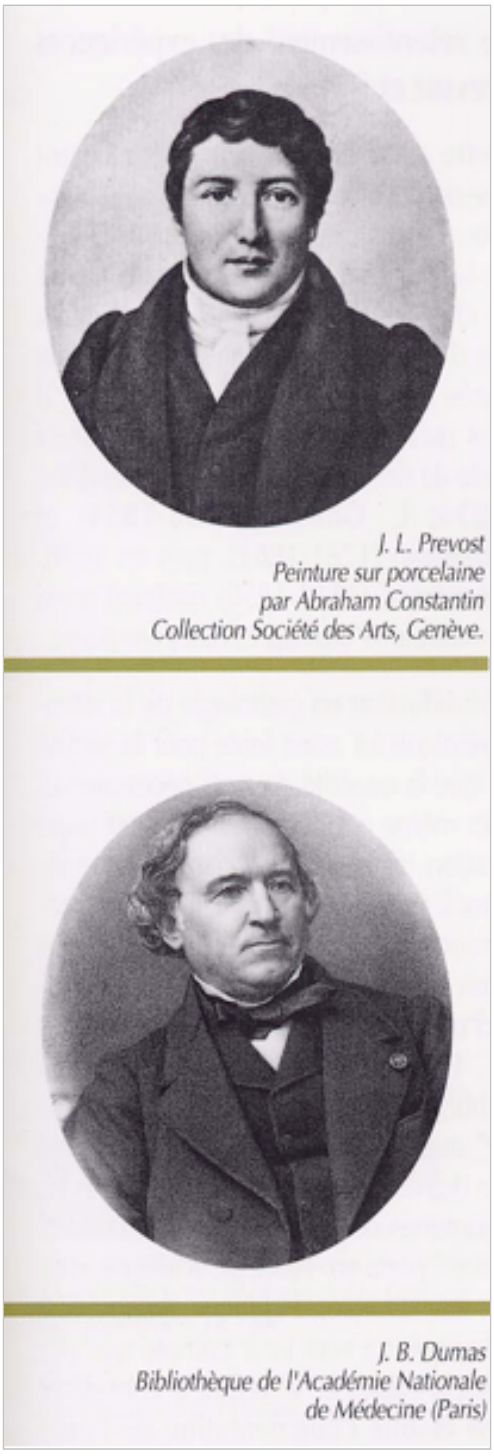

Figure 5.
Jean Louis Prévost (1790-1850) and Jean Baptiste Dumas (1800-1884), of Geneva who showed that the blood urea concentration rose after nepherectomy in 1821. From Richet 1993 (loc.cit.)

Haycraft and hirudin

But a barrier existed which completely prevented the dialysis of blood. Without an anticoagulant, dialysis itself and extracorporeal circuits were impossible because the blood clotted on contact with every surface then known. Until the late 19th century, the only method of anticoagulation was to whisk or stir the blood – which defibrinated it, as Prevost and Dumas described in 1821. But in 1884 an English physiologist, John Berry Haycraft (1857-1922) [22] an Edinburgh graduate, was working in Birmingham after a period with Carl Ludwig in Germany. Later he moved to Cardiff as professor of Physiology. Like many others over centuries, Haycraft had noted that bleeding after a leech bite could last for hours, and that the extracted blood within the leech remained liquid. He prepared a simple 6-8% saline (later alcohol and water) extracts of leech heads [23], which contained a powerful *in vivo* anticoagulant, as demonstrated in dogs and rabbits, in work done by Haycraft on a visit to Strassburg. Since 1950-75 from work by F Markwardt and others, today we know it to be a thrombin-specific protease inhibitor which binds to its target molecule one-to-one, has a MW of 6979 and is a polypeptide of 65 amino-acids. (Incidentally, medicinal leech saliva contains many other bioactive compounds, including a platelet inhibitor, and differs between species).

Haycraft collaborated with Johann Schmiedeberg (1838-1921) in Strassburg, (in Germany since the Franco-Prussian war of 1870), where Haycraft visited and did *in vivo* experiments in 1884. He was possibly there when a young American of German parents, John Jacob Abel was studying there also, graduating in 1888. Schmiedeberg's group, especially Bunge and Jacobij (who called it hirudin), were expert in extracorporeal perfusion of various organs, including kidneys, including the use of blood as a perfusion fluid anticoagulated first by defibrination then later by hirudin. But problems with reactions to leech extracts persisted for a decade in both animals and humans until Friedrich Franz in Halle managed to produce purer preparations of lesser toxicity. In the 1900s hirudin was used in Germany to treat toxaemia of pregnancy, and so a German firm, Sachsse, produced it commercially for two decades or more until heparin was introduced (below).

Thus by around 1905-10, both membranes and an anticoagulant were available: who would attempt to build and use a machine for *ex vivo* dialysis of whole blood to remove toxins, or for other reasons?

The first extracorporeal haemodialysis in animals

The person to conceive this leap was an American son of German parents, John Jacob Abel (1859-1938), Professor of Pharmacology at Johns Hopkins University in Baltimore since 1893 [24] (Figure 6). He had graduated in 1888 in medicine from Strassburg after taking a PhD in Michigan and working as a physiologist, but having studied in almost all the great centres of clinical medicine in Germany. He conceived in 1912 the idea of dialysing blood *ex vivo*.

Why him, why then, and to what purpose? First, Abel had had contact with both extracorporeal perfusion of organs and hirudin when in Strassburg and the step to haemodialysis was relatively small to one possessing this knowledge. Second, laboratory bench dialysis was very much in the news in 1912, mainly because of the disputed and later discredited work of Emil Aberhalden (1877-1950) on pregnancy, and the Nobel-prize winning studies of Fritz Pregl of Graz (1869-1930). It had been in routine use in most laboratories for some time. Abel conceived the idea of using extracorporeal dialysis of blood to allow *in vivo* extraction from it of substances of physiological interest, such as peptide hormones and lesser amino-nitrogen molecules. However when he presented preliminary results to the Association of American Physicians in May 1913, he sketched much broader goals [25]:

"*There are numerous toxic states in which the eliminating organs of the body, more especially the kidneys, are incapable of eliminating from the body at an adequate rate the natural or unnatural substances which are detrimental to life. In the hope of providing a substitute in such emergencies.....a method has been devised by which the blood of a living animal may be submitted to dialysis outside the body, and again returned to the natural circulation....This process may appropriately be referred to as 'vividiffusion'*".

Despite this the actual results, published in detail only in later papers [24], concerned solely the extraction of substances from the dialysate of blood, with no mention of kidney failure, creatinine, and urea was removed enzymatically without measurement to allow study of the remaining nitrogen-containing compounds. This dissociation between the plan and execution of the early experiments has led to confusion and doubt as to what exactly were Abel's goals in this endeavour, and whether in the first place he actually planned to try and ameliorate renal failure.

This work was carried out by two able – in fact indispensable - assistants under Abel's direction. Leonard George Rowntree (1883-1959) [1] [26] (Figure 6) was born in London, Ontario, Canada - a restless individual who had subsequent career in many major centres of excellence, but contributing in all. Previously he had qualified in Canada and been a family physician in Camden, NJ with out-patient hospital duties, but decided to move full-time to hospital medicine in 1908 in the pharmacology department He worked first on the assessment of renal function using what became the PSP test which remained in use for 40 years, only being replaced by creatinine clearance sometime after WW2; during this period Rowntree supported himself by family practice. His role in the dialysis project included the making of the collodion tubing for the dialysis, and the preparation of purified heparin from leeches. Later, the German material from Sachsse was used, which was

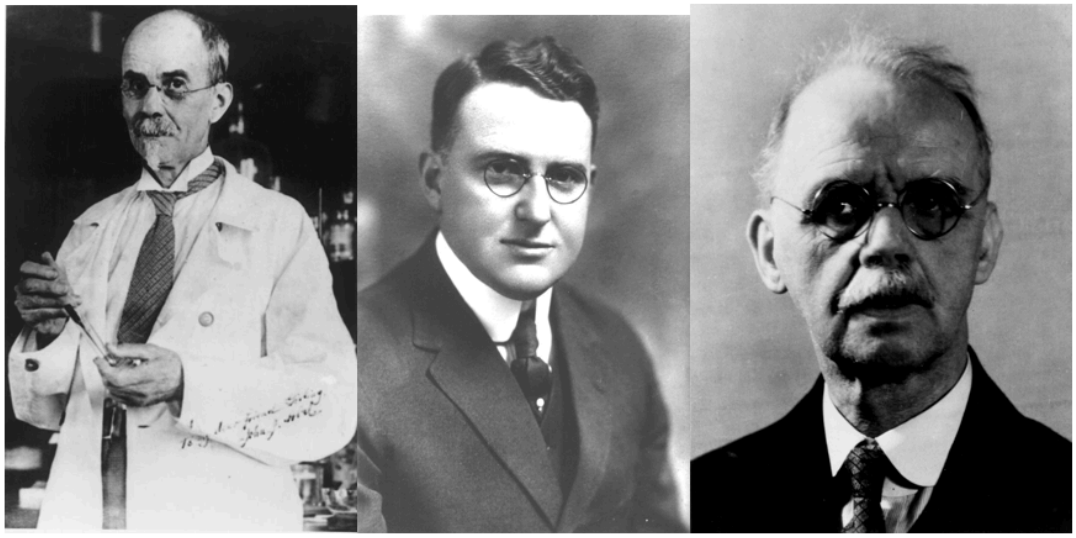

Figure 6.
Left, John Jacob Abel, centre Leonard Rowntree and right Benjamin (BB) Turner, the team who constructed the first apparatus to perform ex vivo haemodialysis in dogs in 1913. (Left courtesy the Alan Mason Chesney Archives of the Johns Hopkins Hospital, centre the NY Academy of medicine and right, University of Indiana Library)

less pure and led to some problems, and then became unavailable because of the World War.

Benjamin Bernard (BB, or bye and bye) Turner (1871-1945) [1] (Figure 6) was a biochemist, English-born of missionary parents in Hong Kong, who like Abel (after a preliminary degree in England) had trained in Germany including Strassburg in 1904, taking his PhD in Goettingen in 1899 after which he went to the United States. In addition to his medical abilities he was a superb linguist, speaking many languages fluently. His roles in the project were to construct and maintain the apparatus including the awesome glass manifolds, which were as an essential component of the dialysis apparatus, and to make biochemical measurements on dialysate.

Their diagram of the dialyzer is shown in Figure 7. It consisted of a series of collodion tubes mounted within a glass casing, through which dialysate could be passed. At either end of the casing were hand-made glass manifolds which determined how many collodion tubes for the blood could be used, or they could be closed off to reduce this. 32 seems to have been a common number of tubes, each made individually on a glass rod from liquid collodion, then peeled off, fixed and tied in place. A pump was used to extract blood continuously from the femoral artery of the dogs and pump it through the collodion tubes, then returned into a large vein. To contemporary eyes it resembles closely a large hollow-fibre dialyser, with a few (32-196) large fibres, the whole made of collodion, glass, rubber, glue and brass, rather than polymers. They re-used the apparatus several times, rinsing and sterilizing it between uses with thymol, and replacing the tubes only as necessary as they were tedious to make and mount.

In 1913 the trio went to Europe and boldly demonstrated their apparatus in action at medical meetings in London, and Groenigen in the Netherlands. It was the sensation of both, and received much attention in the medical and general press. Notably in the *British Medical Journal* it was called an "*artificial glomerulus*" twice, whilst in the *London Times* the enduring description "*artificial kidney*" was first applied to a dialyzer by an unknown staff writer on August 11th 1913. Maybe (s)he heard this in conversation round the demonstration. This term was again used in the *New York Times* on 14th January 1914. Either way, it seems likely that Abel was pushed more and more in the direction of thinking of his machine not as a means of obtaining plasma components and chemicals, but for treating kidney failure – which Abel was asked to do, but declined – he was never, after all, a clinician (unlike Rowntree, who was appointed to the clinical staff at the Hopkins), and witnesses testify that in clinical situations he was inept. He also deprecated the term "artificial kidney", preferring his own "vividiffusion".

This was reflected in the work actually done in the 15 or so months the apparatus was in use from November 1913. It consisted of extracting dialysate and analysed the non-urea amino-nitrogen content. Curiously, Abel then turned the idea of treating renal failure – but not with his dialyzer but with plasma exchange [27], or "plasmapheraesis" which suggests he had little or no faith in vividiffusion for this end. As well as dogs, this technique was applied to one patient in renal failure, but without any benefit.

Abel never returned to the field of vividiffusion, and it is not difficult to see why. He blamed this on difficulties of obtaining hirudin, but the truth is that without either Rowntree or especially Turner, who both left in 1915 the latter for Indiana, he simply was not in a position to continue doing work which was so technically arduous alone. Also, it seems likely that he became clinically and severely depressed at the fate of his beloved Germany around 1916-8. Nevertheless, he kept up intellectually with subsequent developments in dialysis, and publicly maintained, whatever the truth may have been [28], that his object had always been as stated in his introduction on 1913 given above [25]. He corresponded with Necheles, Haas and Thalhimer (see below) and seemed anxious to maintain a role as the "inventor" of dialysis for kidney failure.

Heinrich Necheles (1897-1979)

If Abel was equivocal about the goals of his studies, Heinrich Necheles [27] (Figure 8) and his successors were clear from the outset. The son of Jewish merchant in Hamburg, his medical studies in Berlin had been interrupted by a period of three years in the German army during WWI, and he witnessed soldiers dying of uraemia, many from the "trench nephritis" whose nature is still debated. In addition one of his teachers back in Hamburg medical school was Otto Kestner (1873-1953), who was one of Abel's many friends in Germany. Necheles set out in 1922 for his MD dissertation to study uraemia and its treatment by dialysis in dogs, in a systematic way outlined clearly in the introduction to his thesis [29].

He abandoned the collodion tubes used by Abel Rowntree and Turner, and designed what would be termed today a "flat-plate" dialyser, returning also to the use of gold-beater's skin (Goldschlägerhaut) – the fine, thin smoothed calf's peritoneum used to prepare and support gold leaf. Both Zott in 1886 and Gemberling in 1907 had praised it highly in the comparison studies of membranes for dialysis. In addition two sheets of the membrane could be held in place close together by a supporting nickel-plated wire mesh, giving a low priming volume. However the preparation of the large tubes of peritoneum (flattened to 5 cm wide) which would be supported between the meshes was arduous, involving gluing to achieve a length of 60 cm, treatment with gelatin and bichromate, and irradiation with UV light [27]. Glass tubes were inserted into each end and the dialysis compartment rinsed thoroughly over several days, giving a single plate of a dialyser with a surface area of 350-400 sq cm. (Necheles normally used 6 (2-10) such plates in series, with no complicated manifolds). The blood pressure of dogs was sufficient to ensure flow through the apparatus and back through femoral vessels, eliminating pumps. Various dialysis fluids were investigated for the bath, isotonic glucose

saline or Locke's fluid being preferred. I have given this description in detail, because it so much resembles the Skeggs-Leonards and Kiil pumpless systems widely-used 30 years later, which employed cellulose membranes and rubber or plastic plates but whose design was identical.

Necheles was now ready to dialyse his dogs made uraemic by bilateral nephrectomy [29]. He found that uraemia progressed very rapidly in dogs, with death after at most 4 days without treatment. Usually the animals were in a coma and required no anaesthesia for the procedure. The data given show that his membrane must have had pretty poor permeability for solutes, given the area (up to 4 m2) and duration pf dialysis (4-5 hours) in a dog of at most 11 kg – but blood-flow was not measured, however and may have been rate-limiting.

Another advantage Necheles had was that his hirudin was prepared "in house" with help from Professor Kestner, partly because that from Sachsse was now impossibly expensive, so he avoided this toxicity in the commercial product. This new heparin was marketed later by Passek and Wolff in Hamburg, and was used by Georg Haas (below).

If Necheles had remained in Germany it is possible that dialysis might have begun earlier, but he

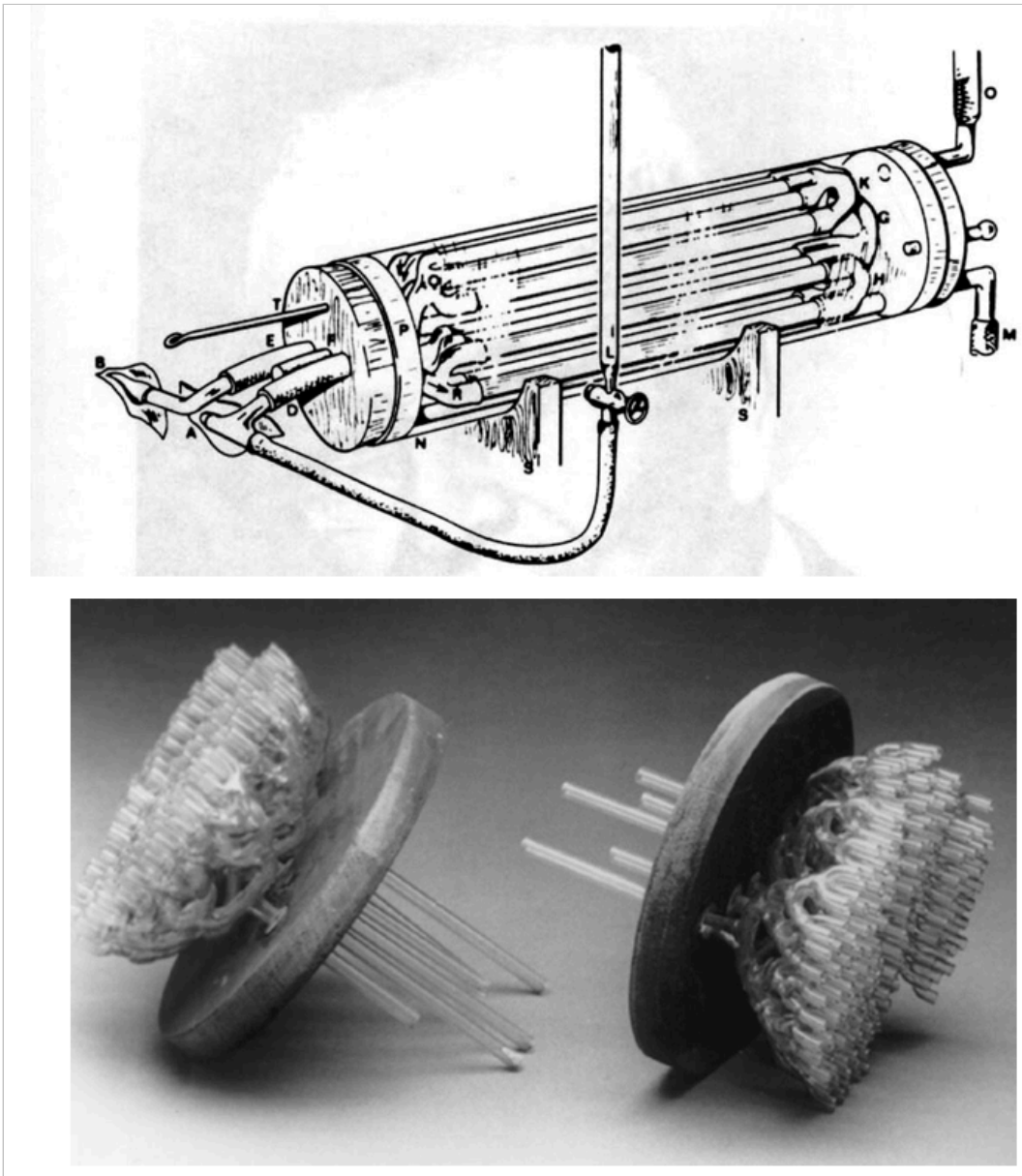

Figure 7.
(Above) a diagram of the 1912-4 vividiffusion apparatus designed, constructed and used by Abel Rowntree and Turner. (From Abel JJ, Rowntree LG, Turner BB. On the removal of diffusible substances from the blood of living animals by dialysis. J Pharmacol Exp Ther 1913-4 5: 275-316). Its operation is described in the text, but dialysis entered and exited the containing bath through the two tubes on the right, whilst blood entered and exited the collodion tubes at the left, using glass manifolds such as (below). (Courtesy Alan Mason Chesney Archives, Baltimore). It is not clear from Abel et al.'s description whether counter-current flow of blood and dialysate was used, or not, but clearly they did not regard this as of importance.

had been supported during his thesis work by a grant from the American Rockefeller foundation, which now gave him a further grant – but to go to Peking (now Beijing) in China, to work in the prestigious Peking Union Medical College, where Necheles spent his next 10 years. During this time he re-used vividiffusion to prepare hormones from blood samples from various parts of the gut (as Abel had intended), together with an Edinburgh Chinese graduate, RKS Lim. In these experiments he used heparin for the first time for dialysis (see below).

Necheles then moved to Chicago as a gastroenterologist, becoming departmental Director at Michael Reese Hospital and publishing several hundred papers. One was about dialysis – in Hebrew, in 1952. He retired from work in 1967 and to California in 1974. Thus he saw the rapid growth of long-term dialysis after 1960; I wonder what he thought about this? Curiously, at the Michael Reese he met and even collaborated with William Thalhimer (below) [37], but the latter remained in ignorance of Necheles' earlier dialysis work, until informed later by Abel.

The first attempts at dialysis in human patients – Georg Haas (1886-1971)

Haas [30] (Figure 10) came from a wealthy family who owned an iron foundry and an engineering factory, run by his father Eduard. Thus, although a doctor he had much contact with machines from an early age in Nuremburg. Haas trained in medicine in Freiburg and Munich, qualifying in 1911. Like Necheles and Abel, he went to the Mecca of German medicine, Strassburg, for his postgraduate training. By this time Franz Hofmeister (1850-1922) was in charge of the physiology laboratory, where Haas studied organ perfusion including dialysis using reed stalks with Franz Mandel. In 1914 young Georg left for the small town of Giessen just North of Frankfurt where he was to spend his working life, interrupted only by military service in 1914-6 when he served in the army, in Romania. As with Necheles, his war experiences steered him towards trying to help those dying of kidney failure. He set out to use reed tubes in dogs for haemodialysis, then paper, then peritoneum, on a journey which Haas called a *via dolorosa.* Finally he decided on collodion tubes as Abel and his colleagues had used – although he was apparently ignorant of their work, Haas learning about collodion from Fritz Pregl, Nobel prize-winning microanalyst. Haas employed hirudin as all others had, but apart from its variable toxicity the cost of the agent in post-war Germany was prohibitive. Haas became aware of Necheles' work and they exchanged opinions in *Klinische Wochenschrift* in 1923 about the topic, Haas proposing citrate as an alternative, but Necheles finally persuaded him that if he purified his hirudin all would be well [28] [30].

Haas designed a dialyser [31] (Figure 11) with collodion tubes within individual glass tubes containing dialysate (Ringer's solution), whose number could be varied. In October 1924 he felt able to perform dialysis in a patient in chronic renal failure, using fractionated withdrawal and reinfusion of blood using a pump, rather than a continuously flowing system as in Abel's and Necheles' apparatus (Figure 11). He was assisted by surgeon Dr van Hulten. This dialysis lasted only 15 minutes, but a second patient, a young boy dying of uraemia, was dialysed in Feb-

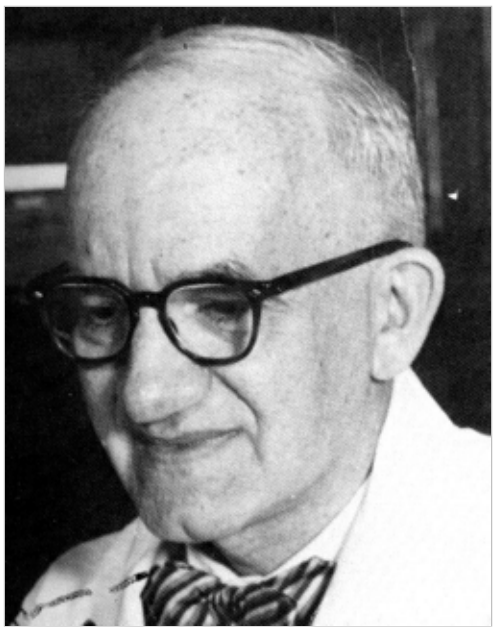

Figure 8.
Heinrich Necheles 1897-1979 (From McBride PT (1987) The genesis of the artificial kidney 2nd Edition. Baxter Healthcare, Chicago

Figure 10.
Georg Haas (1886-1971), around 1935. (Courtesy Dr H-G Sieberth)

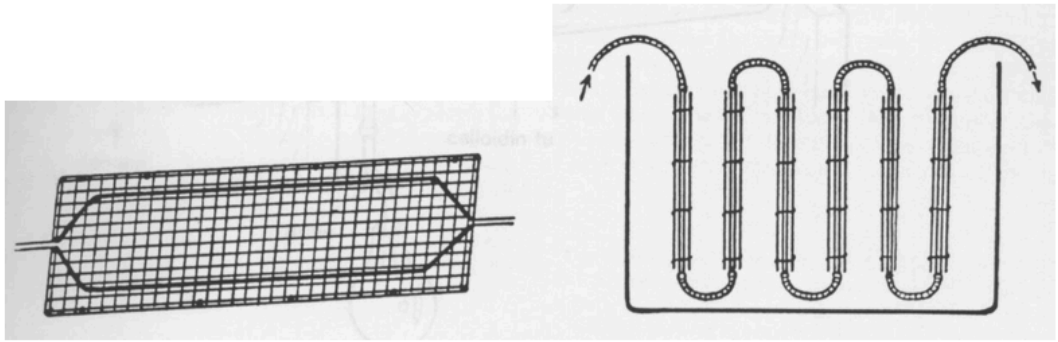

Figure 9.
Details of Necheles' "flat plate", low-resistance pumpless dialyzer using flattened wide tubes of prepared peritoneum with glass tubes each end for connection to rubber tubing. The separate units Left) and their flattening supports were perfused with blood serially, whilst immersed in a bath of warmed, aerated dialysis fluid (glucose saline, or Locke's solution). Up to 10 modules were used (right), giving a maximum dialysing surface area of 4 m2. From reference [29]. Note that the serial design is much less efficient than a parallel design such as that of Abel and colleagues, but this requires some form of complicated manifold.

ruary 1925. The patient's symptoms improved but within 6 days he was seriously ill again with uraemia. Four more patients were dialysed that and the following year for 30 minutes each session (Figure 12), but toxicity of the hirudin limited the duration. Haas discontinued his experiments.

Clearly a new anticoagulant easier to prepare, standardise and less toxic was required. In fact, it had already been extracted from liver [32] [32].

The controversial discovery of heparin

In 1916 a young 2nd year medical student was working, unpaid, in the Laboratory of Professor William Henry Howell (1860-1945) (Figure 12, left) at Johns Hopkins medical school. His name was Jay Maclean (Figure 12, right). He was 25 years old, and had been orphaned aged 4 when his father, a surgeon, died. He worked as a labourer for some years to support himself, but was able to get an education and enter medical school in 1915. Howell asked Maclean to study the coagulant properties of liver thromboplastins, and challenged Maclean's accuracy when he showed in contrast that the supposed "hepatophosphatid" he had obtained inhibited clotting strongly. The result was a couple of single-authored papers in reputable journals under Maclean's name alone which attracted little attention. He left Hopkins in 1917 for Philadelphia and did more work there but not on his original hepatophsphatid. Meanwhile Howell had reconsidered Maclean's data, and employed a retired paediatrician Luther Emmett Holt (1855-1924) (again unpaid!) to carry on with the work. They purified the agent further, showed it was not a lipid nor did it contain phosphorus, and in 1918 named it "heparin", although they did mention Maclean's role in their papers. Now named, the agent had an independent existence, and the importance of Howell and Holt's discovery brought fame. By the end of the 1920s heparin had been purified by Howell and by workers in Toronto including Murray and Best (below), and was in clinical use as a reliable anticoagulant, commercially available. Meanwhile Maclean led an unhappy peripatetic existence, attempted to take up surgery at the Hopkins, for which he had no talent, and did more work on the now available heparin whilst attempting always to promote his role in its discovery, but without success, eventually going into medical administration. Only his death in 1957 re-instated him.

Heparin immediately aroused interest for perfusion, and was studied in extracorporeal circuits by Leonard Rowntree, now at the Mayo Clinic [33], as well as used by Necheles in Peking for his vividiffusions [28]. But for this narrative, its most important immediate action was to promote Georg Haas to begin again the dialysis of patients in renal failure with his dialyser. He dialysed three further patients using fractionated withdrawal of blood and a 1.5 m2 dialyser, reducing the blood urea concentration from 125 to 50 mg% in one. He noted withdrawal of water from the patient, and speculated this could be useful in treating nephrotic and other oedemas. But when he presented this newwork to a Congress of German physicians in Wiesbaden in 1927 [34], he was heavily criticised for endangering his patients and failing to alter the underlying disease, almost certainly from (or including) the hugely influential Franz Volhard (1872-1950), the leading physician in Germany at that time and himself the expert on renal disease. Haas gave up. Haas seems not to have considered using his machine for temporary acute renal failure, even though such cases occurred from mercury poisoning and in pregnancy, and increasingly after incompatible transfusions and haemolysis, and treatment with peritoneal dialysis had been attempted. But also he took on onerous administrative responsibilities, both in medicine and the nursing school about this time, which left him little room for research. He lived

on to see a regular dialysis unit in his hospital, in which he took a great interest; he died in 1971.

A new-old membrane: cellulose. William Thalhimer brings heparin and cellulose together, and clinical dialysis begins

Whilst Necheles and Haas were struggling with peritoneum and collodion for dialysis, all the time a cheap, tough, thin, porous membrane was available but unknown to medicine: cellulose, especially in acetate form. This had been synthesised first in 1908 by Joseph Brandenburger in sheet form, and was available commercially for wrapping from 1910 as "Cellophane" ® from the Société Industrielle de Thaon in France. It was used for laboratory dialysis during from 1927, but the clinicians did not read these papers. Then around the same time the Visking company of Chicago made cellulose tubing for sausage manufacture, to replace the intestine previously required. Kalle in Wiesbaden also made a similar product which was used later by Kolff and

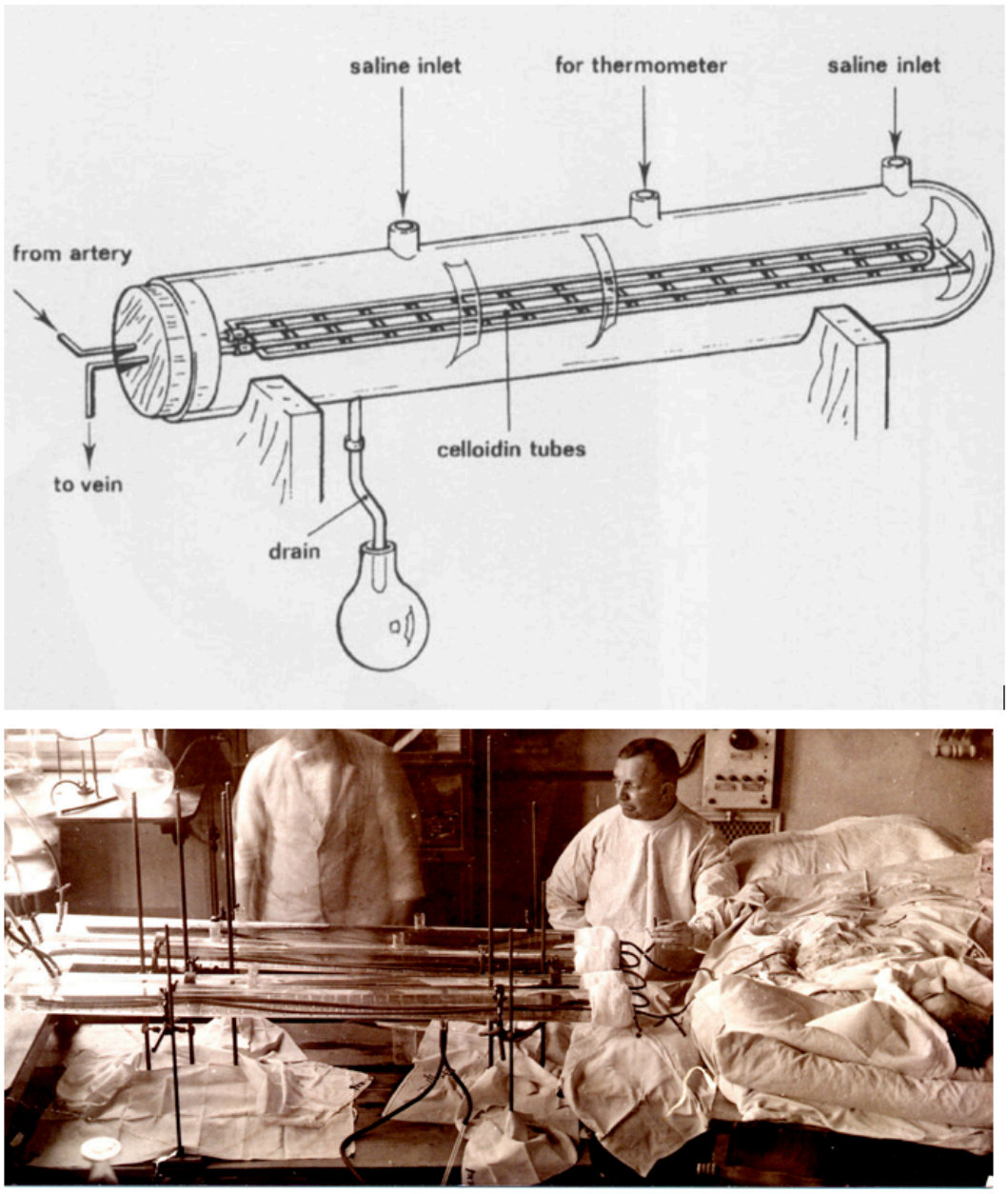

Figure 11.
(Above). One unit of Haas' dialyser. Several such units could be employed, as in the young woman being dialysed in 1926 by Haas using 3 such units in series (below). Blood was withdrawn from the patient into the dialyser, allowed to equilibrate then re-allowed to flow back into the patient. This form a "fractional" dialysis was used in his first experiments by Kolff, and in some dialyser designs into the 1950s [1]. (courtesy Dr Jost Benedum)

Alwall. As well as its other properties it was almost free of microscopic holes. It was used immediately for laboratory dialysis by Andrus in 1928 [35], but again clinicians did not notice – after all, haemodialysis had been tried - and found wanting, had it not?

The individual who saw this as a material for haemodialysis was William Thalhimer (1884-1961) [36] [37], (Figure 13) another unsung giant of our story. William Montefiore Thalhimer came from Richmond Virginia (although born in San Francisco) from a department store family. He had a bent for science and entered Johns Hopkins in 1903, graduating in 1908 and was a pupil of Abel. From then he changed posts between hospitals, especially to Mt Sinai in New York (1908-1918) and Michael Reese in Chicago (1929-1936), giving up clinical for clinical laboratory work and concentrating on blood banking and serum therapies on return to New York. This change of field fostered his links with the group in Toronto studying heparin including Gordon Murray, and Charles Best of insulin fame.

He worked using cellophane dialysis for serum concentration, and also employed heparin in cross-circulation experiments done jointly in Toronto, to treat dogs uraemic after nephrectomy[(2)]. He alone perceived that the combination of now pure standardized heparin and sausage cellophane tubing made clinical dialysis much easier and now feasable, built such a dialyser almost as a side demonstration to his usual work, and reported its success in dogs in an addendum to the work on cross-circulation [38]. He corresponded with his old teacher Abel about this [37]

..”*during the past Summer* (1937) *I started work with an artificial kidney prepared with cellophane tubes, which are available as sausage casings. It is very simple to make an artificial kidney with this material, and purified heparin was used to prevent coagulation..*”

Abel in return informed him about the work of Necheles and Haas, of which he was until then unaware, adding a note to his paper in press.

Why Thalhimer did not proceed to human dialysis is probably explained by the facts that he was not a clinician, had no access to renal failure patients and no particular interest in renal failure. Also,

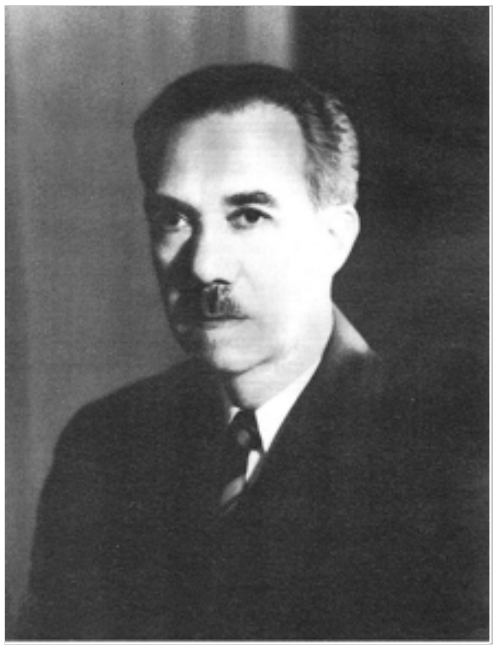

Figure 13.
William Thalhimer (1884-1961) (courtesy NY Academy of Medicine). His work in dogs using cellophane tubing and heparin for the first time together triggered the independent multiple successful dialyses of the 1940s.

Figure 12.
Jay Maclean (1880-1957) (left and center) and William Henry Howell (1860-1945) (right) From: Baird RJ. (1992) The story of heparin - as told through sketches from the lives of William Howell, Jay Maclean, Charles Best and Gordon Murray. J Vasc Surg 11: 4-18

he was aware (as he noted in his paper) of the work in Toronto led by Gordon Murray in which Best had been involved, to use heparin for dialysis in humans. Thalhimer's contribution was to tell the Toronto group to use cellophane tubing, which they did – but not until Murray had done extensive experiments with different forms of membrane, but come back to sausage skin again! Finally he became busy with the great expansion in blood banks, as war loomed.

In fact all three of the simultaneous and independent pioneers of clinical dialysis in the 1940s: Willem (Pim) Kolff (1911-2009), Nils Alwall (1906-1986) and Gordon Murray (1894-1976) [1] [3] cited Thalhimer's paper as an inspiration to their efforts and used cellophane tubing in their dialysers. As Kolff modestly put it 20 years later [39]:

"*Thalhimer had indicated the use of both cellophane and heparin.....since I had both heparin and cellophane.....all that remained to do was to build a dialyzer of sufficient capacity to make the clinical application worthwhile*"

From September 1945 to October 1946 a trickle of patients survived temporary acute renal injury, as a result of dialysis by the three pioneers (and Bywaters in London, to whom Kolff had donated a dialyzer). By coincidence, the first such patient survived thanks to peritoneal dialysis also in September 1945, in Boston USA – but that is another story, to be told on another day.

[(2)] A group in Philadelphia repeated this experiment un-noticed [27], in three uraemic humans in 1940, with clinical benefit. Others attempted this in acute renal failure also into the 1950s.

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