

### Nils Alwall - a personal appreciation



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#### ABSTRACT

I first met Nils in 1964 at the founding of the EDTA (sic) in Amsterdam. I was 29, he was 60. Later I worked with him, now retired from clinical work, on committees over the next couple of decades. During this time he assumed Presidency of both the EDTA and the ISN; he was one of the major founders of Nephrology, as well as a pioneer of and major contributor to electrolyte balance, haemodialysis, ultrafiltration and related techniques. He had introduced renal biopsy in 1944, but remained silent on this subject until after Claus Brun published his work 8 years later. Nils studied arteriovenous shunts for repeated dialysis during the 1940s, but was blocked by the red rubber and glass tubing – all that was then available. I was immediately impressed by the quiet modesty of this most original man; but despite this he achieved international fame in Europe, although was never well known in the United States. His *Festschrift* in 1985 in *Nephron* amply demonstrated his status. His “rival” Pim Kolff (1911-2009) was in contrast slightly younger, outlived Nils by 20 years, and was a fine communicator and great extrovert. Nils was a physiologist and pharmacologist until 36 years old, only then becoming a clinician. Strangely Nils had performed the first haemodialysis at my alma mater, Guy's Hospital London, in 1948 on a visit, 15 years before we established a renal unit there. Characteristically, he never told me about this event, and I only discovered the story after his death.

**KEYWORDS:** Nils Alwall, History of haemodialysis, history of nephrology

#### Introduction

I am grateful to Dr Håkon Westling (1, 2) for some of the following details of Nils' early life, about which he never spoke, at least with me. Nils Andersson was born into a rather poor farming family in 1904, in an undeveloped area of Kristianstad in NE Skåne in the far SW of Sweden. His elder brother took



**Figure 1 - A portrait of the young Alwall by Britta af Klercker. (Courtesy of Dr Håkon Westling).**

over the family farm, but Nils – who was early on a bright scholar – matriculated and was able to go to university in nearby Lund in 1923 when only 17 years age, but only with continued financial help from an uncle, who remains a shadowy figure. Nils was a brilliant student in his undergraduate career, attaining the highest marks in almost all subjects. To begin with, he studied classics – Latin and Greek – and only later decided to read

medicine during his first year in Lund, becoming an unpaid physiology research assistant in 1926. This had the advantage of providing him with somewhere to live, as well as a small laboratory and office. Three years later in 1929 he moved from physiology to pharmacology, and graduated MD in 1932. He played an active part in student organizations, social and intellectual. He became close to the historian Lauritz Weibull and spent much time in

the latter's house. Despite his quiet exterior, Westling describes the young Alwall (he changed his name from Andersson in 1927, because “there were too many Anderssons”, but perhaps also as a break from his background and childhood) as a “pusher”, a tough customer who would fight for what he wanted (Figure 1). His politics were radical and he was concerned about the physician's role in society. He believed strongly in education as a motor for change and better health, and gave public lectures regularly in Southern Sweden for more than 20 years.

#### Early research

In his physiological studies he worked for Professor Torsten Thunberg on intermediary metabolism. Then in 1932 he changed to pharmacology headed by Gunnar Ahlgren again on intermediary metabolism, studying dinitrophenols and thyroxine, showing that they acted similarly and synergistically. He publicly defended his PhD thesis in 1935, in the manner of the time. Sitting in the room that September afternoon was Nobel Prize-winner August Krogh, a friend of Thunberg's whose work Nils much admired, who was to receive an honorary degree during the same session. Krogh's work and thinking on capillary fluid exchange were an important influence on Nils' thinking, and led him eventually into ultrafiltration and then dialysis.

In 1935-6 he spent a year in Pécs in Hungary working at pharmacology. Around this point he made a momentous decision to start clinical work. What led to this change of direction we do not know, but he started work with Sven Ingar in the Medical clinic in Lund. Meanwhile the second world war soon swept through Europe, and although Sweden remained neutral, he did military service as a doctor, being sent to Germany to study the effects of the wide use of amphetamines and other stimulants in Hitler's forces – a subject which has re-surfaced recently\*.

\*Footnote : Here I am quoting Dr Westling – Alwall himself wrote in 1980 “*from the beginning of World War II until 1949 I had no opportunity to go abroad*”. Perhaps he wished to conceal this episode.

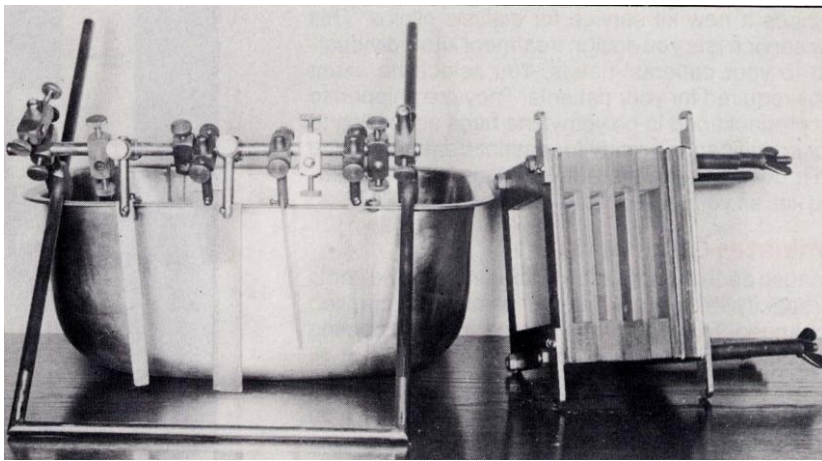


Figure 2 - Alwall's early flat-plate dialyser/filter, which he writes was constructed in 1941/2. He used it to study fluid overload in rabbits, some of whom were nephrectomized. From refs 13/15.

About this time, in 1941, he began to study fluid exchange, and to forward this work, designed an ultrafiltration apparatus for use in rabbits (Figure 2).

A well-known story, which parallels Kolff's use of material from a downed German plane to make his dialyser, is that Alwall used the new plastic Plexiglass® employed in the cockpit of an American aircraft forced to land in Sweden. He did some experiments on nephrectomized animals which could be maintained in a state of overload, and realised his ultrafilter could also remove potentially toxic solutes. Thus his work on the "artificial kidney" began – but as a secondary output from work on ultrafiltration.

He was particularly interested in accumulation of fluid in the lungs, and studied this in detail radiographically in his rabbits, some of which had been nephrectomized. He was influenced in this thinking by Krogh's work on fluid exchange in capillaries. At first he used a flat-plate dialyser for his rabbits (Figure 2), but he was aware of the work of haematologist William Thalheimer (1884-1961) in New York, who had used cellophane sausage tubing to dialyse dogs, and managed to obtain some of this despite the restrictions of war, and built the first model of a static coil type of dialyser (Figure 3).

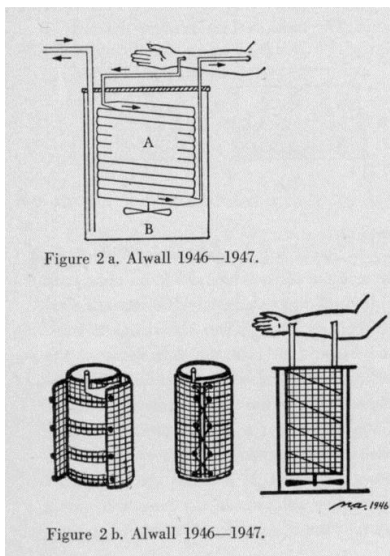


Figure 2 a. Alwall 1946–1947.

Figure 2 b. Alwall 1946–1947.

Figure 3 - A drawing of Alwall's early static coil dialyser/ultrafilter. The casing was either of glass, or later bentonite, then steel.

All this was in complete ignorance that Thalheimer's ex-collaborator, cardiac surgeon Gordon Murray (1894-1976) in Canada, would go on to build a couple of years later a similar

static coil dialyser – but without any ability to control ultrafiltration. The unique feature of Alwall's dialyser was that it had an outside glass container as well as the metal inner support for the tubing wound on it helically, which allowed the controlled ultrafiltration he sought, unlike Kolff's rotating drum machine (of which Alwall was equally oblivious) one of whose major disadvantages was wild uncontrolled swings in the volume of body water during dialysis. Alwall pioneered the view of water as major toxin in uraemic patients. He attended the first international meeting on The kidney organized by the Renal Association of the UK in London in 1953, and described his work on in vivo ultrafiltration, and precipitated a vivid and wide-ranging discussion. In this conference dialysis was not mentioned anywhere in the programme! – and Kolff did not attend.

During the mid-1940s Alwall slowly developed his coil machine with the idea of treating renal failure in humans (3), but unlike Kolff – who never asked if he could dialyse patients, had no lab and no animal experiments – he was restrained from trying it in a human subject until June 1946, when : "...we were finally allowed to perform our first treatment in a moribund patient....As an associate professor I depended on the permission of the director of our medical department, who feared the new method. The general opinion was adverse".

Altogether 8 patients with various types of chronic irreversible uraemia were dialysed in 1946-7 (4), but not surprisingly they achieved little long-term benefit – although temporarily they mostly felt much better for a while. However the second patient, treated in 1947 (case no 702 in ref 10, Fig 1.7 Chapter 1) had severe anuric acute glomerulonephritis, was dialysed once – and survived. The first patient treated with dialysis for acute renal failure from mercuric chloride suicidal poisoning was fitter and also survived, but local physicians' opinions were heavily against this form of "active" treatment, and the (to us now expected) persistent mortality of around 50-60% even in "reversible" forms of acute renal insufficiency which emerged led to a term in Sweden to describe a patient who was "Alwallized" – that is, dialysed and who then – died. Although an article in the Lancet in 1948 (5) helped greatly to disseminate knowledge of his work, the general opinion from 1945-50 was that dialysis added nothing to conservative treatment with fluid restriction and anti-catabolic nutrition (6).

This was a bleak time for him. His work, although intellectually satisfying, published and clinically useful, was however not generally accepted, he had little money despite being in his 30s, and promotion eluded him: despite having been acting professor for two years following the death of his supervisor, in 1948 he applied but failed to obtain a Professorship in medicine following Ingar's death. Only in 1957 did he finally obtain a personal chair in Lund, in renal diseases, as his international

reputation had been established. His unit in Lund, which started dialysis in June 1946, still exists and is the longest-serving dialysis unit in the world after 71 years. Ironically, not being appointed to a general medical position and finally being able to specialize saved him from the burdens of departmental responsibility, which might have allowed him no time to work and sterilized his intellect.

### Alwall introduces needle aspiration renal biopsy

Before we consider his work in dialysis in greater detail, we must mention also his work on renal biopsy in 1944, still during WW2. By this time needle liver biopsy was well-established, and some practitioners had already obtained samples of kidney by accident. But Alwall was the first to set out deliberately to study renal tissue. He performed renal biopsies on 12 patients without incident and success in obtaining useful tissue in 10; two patients showed amyloidosis, the others – mostly with minor proteinuria or haematuria – showed tissue within normal limits judged by the technology of the day. In the unfortunate 13th patient the left kidney could not be seen on the X-ray plate but Alwall proceeded with biopsy of the right kidney obtaining inadequate tissue: the patient bled, went into shock and became anuric, despite a renal decapsulation (a technique in favour at that time) and died. Alwall published these results (7) (Figure 4) only after the Danes Claus Brun (1915-2015) and his mentor Bjarne Iversen (1889 – 1966) had written their paper on successful renal biopsy in 1951. This death must have been well-known locally, and may in part explain some of the hostility later to his promotion.

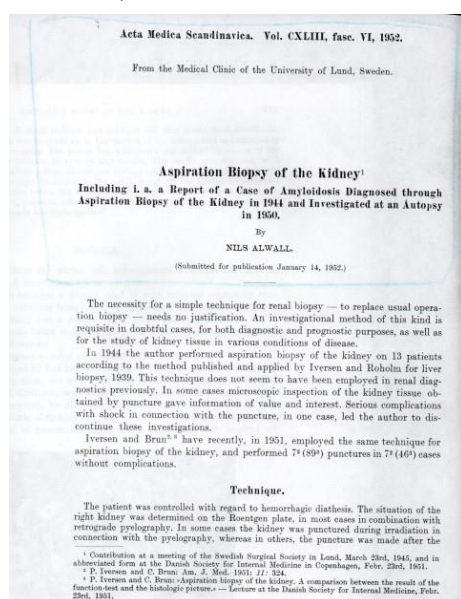


Figure 4 - The opening page of Alwall's little-known paper of 1952 (5) about his pioneering needle aspiration renal biopsies performed in 1944.

1947 was an important year as Nils made first written contact with Pim Kolff, who sent him some valuable Visking cellophane tubing, and his unit dialysed 11 patients from all over Sweden with a few from the rest of Scandinavia, on 21 occasions. Most had exacerbations of chronic disease. He talked in Copenhagen and at the Scandinavian Congress of Surgery, and in May 1948 finally met Kolff, who had been invited to meetings in Stockholm and Lund.

### The arteriovenous shunt and developments in dialysis machinery

Problems with access led him to research the idea of an arteriovenous shunt, which he wrote about in 1948-9 (8). Even

though these rubber and glass shunts (Figure 5) failed eventually in both rabbits and humans, a number allowed repeated dialysis (9), and it is often forgotten that by the 1950s he was able to dialyse a number of patients for 6 months or more. In 1963 (10) he wrote "these procedures – arteriovenous shunt and filling of closed tubings with heparin...- were also used in the treatments of patients ... the present writer later abandoned the use of arteriovenous shunt or any other form of permanent cannulation, because of local infection and the difficulty of avoiding blood-clotting..."

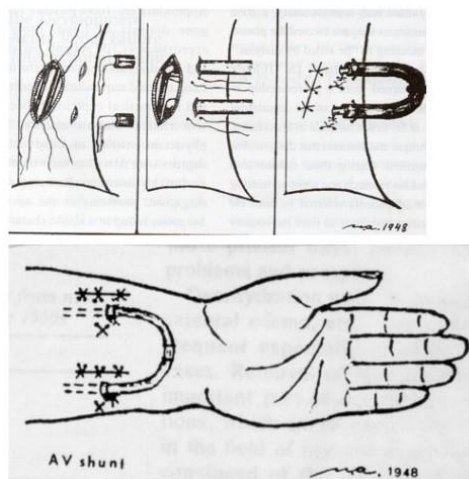


Figure 5 - Alwall's attempts to create an arteriovenous shunts in rabbits and man. (top) A rabbit arteriovenous shunt (8) in the neck (bottom) an arteriovenous shunt in a human, used by Alwall in 1949-50 for clinical dialysis. This signed sketch is the only one of his shunt for clinical use by Alwall I can locate, and is taken from his ultimate summary of the history of dialysis in 1986 (11).

For the first time Nils was able to obtain grants for his work, but even more important was collaboration with two commercial companies to build his dialyser – the Trelleborgs vulcanite company, and the Avesta steel works. He built machines using both materials (Figure 6), but by 1950 was working entirely in steel, which had the big disadvantage that the large apparatus with its double layer of metal was very heavy and difficult to lift. The detailed evolution of his machine is summarized by Carl Kjellstrand and his colleagues (12).

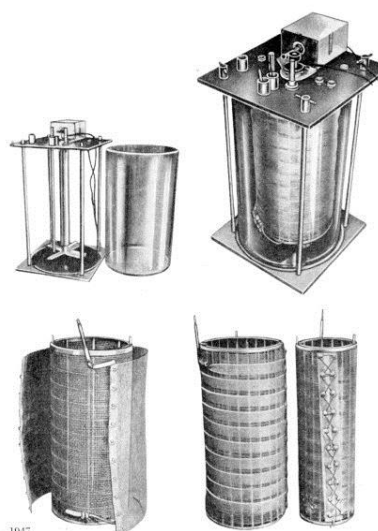


Figure 6 - Later models of Alwall's clinical haemodialyzer/ultrafiltrator. This was made entirely of stainless steel and, it has to be said, was large, could only be lifted with difficulty, was clumsy to assemble and use, and was associated with frequent membrane leaks (Walter Elliot and David Kerr, Newcastle, personal communications).



### The wider world

Nevertheless there was wide interest in using his machine. Franz Volhard (1872 -1950), having survived Hitler's Germany despite his prolonged opposition to Nazi politics, wrote asking if Alwall could loan him a machine, but at that point Alwall could not oblige. This is interesting because Volhard had opposed the use of dialysis when Georg Haas (1886-1971) used it in the 1920s in Germany (6). Alwall and Volhard met in Munich in Germany in 1949, but further collaboration with Volhard was terminated when the latter died in a car crash in 1950. But during the 1950s Nils' machine was used in about 50 units worldwide, including first Copenhagen and Cracow (Dr Hanicki), to which he donated machines, Haifa in Israel, Newcastle in the UK, in Australia, Israel, Cuba, Australia and even the United States, where TS Danowski used it for dialysis in children in that year, and George Jernstedt of Pittsburgh collaborated to make a commercial model together with the Westinghouse company, which however did not sell in competition with newer, easier-to-use models such as the Kolff-Watschinger twin-coil disposable dialyser from Baxter Inc. Many others in central and Eastern Europe used the Alwall dialyser in the 1950s. Alwall was particularly concerned with development in of Nephrology in the then Communist bloc, and collaborated with Dutz and Klinkmann in Germany, with others in Russia, and in the (then) Czechoslovakia.

During the 1940s and 1950s Alwall collaborated mostly with surgeons who were more receptive to the idea of an artificial "kidney" than their physician colleagues. During 1947-9, 35 patients were dialysed 56 times in Lund, but elsewhere both in the USA and the UK, so-called "conservative" treatment for acute renal injury, including volume restriction and high energy diets to decrease catabolism, became more popular. This could tide patients over in relatively non-catabolic situations which included the majority of acute renal injury in that period, as a result of abortion, mismatched transfusions and haemoglobinuria, mercury poisoning and sulphonamide crystalluria in younger, previously-fit patients (6). Opinion swung against haemodialysis for a decade; in addition many surgeons and urologists used peritoneal dialysis, which had developed in parallel. For example, no haemodialysis at all was done in the United Kingdom from 1949 to 1957.

But Alwall never gave up and went on treating the rapidly increasing number of patients referred to Lund, still the only unit doing dialysis in Sweden. He worked hard to ensure that this situation did not persist, but beginning with a second unit in the North of the country in 1958, within a few years there were 17 dialysis units in the country of 7.5 million inhabitants. The struggles that he endured and overcame during the 1950s are detailed in his own account (13), and in the biography by Carl Kjellstrand and colleagues (12). By the end of the decade he had a bigger unit to head, recognition of the specialty, more staff and a personal chair – but after what a huge struggle! It took an Act of the Swedish national parliament to achieve the final steps.

By the end of the 1950s an amazing 1000 patients had been dialysed in Lund, mostly for acute renal failure, but some also knowingly or with undiscovered chronic renal insufficiency, and Alwall thought it time to summarize his experience. His book of 1963 *Therapeutic and diagnostic problems in severe renal failure*, (10) (Figure 7) although little known or read today, is one of the landmark publications in Nephrology. An amazing amount of data are presented, most in the form of graphs of data from individual patients, each drawn by Alwall himself and autographed. It is meticulous, but difficult to read and extract broad data from. It does however contain for the historian of dialysis an amazing bibliography of over 95% of all papers published until then on the subject of the artificial kidney –

nearly 1400.

Medical advances in the field of acute renal failure and dialysis were many in the 1950s, but two require mention: in 1955 Nils described contrast-induced acute renal failure (14), and began in the early 1950s to explore the role of dialysis in the treatment of patients with overdoses of various medicines, beginning with barbiturates (15).

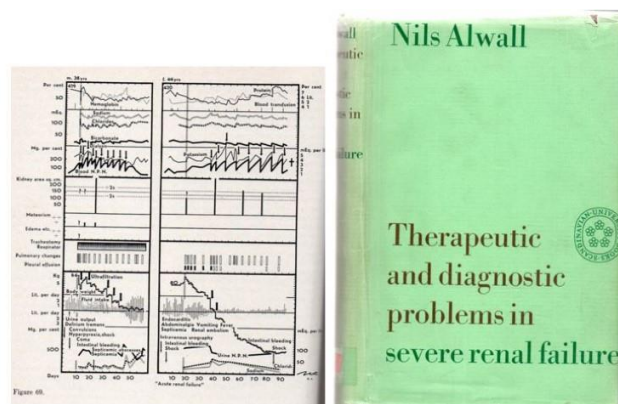


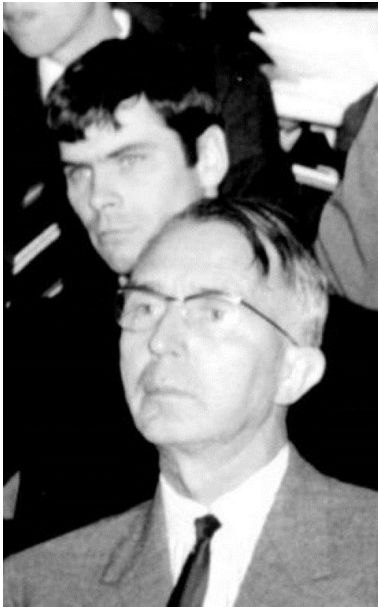
Figure 7 - Nils Alwall's book of 1963 (10). Each of over 1000 patients discussed has a graph of their findings drawn by Alwall himself and autographed (left).

### Long-term dialysis and its consequences

As is well known, in 1960 Scribner had his colleague Wayne Quinton make an arteriovenous shunt from the new electrical insulator material PTFE (Teflon®). Quinton rapidly added silicone rubber to the design, and by two important meetings later in the year (the ASAIO and the first meeting of the ISN), three patients had been using these shunts for regular dialysis for a numbers of months. In Evian at the ISN meeting, just 12 people formed the audience for Scribner's epic paper; one of them was Nils Alwall, to whom Scribner gave some material to make a shunt.

At the end of his 1963 book (10), Alwall presented depressing data on his early attempts to use the arteriovenous shunt to treat end-stage renal failure. All 10 patients had died quite early after starting long-term dialysis. This surprise was part of an experience noted worldwide, and many wondered what "magic" Scribner and his colleagues concealed. Nils thus quietly went off to Seattle to work for some months himself there, to learn on site how to do long-term dialysis – and found that meticulous attention to detail, the use of pumpless dialysis with long sessions (6-8h) and meticulous control of weight, salt and water intake and blood pressure were the main components of the "magic"(6). He returned and re-started a now successful programme of long-term dialysis in Lund in 1964.

Only at this point when he had done so much, did I meet Nils Alwall. It was at the founding meeting of the EDTA (or ERA as it later became) – in Amsterdam, in 1964. Nils was 58, and I half his age, having worked in what became Nephrology for only three years. By chance, I have a photograph of our meeting (Figure 8), when pictures of the audience were taken during a session by Willem Drukker, one of three founders of the Association. I was in awe of this quiet, modest man who had done so much. From then, however I met him regularly through the Councils of the ISN and the EDTA-ERA during the following fifteen years, when his political achievements gradually took over from his innovation in dialysis.



**Figure 8 - The author and Nils Alwall in a session of the founding meeting of the European Dialysis and Transplant Association in 1964. (Courtesy Wim Drukker).**

### Sweden, Europe and the world

With long-term dialysis looming as a treatment for a large number of individuals in irreversible renal failure, in all developed countries, a heated debate ensued as to what to do. Alwall played a central role in this debate not only in Sweden, but world-wide. In 1965 as he had drawn the attention of the government to the problem repeatedly, he was asked to prepare a report, which was finally accepted but only after a long struggle: 7 dialysis units in the regions of Sweden each serving a million inhabitants, were planned and executed with expansion of transplant facilities in parallel. At that time the huge size of the problem was not apparent: even Scribner pictured just a few thousands per year in the whole USA entering end-stage renal failure. And everyone forgot the patients would accumulate with successful long-term outcomes, unless transplantation could meet demand –which it still fails to do. But Alwall had done his homework better – and proposed that eventually 70 people per million per year would need treatment in Sweden, a figure close to the actual Swedish data today. Many other countries, especially the United States, showed a much greater proportion of the population requiring treatment, for reasons that remain under discussion. Had governments with central health systems realized that this 0.1% of the population with renal failure would consume more than 1% of the total health budget, their response in Sweden and the UK might have been very different. In the UK, a similar plan had been suggested by another giant of early Nephrology, Hugh de Wardener, and accepted for 35 units, but after a promising start ran aground 5 years later when costs became apparent and hepatitis ravaged the nascent hospitals.

His experience of organization and leadership in Sweden made Nils an obvious candidate for the Presidency of the ISN, on whose council he had served since it was formed in 1960, and from 1975 to 1978 he served in this high office. During this time a new constitution was designed and accepted, the finances put on a more secure footing, and a Society organization set up. He had been also President of the European Dialysis and Transplant Association in 1971 – an annual rotation with the meeting, which was held in Stockholm that year, but he served as president the following year.

### New dialysers

Having forged his work-horse machine for dialysis in acute renal

failure, Nils in the 1960s turned his attention to regular long-term dialysis. A disposable dialyzer for placement in a machine was already in use in many units for acute dialysis (the Kolff-Watschinger twin coil), and this suggested that disposable rather than re-buildable dialysers for regular long-term dialysis would be needed. After a short flirtation with coil models, he designed a flat-plate dialyser mimicking the Kiil mode, together with Holger Crafoord of Tetrapak, who founded Gambro AB as a company to manufacture this dialysis machinery. This disposable dialyser (Figure 9) came out in 1967; it was heavy with a metal clamping frame, but did the job. By 1970 it had been completely redesigned in plastic as the Gambro Lundia dialyser (Figure 9) and its successors, and were widely-used for long-term dialysis, until capillary hollow-fibre dialysers took over in the 1990s. Gambro became one of the largest manufacturers of dialysis machinery in the world.



**Figure 9 - (top) The Alwall-Gambro disposable flat-plate dialyser of 1968, and (below) with the sleek, lighter all-plastic disposable Gambro Lundia dialyser it gave rise to 3 years later, which was very popular.**

In 1971 at the age of 65 Nils retired as university rules required, but remained active. He worked hard as President of the ISN from 1975 to 1978, and as at that time the President did much of the work of later delegated to the Secretary General, this occupied much of his attention. At that time there was no permanent office with only a couple of paid staff in the Treasurer's office, and things were run on a very cheap basis with the President and Secretary General (John Moorhead) again doing most of the work themselves (16).

During this decade also he became interested in the problem of urinary tract infections, especially in women, and he published a number of papers on the epidemiology, diagnosis and management of this problem. In the 1980s he published a series of papers in Dialysis and Transplantation giving a detailed history of his work concentrating on events in Sweden, and later Europe and the world (13).

In 1985, the journal Nephron devoted a number to a valediction of Nils Alwall. The dedication was written by his pupil Carl Kjellstrand (14), who had worked with Nils in Lund in the early 1960s, and was a co-author of part of his giant book of 1963

(10). The same year he was invited to lecture by the International Society for Artificial Organs, and the text of this talk summarizing the development and impact of the artificial kidney was published in its journal in 1986 (11) – posthumously; Nils had died, aged 81, earlier in that year. He had left behind him an enormous legacy, which Carl described more fully in his biography of Nils in the book he edited in 2012 (12).

Numbers of people have commented how Nils' legacy has to some extent been forgotten – or never appreciated, notably Kjellstrand (12, 17), Klinkmann (18), Shaldon (19) – and the present author (6). One problem from the beginning was that Alwall remained one step behind Kolff in the design, production and use of his clinical artificial kidney (dialyzer). Also, he never promoted the treatment as vigorously as Kolff. The two were opposite poles: Kolff visibly energetic, outgoing, travelling, talking, making and giving his machines on a scale Alwall could never match. Most important of all, Kolff was invited by Isidore Snapper, also Dutch, to go to New York shortly after WW2. His talks were heard by the pioneering Boston group, and his kidney updated and modernized by them as the Kolff-Brigham dialyzer, and then employed in the battle casualties in the Korean war which gave enormous publicity and momentum to the treatment, and swung opinion against conservative treatment in traumatized and postoperative patients (6). Finally Kolff took Irvine Page's invitation to immigrate to Cleveland, Ohio, and he never returned to Europe.

In contrast, Alwall had little or no profile in the United States, and still has not today. The great majority of his papers were published in Scandinavian journals little read in the Anglo-Saxon speaking world – or in France, where Nephrology was blossoming in Toulouse, Lyons and Paris in the 1950s. I can find

no mention of any visit to the United States in the 1950s or even the 1960s, although he travelled extensively within Europe and went to Egypt in 1956. Only in 1978, because of the ISN, did he go to North America, to Montreal. Until then, no-one invited him with expenses, and he writes he lacked the means to travel to (for example) to the annual ASAIO conferences in the 1950s and 1960s. He did have visitors to Lund from the USA however – including Stefan Rosenak in 1952 (another forgotten pioneer (6)) and Scribner in 1958 whilst the latter was working in London. Scribner visited again in 1960. Finally, his disposable dialyser came a decade after Bruno Watschinger and Kolff's massively popular twin coil, manufactured commercially by Baxter's. As an example, in the United Kingdom only the Newcastle Unit led by David Kerr used Alwall's machine, then quietly abandoned it for static coil dialysis. At root was Alwall's quiet, meticulous careful and modest personality. In short, he did not "sell" himself. The steely determination remained hidden.

I will finish on a personal note. In 1948, Nils was asked by a Dr Adler to come to London to dialyse a patient in my own hospital, Guy's Hospital. The patient had polycystic kidneys and dialysis relieved much of his symptoms. An account of this episode was published (20), but it was 14 years before we at Guy's took up dialysis for acute renal failure. I was still at school when this early dialysis occurred and characteristically, Nils never told me about it, and I discovered the story only some years after his death in 1986, when doing research for my book on the history of dialysis (6).

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