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The role of technological progress vs. accidental discoveries and clinical experience in the evolution of dialysis

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The 50th anniversary of dialysotherapy celebrated by nephrologists around the world in 2012 provided an opportunity for discussion on the role of clinical experience in relation to technological progress in the evolution of dialysis, especially of recently observed inadequate decrease in mortality/morbidity rates of patients on chronic dialysis. My report, based on almost 50 years of career in nephrology, refers the evolution of dialysis, from catharsis to modern dialysotherapy with special attention devoted to nowadays gravely underestimated role of clinical experience and personalized professional care for patients.

Key words: **catharsis • dialysis • pioneers of dialysotherapy • technological advancement • accidental discoveries • clinical experience**

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Background

The 50th anniversary of dialysotherapy celebrated in 2012 by nephrologists around the world provided an opportunity for discussion on the role of clinical experience in relation to technological progress in the evolution of dialysis, especially of recently observed inadequate decrease in mortality/morbidity rates of patients on chronic dialysis [1]. Last thirty years of XXth century were a time when dialysis evolved from a life-saving intervention – as it was during its pioneer era – to a long-term method of treatment, not only prolonging, but also improving quality of life for chronic kidney failure patients. The shift came along due to a dynamic development of basic and clinical research coupled with an immediate technological advances [2].

Advancement in dialysotherapy that occurred in that time caused dramatic increase in the number of patients with irreversible renal failure undergoing renal replacement therapy. Currently number of such individuals amounts to 2,366 mln worldwide, counting those treated with hemodialysis at 2,105 mln and 261 thousands on peritoneal dialysis with annual increase about 5% [www.gambro.com]. Modern chronic dialysotherapy program targets patients who were previously eliminated from treatment entirely, for example patients of advanced age, many cardiovascular and metabolic complications of chronic kidney disease, diabetes or systemic diseases [3]. This lack of selection caused an urgent need of developing high quality biocompatible dialysis procedures oriented on the individual patient, especially cardiopulmonary unstable and/or suffering from intradialytic hypotension.

In hemodialysis therapy, intrinsic elements of technological advancement in recent years have been the following: a constant improvement of the system's *heart* i.e. dialysis membrane; perfecting and personalizing the biological systems of control over hemodialysis therapy process as well as introduction of hemofiltration and hemodiafiltration to clinical practice. Also in peritoneal dialysis new CAPD/APD programs have been developed. These programmes employed new personalized cyclers, 24 h blood glucose monitoring and highly biocompatible dialysis fluids [4–7].

Despite the significant progress, recent statistics show that technological advancement does not translate into reduced mortality or morbidity of chronic dialysis patients. The stagnation of clinical effectiveness in dialysotherapy became now reality across the world [3,8,9]. This situation creates the need to revise the diagnostic and therapeutic standards and adapt them to personalized needs of a patient [8,9].

My report, based on almost 50 years of career in nephrology and dialysotherapy, refers the evolution of dialysis, from catharsis

to modern dialysotherapy with special attention devoted to nowadays gravely underestimated role of clinical experience and personalized professional care for patients.

Dialysis as an Universal Idea in the Past: From Catharsis to Graham's Law

Catharsis, a concept derived from Greek verb *cathero*, meaning to cleanse, is an ethymologic progenitor of dialysis. This full-fledged medical treatment has been employed as far back as ancient Mesopotamia and consisted of cleansing blood of impurities, as impure blood was thought to cause most diseases. Catharsis employed mostly skin and gastrointestinal tract. Hot baths, inducing vomiting, enemas and laxatives were most prescribed means to physical catharsis. Bloodletting was also meant to be highly effective.

Hippocrates (460–377 b.c.) and Galen (130–200 a.c.) are considered to be fathers of the idea of catharsis. In his theory of four humors, Hippocrates says: „those things which require to be evacuated should be evacuated” and „diseases which arise from repletion are cured by depletion; and those that arise from depletion are cured by repletion; and in general, diseases are cured by their contraries”. These theories were not shared by Galen, who presumed the source of sickness laid in contamination of blood with toxins (humors) and, in his mind, the only cure was to remove them straight from cardiovascular system through repeated procedures [10].

The word *dialysis* comes from late Latin and means dissolution, after Greek *dialyein*, where *dia-* means apart and *lyein-* to loosen. Up to the second half of XVIII century the concept of dialysis was understood as separation, disconnection: in law – the treaty of dialysis provided means of arbitration; in military dialysis was disengagement of troops on the battlefield; in grammar, separation of two vowels and in music separation of two sounds in meter (separation of two diphthongs in sung poetry) [11]. What is more, Priest Jacob Wujek, who translated the Bible to polish used the term in his paper – „*Dialysis*, dissection of Mr Jakub Niemojewski's assertion. Poznań 1580, a retort to J. Niemojewski, who changed his faith as he used to change gloves and in his public disputes abused the Catholic Church” [12].

It is said, that the idea of catharsis as a method of cleansing the organism from uremic toxins was in use up until the XVIII century [10]. Nevertheless I have found it in medical writings of XXth and XXIst century. For instance, a medical handbook „*Kidney diseases: a companion to medical practitioners and students*” penned by Max Rosenberg in the beginning of XXth century and translated to polish in 1930 brings us the following recommendation.

„In case of severe symptoms of uremia, bloodletting gives the patient a significant, although passing relief, similarly and from the same reasons as in case of acute uremia. Having in mind more pronounced anemia, bloodletting in acute uremia has to be done carefully and with restraint: in case of severe anemia, not more than 300 cm³. Regarding the treatment of individual symptoms of uremia, an utmost care must be given to mouth cavity. Novocain or anesthetics, or couple drops of iodine diluted in a small amount of water may be used as anti-emetic measures. In case of persistent ailments gastric lavage may be helpful. (...) An enema consisting of: paraldehydi (...), scopolamini (...), mucilaginis gummi arabici (...) gave us best results. As the end of catastrophe approaches, a gentle physician will prescribe even bigger dosages of above mentioned means to mitigate the hopeless torment that the patient suffers” [13].

It should be stressed that only 15 years separated Rosenberg's recommendations from the first successful hemodialysis performed by Willem Kolff in 1945 and 28 since first successful treatments in Poland – November 1958 in Poznań and January 1959 in Warsaw [14,15]. At present the idea of catharsis is raised in relation to contemporary theories of removing uremic toxins such as p-cresol sulphate and indoxyl sulphate produced by intestinal bacteria using only laxatives or sorbents administered internally without the necessity of prolonging or increasing frequency of dialysis [16].

Thomas Graham (1805–1866) was the pioneer of dialysis, as a chemical reaction, whose research on gas diffusion led to development of „Grahams law”. His work on separation of crystalloids from colloids with the so called dialyzer gave birth to a whole new branch of chemistry – the colloid chemistry [17].

The origin of experimental and clinical dialysis in XXth century

James S. Cameron, a prominent British nephrologist in his article entitled *History of the treatment of renal failure by dialysis* wrote the following.

“The history of dialysis is no different from the history of any other medical or scientific topic... In truth, the reality is almost always a much more messy process, with ideas forgotten or neglected, and later rediscovered more than once, false starts, blind alleys and periods of stagnation... Again, we must not make too logical the advance of the art in this area or any other: whilst technology had much to contribute to the evolution of hemodialysis, empiricism had even a greater role to play” [1].

The beginning of XX century brings the experimental studies in the field of hemodialysis (HD) as well as peritoneal dialysis (PD). The year 1913 marks the emergence of John Jacob

Abel's, Leonard Rowntree's and Bernard Turner's method, which was a proof that “blood of living animal can undergo dialysis outside the body and then returned to natural circulation” [18]. Ten years later, in 1923 George Ganter published his data on experimental removal of uremic toxins in animals by peritoneal and pleural lavage with sodium chloride. He also presented the results of the first clinical trials. That was the beginning of intracorporeal dialysis in the form of peritoneal dialysis [19].

The godfather of artificial organs technology, amongst those the artificial kidney, Willem J. Kolff created in 1943 the first hemodialysis apparatus (a rotary kidney) using cellophane tubes, soda cans, water pump from the Ford engine and a washing machine. For two years he proceeded to treat acute renal failure patients with his invention – unfortunately without any success. In 1945 he succeeded in case of 67 year old patient with chronic kidney failure, who afterwards was on dialysis for seven more years [15,20]. Nils Alwall (1906–1986) in 1984 modified Kolff's kidney and his device was entered into service all around the world. Alwall also propagated the idea of dialysotherapy in irreversible renal failure. Unfortunately his concept has not been executed due to inefficiency of the arterio-venous fistula that he proposed [14].

March 9th 2010 marks a 50 year anniversary of the first effective hemodialysis performed with teflon made external arterio-venous fistula by Belding Scribner, Wayne Quinton and David Dillard. Intervention on Clyde Shields, a 39 year old patient with uremia due to chronic glomerulonephritis lasted 72 hours. Afterwards the patient has been undergoing nighttime dialysis, first in hospital, than home for 11 more years. Belding Scribner himself did not, in his words, foresee the extraordinary impact this „noble experiment” had on the evolution of hemodialysis. Later, the effort of Belding Scribner and his Seattle team began in 1960 an era of long nightly hemodialysis [21], and in 1964 in Edmonton (UK) Stanley Shaldon started the first in the world programme of home hemodialysis performed independently by a patient – two times a week for 14–16 hours straight [22]. A true breakthrough in hemodialysis therapy came in 1966 with introduction of an arterio-venous fistula planted in the forearm and crafted from subjects own blood vessels created by a team - Michael Brescia, James Cimino, Keith Appel and Baruch Hurwich [23].

Much has changed in peritoneal dialysis since Ganter's times. In 1958 Mort Maxwell published his paper on the new method of inserting the stylet catheter into the peritoneal cavity and *ipso facto* establishing the program of intermittent peritoneal dialysis (IPD) [24]. Another big turn in peritoneal dialysis came with Fred Boens thesis *Peritoneal Dialysis – A Clinical Study of Factors Governing Its Effectiveness* published in 1959

based on the studies of peritoneal low molecular uremic toxins transport, in particular urea, in 22 subjects on 32 peritoneal dialysis treatments [25]. During the 50 year anniversary of this publication in 2009 it was stressed that Boens studies constituted a tipping point in a route of peritoneal dialysis from experimental treatments and anecdotal evidence of its clinical use to a *bona fide* medical procedure, that not only saves lives of acute renal failure patients but also might be primary method of home dialysis [26].

Pioneers of World Dialysotherapy and Their Patients in 40s–60s of XXth century

Pioneers of dialysotherapy possessed certain traits that become evident in their memoirs. Those scientists and physicians focused their efforts on saving patient's lives at all cost but also were:

- innovative and persistent in achieving their academic goals, and at the same time attentive and closely attached to the patient in their daily clinical work – attitude of „I can do it” and „I can do it better than others” was a given;
- determined to acquire funds for their projects, frequently circumventing formal routes;
- extremely conscientious in their everyday practice, in which they tried to implement the effects of their scientific exploits.

Willem Kolff – inventor of the first artificial kidney, recalled his first patient with uremia as follows.

„His name was John Bruning. He was 22 year old son of a small farmer from village near Groningen in Holand [...]. I had to tell his mother, that he will undoubtedly die. And I felt an untold impotence. I asked myself, time and again, if there is no possibility to remove at least 20 grams of urea or other products of metabolism from his blood and stop uncontrollable vomiting? Isn't it possible to remove 20 grams day by day and keep him alive?” [27].

Leonard T. Skeggs and Jack Leonards inspired by Willem Kolff's work decided to create their own artificial kidney. In year 2000 Leonard T. Skeggs wrote about his achievements of that time: „I thought we could do better. Jack liked my idea, took departmental funds committed to other projects, and had first kidney made by Sieberling Latex Products. Because I was also been paid by the Chemistry Laboratory for a over 1000 bed hospital and my technicians had hundreds of manual operations every day, I dreamed of a machine that would do analyses without error. One day it suddenly occurred to me that analyses could be done in continuously following stream rather than batchwise or discreetly. I told Joe Kahn what I was thinking. He urged me to build such a machine and loaned me the money that was needed to get started” [28].

Auto analyzer constructed by Technicon Corporation, and designed in 1957 by Leonard T. Skeggs employed continuous flow analysis and was primarily used for medical diagnostic devices in the form of SMA 12/60. In Poland, the first such analyzer capable of processing 720 samples per hour was introduced in Warsaw Military Institute of Medicine thanks to the Head of the Hospital's Central Laboratory and an enthusiast of progressive medicine, doctor Norbert Symonowicz, whose methods of procuring funds to realize his ideas were not far off from the practices of his American colleagues.

Patient Robin Eady, published in 2009 his experiences of 45 years of renal replacement therapy, including 25 years of home HD and 20 with functioning kidney transplant.

„I was very fortunate to have as my physicians, first Belding Scribner, and later, after my return from the USA to England, Stanley Shaldon. Both were innovative, and dogged in demeanor, and exhibited a „can do” attitude to medical challenges. Both also encouraged me to adopt an active role in the management of my own dialysis and other aspects of my medical treatment. I have also been lucky in having a wonderful family. Actual survival alone has never been enough. What is the point of staying alive? It is living the fulfilling life that really seems to make a difference” [29].

Evolution of Dialysotherapy in 70s to 90s of XXth century

The evolution of dialysotherapy in the last 30 years of the XXth century was possible thanks to dynamic development of basic and clinical research coupled with an immediate technological advances. The most important accomplishments of this era are as follows: the discovery of uremic toxins with molecular weight from 500D to 50kD achieved by Carl Kjellstrand (1975) and Jonas Bergström (1976), and Lee Henderson's (1976) pioneer work on a role of convective transport in dialysis. These achievements became a starting point for development of biocompatible dialysis procedure, biocompatible hemodialysis membranes, biocompatible peritoneal dialysis fluids and – improving the effectiveness of dialysis by way of convective transport – hemofiltration and hemodiafiltration. Frank Gotch's research on kinetic of the transmembrane transport of low molecular uremic toxins, in particular urea (1985) resulted in establishing Kt/V urea clearance as an indicator of „dialysis dose”. His Kt/V urea clearance formula has become an index of adequate dialysotherapy for the last 30 years. A huge improvement in the quality of life in dialysis patients was an introduction of erythropoietin by Joseph Eschbach (1989) [2].

What's New in Hemodialysis?

In place of previously used regenerated cellulose dialysis membranes, which frequently caused early (anaphylactic reaction), as well as distant complications (dialysis amyloidosis), came new – more or less – biocompatible dialysis membranes. The characteristic feature of these membranes was a varying – dependent on their structure – ability to remove uremic toxins of low and medium molecular weight and due to disparate charges on the inner surface of the membrane – a varying biocompatibility. Biocompatible membranes were supposed to have many positive effects on the clinical effectiveness of dialysis, such as less severe course of chronic inflammation responsible for most clinical, long-term complications and hemodynamic instability during the treatment. Polysulfonic, polycarbonic, polyamidic and polymethacrylonitrilic variations of the biocompatible membranes were used predominantly [30].

Bruno Perrone brought attention to the role of accidental discoveries („serendipity”) in the advancement of science, in this case – dialysotherapy. In the 70's the first biocompatible and highly permeable dialyzer was manufactured and brought to the market by a French company Rhone-Poulenc. It employed both flat-plate and hollow-fiber technology and was equipped with a electronegative dialysis membrane AN 69® [31]. In late 80's an epidemic of hypersensitivity reactions swooped through dialysis community. It was soon discovered that reactions were caused by AN 69® membrane, which activated the kinins system. Further existence of Rhone-Poulenc on the market was at that point uncertain. The company undertook an effort to find a way of changing the charge on a membrane to neutral through concealment of the negative charge under a layer of polyethyleneimine cationic polymer (PCP). At the same time Rhone-Poulenc researched a possibility of pre-rinsing the dialyzers with a bicarbonate solution. New hollow-fiber dialyzer AN 69 ST® did not cause the hypersensitivity reactions anymore but that was not all. The “serendipity” effect appeared. It occurred during the pre-rinsing of the dialyzer with heparin saline. Heparin bonded with PCP and allowed hemodialysis treatment to carry on without introducing heparin to bloodstream. Thus was born a wholly new generation of dialyzers – Nephral ST® that provided a possibility of safe dialysis for patients with high risk of bleeding. Positive experiences with Nephral ST were a subject of many publications, amongst those article by Jerzy Kopeć [32].

The evolution of dialysis fluids proceeded, as Ingrid Ledebor wrote „from tap water to water for dialysis”. In 70s, water for dialysis treatment was pre-treated and filtered by RO modules in order to rid it of heavy metal contaminations, mainly aluminum. Only in turn of 80's–90's standardized dialysis fluids were developed. They consisted of standardized concentrates

and standardized quality of water, and were distributed in dialysis stations by way of individual or centralized systems [33].

Intensive nephrological therapy was enriched in the 90's by hemofiltration and hemodiafiltration. Obtaining isotonic ultrafiltrate in case of both those methods equals reduction of hydrostatic pressure and better hemodynamic control of the treatment. Those positive effects result from the lack of negative stimulation of the Renin-Angiotensin-Aldosterone System (RAAS) and adrenergic system. Hemofiltration focuses on removing water along with molecules from plasma by way of convective transport. Hemodiafiltration, on the other hand, merges convective transport in hemofiltration with diffusive transport of traditional dialysis [34,35].

The introduction of hemofiltration to intensive care wards evoked another example of „serendipity” at work. In 1997 Peter Kramer, who at the time was engaged in experimental and clinical research on hemofiltration, accidentally installed hemofilter into the femoral artery instead of femoral vein, as planned. This occurrence gave birth to constant arterio-venous hemofiltration, used successfully up to now [36].

What's New in Peritoneal Dialysis?

A breakthrough similar to that of Brescia et al. in hemodialysis therapy – introduction of a natural arterio-venous fistula was achieved by Henry Tenckhoff, who developed in 1968 a silastic catheter permanently implanted into a peritoneal cavity as a way of facilitating the chronic peritoneal dialysis [37]. A basic peritoneal dialysis technique of that time – IPD – was not efficient and burdensome, both on a patient and medical staff. Attempts were made to modify IPD using Boen's and McDonald's method of Rapid Intermittent Peritoneal Dialysis. RIPD consisted of a increased flow of dialysis fluid and automatization of the whole dialysis process, in particularly by independent dialysis devices, that regulated cycles of dialysis fluid supply and removal from the peritoneal cavity [4].

Years 1976 to 1978 were a time when R. Popovich et al. (USA) and D. Oreopoulos et al. (Canada), proposed a method of continuous ambulatory peritoneal dialysis (CAPD), as a new form of home dialysis. Polish nephrologist Zbylut Twardowski, who participated in R. Popovich's work and later invented a peritoneal *swan neck presternal catheter* and tidal peritoneal dialysis (TPD) also implemented to clinical practice the peritoneal equilibration test (PET) [38–41]. In 1981 we published our clinical experiences in CAPD including the introduction of our centers first produced in house sterile dialysate distributed into containers of our own idea and start-up of the CAPD clinical programme. It should be stressed that in contrast to then popular western systems ours was a separable one [42].

Evolution of peritoneal dialysis didn't bypass dialysis fluids – from the standard fluids in glass containers and glucose levels at 1,5% and 6%, in the 70s through modified glucose, sodium and calcium levels and replacing glass with plastic containers in 80's, finally arriving at invention of biocompatible dialysis fluids, containing icodextrin and amino acids as well as an introduction of automatic peritoneal dialysis (APD) [3,5].

Dialysotherapy After 50 Years – Further Development or Stagnation?

In hemodialysis therapy a significant progress towards optimization of the dialysis membrane was brought by the use of synthetic materials and in turn and invention of high-flux type of membranes (HF). In short time, this type of membrane dominated the market in highly developed countries and replaced low-flux type (LF) [3]. In HF dialyzers the molecular transport happens both through diffusion and convection. Effective removal of low molecular toxins, such as urea, creatinine, potassium or mean molecular toxins (mw. from 500 D to 50 kD) of which β_2 microglobulin (β_2M , mw. 11,8 kD) is surrogate depends on porosity of the membrane. It has been said, that mean molecular uremic toxins are mostly responsible for cardiovascular complications and dialysis amyloidosis. Safe usage of HF type membranes was unfortunately not possible without coupling it with a device continuously monitoring ultrafiltration during dialysis treatment, since uncontrolled ultrafiltration leads to significant disturbances of blood volume. It is worth noting, that the ultrafiltration coefficient (K_{uf}) for the HF type membrane usually exceeds 20 ml/min/mmHg, meanwhile in LF type dialyzers the coefficient does not exceed 10 ml/min/mmHg. Newest generations of the HF type membranes with cut-off point nearing that of albumin (approx. 60 kD) were found to be useful in removal of high molecular uremic toxins, such as indoxyl sulfate and p-cresol sulfate, which are impossible to effectively remove during standard dialysis treatment. Recent research, i.a. Hemodialysis Study and MPO (Membrane Permeability Outcome), points to such merits of HF type membranes as improved cardiovascular stability during the treatment, improved insulin sensitivity and improved survival in patients with diabetes and/or hypoalbuminemia, undergoing HD treatment for at least 4 years. These studies didn't prove however reduction in all-cause mortality in relation to mortality in patients dialyzed with LF type membrane [30,43–46].

Limitations in use of HF type dialyzers up to this point were double. Firstly, up to now, high cost of the procedure in comparison to the LF type dialyzers. Secondly, the possible penetration of bacterial endotoxins into the patient's blood, in case of deficient sterility of dialysis fluid. It should be mentioned that ultrafiltration of dialysis fluid in newest HD dialyzers effectively prevents bacterial endotoxins from entering patient

bloodstream. Raymond Vanholder and Luciano Pedrini stressed in the differences between HF dialyzers, especially when it refers to their „removal capacity”. They found that: „All high-flux membranes are equal but some high-flux membranes are less equal than other” [47].

A new potential means of saving patients in 4. or 5. stadium of chronic kidney disease in multiple myeloma or dialysis amyloidosis came in the form of High Cut-Off (HCO) type highly permeable dialyzers, which have a high cut-off point for medium and high molecular uremic toxins (approx. 45 kD). They permit effective removal of light immunoglobulin chains below the point of nephrotoxicity, which improves survival rate in patients with multiple myeloma, who are not dependent on dialysotherapy and prevent the development of chronic kidney disease in patients with myeloma kidney. Some studies show, that treatment using first generation HCO membranes with dialysis surface of 0.5 m² and varying pore size results in low urea, creatinine and potassium clearance, and high significant loss of albumin [48,49]. On the other hand, the second generation of HCO (Theralite®) due to bigger membrane surface (2.1 m²), high cut-off point and uniform pore size permits removal, not only of low and medium molecular uremic toxins, but above all chains of immunoglobulins without loss of albumins [50].

In patients suffering from sepsis with acute kidney failure and resistant to standard therapy, the second generation HCO SepteX® membrane produced beneficial clinical effect, thanks to its high cut-off point (60 kD), which allows removal of cytokines responsible for septic shock [51]. In Poland, this treatment was reported successful for the first time by our Center [52]. HCO membranes, thanks to their ability to remove myoglobin, can also be used in the treatment of post-traumatic rhabdomyolysis with acute kidney injury [53].

Subsequent contemporary advancement of hemodialysis is *on line* dialysis fluid production, both for standard techniques as well as hemofiltration and hemodiafiltration, and production of bicarbonate concentrates for individual hemodialysis procedures [34,43].

Modern dialysis systems, such as Gambros Artis System® or Fresenius' 5008S System®, control all basic hemodialysis processes and record them accordingly, so they can be played back on demand, which releases experienced staff to more ambitious tasks and ensures maximum recurrence and safety of the therapy. These characteristics provide universally the optimal hemodialysis in constantly growing and diverse population of patients [8].

Modifications of standard HD, such as hemofiltration and hemodiafiltration *on line* are more widely used in intensive care

of unstable cardiopulmonary patients. Hemodiafiltration has been already adapted by over 10% of dialysis patients in Europe, and in certain countries, like Switzerland this percentage exceeds 60%. This method significantly improves survival rate and lowers the possibility of uraemic complications. This constitutes a strong premise to use it in place of more frequent or longer dialysis sessions proposed by some authors [46,54].

Substantial progress took place also in peritoneal dialysis. New CAPD/APD programs have been developed. These programmes employed new personalized cyclers, 24 h blood glucose monitoring and highly biocompatible dialysis fluids [4–7].

Fundamental importance of peritoneal dialysis in integrated nephrological care, a thesis supported for years, but never conclusively proven, finally found support in American nephrologists, who encourage their colleagues to prescribe peritoneal dialysis more frequently as a first option of kidney replacement therapy, because of its proven effectiveness during first three years of this treatment [9].

Newest development is introduction of two ultrafiltration techniques – extracorporeal ultrafiltration (using dedicated devices) and peritoneal ultrafiltration (using slow everyday treatment) – in therapy of congestive heart failure (CHF) in stadium 3–4 of chronic kidney disease [34,35]. Our Center was a first polish institution to introduce peritoneal ultrafiltration in place of extracorporeal ultrafiltration as a treatment method of patients with CHF [35,55,56].

Despite the significant progress, recent statistics show that technological advancement does not translate into reduced mortality or morbidity in chronic dialysis. Yearly mortality in the group of patients with chronic kidney failure in stage 5 D varies from 6.6% in Japan, through 15.6% in Europe, to 21.7% in United States of America. Though most guidelines optimizing therapy were implemented with maximum efficiency, morbidity of hemodialysis patients in US decreased only by 1% per decade and the average duration of hospitalization didn't fall below 15 days per annum. Significant differences between European countries, Japan and US are attributed to shorter dialysis sessions performed in US, preferred tunneled catheters for vascular access, and economic policies, such as reuse of dialyzers and replacing experienced nursing staff with medical technicians. That means the stagnation of clinical effectiveness in dialysotherapy became now reality across the board [3,8,9].

Widely celebrated 50 years anniversary of dialysotherapy provided an opportunity for discussion. Prominent American nephrologists – Thomas Parker, Raymond Hakim, Allen R. Nissenson, Theodore Steinman and Richard J. Glassock published an article entitled „Dialysis at the crossroads: 50 years

later” in which they presented their take on the causes of this unfavorable state of affairs and proposed ways to improve the situation [9]. Francesco Locatelli and Bernard Cannaud published in 2012 an article of similar undertone entitled „Dialysis adequacy today: a European perspective” [8].

Both teams diagnosing the phenomenon came to identical conclusions and emphasize the need to revise the diagnostic and therapeutic standards and adapt them to personalized needs of a patient. Essential elements of this recommendation are as follows.

- Rather than an early start of dialysotherapy based on strictly determined eGFR value, follow the recognized clinical parameters, such as – the *hitherto* course of chronic kidney disease (slower in older patients), the amount of residual renal failure diuresis, good response to loop diuretics, no signs of malnutrition and, most of all, no signs of left ventricular hypertrophy in echocardiography, as the prognostic markers of the CKD's further course. American authors stress also the need to start dialysis programs with peritoneal dialysis, which they deem the most effective method for the first three years of renal replacement therapy.
- Supplementing the evaluation of dialysotherapy effectiveness, now expressed only with Kt/V to urea ratio, by regular hydration evaluation through electrical bioimpedance or other available methods. Both research teams consider assessment of hydration based solely on single measurement of body weight before and after HD as inadmissible. What is more, Locatelli and Cannaud judge elongation of dialysis sessions to be crucial for further improvement of treatments effectiveness. To evoke the New Zealand and Australian research – it has been proven, that adding even half an hour to standard dialysis session reduced the risk of mortality by 7%. Locatelli and Cannaud therefore propose a new standard for hemodialysis – a minimal single session duration to be set on 4.5 h with ultrafiltration not exceeding 10 ml/h/kg of body mass, considering the schedule of 3 treatment sessions per week. The replacement of Kt/V coefficient proposed by Gotch 30 year ago with an equation of urea clearance (K) multiplied by duration of a treatment session (t), which more accurately estimates the desired dosage of dialysis, is still an object of discussion [8].
- Devoting greater attention to left ventricular hypertrophy – *mind the left ventricle!* – as an indicator of unfavorable course of dialysotherapy. American nephrologists suggest that the long term overhydration, which most frequently accompanies chronic dialysis patients, has a more adverse effect on remodeling of left ventricle than hypertension and atherosclerosis. The systematic assessment of hydration by bioimpedance and the left ventricular through echocardiography should increase the survival rates of dialysis patients much more than currently, widely prescribed lipid lowering and antihypertensive therapies.

- Replacing the demanding low-protein diet with more lenient but restrictively limiting salt consumption even during dialysis.
- In the end both research teams come to the same ultimate conclusion – even the biggest technological advancement cannot substitute the clinical experience, nor the personalized professional care.

This last statement brings life back to Claudio Ronco's Dialysis adequacy index: Md_{time}/P , which calculates the time, a physician needs to devote his dialysed patient. This theory was proven to be correct by DOPPS study, which confirmed that longer and more frequent contact with a patient lowers the morbidity rates in dialyzed patients [57].

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Conclusions

The evolution of the idea of dialysis, from *catharsis* to clinical dialysis, its distinguished pioneers and dynamic technological progress, makes it one of the most important therapeutic methods, central to health and wellbeing of the world population. I, for my part, hope that this article will serve as a strong backbone for a statement authored by a prominent British nephrologist Stuart Cameron: „... whilst technology had much to contribute to the evolution of hemodialysis, empiricism had an even greater role to play” [1].

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