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Artificial Organs WILEY

EDITORIAL

The journey

On the occasion of the 70th Anniversary of the American Society for Internal Organs (ASAIO) I was invited to give a keynote address. I entitled my presentation "The Journey," my journey, your journey. I'm appreciative to the Boards of ASAIO and the International Federation for Artificial Organs (IFAO) and, in particular, Dr. Bonde for this invitation. In the words below I summarize this presentation. The key points discussed were the spread and breadth of artificial organ technologies and their clinical applications, the role of artificial organs in academic disciplines and societies, lessons I have learned from the application of renal support technologies and their expansion to treat other diseases, and the role of artificial organ technologies from the treatment of end-stage disease treatments to therapeutics, and health and wellness.

1 | THE SPREAD AND BREADTH OF ARTIFICIAL ORGANS

While the definitions of artificial organ may vary for the purpose of this discussion it is defined as man-made devices that are implanted into, or integrated onto, a human to replace, recover, or regenerate a natural organ function. The introduction of artificial organ technologies was the introduction to modern-day medicine. Some highlights though not exclusive include: W. Kolff applying the artificial kidney in the form of dialysis for acute renal failure in 1943, J. Gibbon performing the first successful open heart surgical procedure with heart-lung bypass in 1953, P. Salisbury conceived of the formation of ASAIO in 1954, A. Senning implanted the first heart pacemaker in 1958, J. Charnley performed the first hip replacement in 1962, Mikami, Mito and Nosé performed the first clinical liver support using liver slices in 1963, D. Cooley performed the first clinical use of a biventricular device in 1969, the United States government legislated payment for end-stage renal disease patients in 1972, and W. DeVries in 1982 performed the first permanent artificial heart in Barney Clark. A more extensive listing of Milestones in the fields of artificial organ and transplantation application is in the web site icaot.org.[1]

Regarding Dr. Kolff, I am reminded of a story told to me by one of his colleagues. Dr. Kolff had just finished an experiment that did not go well yet he was laughing. My friend asked him why he was laughing and he said "now I know not to go in that direction." We must accept failures and not be afraid to fail and move on.

In a ranking by Neil Armstrong, the first human to land on the moon, of the 20th century's top engineering feats health technologies including artificial organs is ranked 16th.[2] The field of artificial organs is broad and encompassing. It relates to implantables, extracorporeal processes, biomaterials, engineering, and clinical applications. It is multidisciplinary in its approach and includes medical, scientific, and engineering principles and professionals associated with such. As a field, it crosses political and religious boundaries. Various academic disciplines are engaged including but not limited to biology, biochemistry, chemistry, all engineering disciplines, most medical areas of medicine, and business/finance.

The development of an artificial organ technology has typically initially borrowed concepts from other fields (i.e. membrane technology, engineering principles for machine design, surgical concepts for blood access, and anticoagulation for dialysis). Initially, practical devices must be built and then the clinical needs and applications pursued. With time, the developments are refined and the clinical applications are expanded.

Some artificial organ technologies include blood filtration and separation for renal support and detoxification (i.e. dialysis, hemoperfusion, apheresis) and biological support; pumps for cardiac and pancreatic support; gas exchange for pulmonary support; mechanics/biomaterials for orthopedic and dental support; biological constructs for orthopedic, neuromuscular, liver, and pancreatic support; materials for vascular support and blood replacement; and electronics for visual, orthopedic, and neuromuscular support, brain stimulation and devices for power, sensing, and controls. Investigative areas include blood, cardiac, liver, musculoskeletal, neural, pancreas, placenta, pulmonary, renal, soft tissues, organ preservation, xenotransplantation, and hybrid systems.

It was reported in 2004[3] that over one billion devices were used annually worldwide in 2003: catheters 200 million, renal/dialysis treatments 45 million, blood bags 40 million, contact lens 30 million, intraocular lenses

2.5 million, coronary stents 1.5 million, dental implants 910 000, pacemakers 400 000, heart/lung (oxygenators) 300 000, vascular grafts 300 000, breast prostheses 250 000, hip prostheses 250 000, knee prostheses 250 000, heart valves 100 000, and cochlear implants 60 000. It is estimated that presently over 3 billion devices are used.

From review of the number of patients on the transplant list and transplants performed in the United States in 2023[4] 46 623 transplants of all types were performed with 103 839 patients on the waiting list and 4856 died while waiting (over 13 patients died while waiting). There were 27 322 kidney transplants, 10 660 liver transplants, 4545 heart transplants, and 3026 lung transplants. At present, there are over 800 000 patients on dialysis. While life on dialysis is not perfect, it is a life-sustaining technology, and some patients survive on it for decades. Conventional human organ transplantation presently has its limits. Major efforts continue exploring xenotransplantation with some success in the past year. Artificial organ support remains the present hope for meeting clinical needs.

The impacts of artificial technologies remain. Medically, they can assist organ system functions, provide therapeutic applications, and extend life in a diseased state. Scientifically, new knowledge can be gained of physiology and biochemistry. Try removing the natural organ and replacing it with an artificial substitute; one can more fully appreciate the complex functions performed by the natural organ and the limitations of the artificial substitute. Developmentally, they pave the way to develop new technologies for applications. Economically, they have created industries and in a major way impacted healthcare costs. Market studies show that the compound annual growth rate (CAGR) for artificial organ devices is about 9%. With a present market of over $30 billion, the estimated sales of $55.4 billion by 2031.

I am not aware of anyone that would prefer an artificial organ substitute to the natural one but it is reassuring to know that a substitute can be life-saving and we can be appreciative of the scientists and researchers and companies that continue their efforts to improve the technology and advance the studies in organ failure. I am appreciative that when I developed serious complications of COVID 4 years ago, my physicians at the Cleveland Clinic could apply lung support to save me.

2 | ROLE OF ARTIFICIAL ORGAN SOCIETIES

The spread of information on artificial organs can be through publications, meetings such as this ASAIO Conference, the growth of societies and their publications, and of course the personal interactions and exchanges among researchers, developers, and clinicians such as at conferences. When the ASAIO had its first meeting in Atlantic City in 1955 it was a unique setting for those that attended to describe their work on the artificial kidney, blood oxygenation and heart-lung bypass and other topics. At that time the field was developing and the discussions were encompassing. As the field grew and the specific organ support systems developed, individual organ related societies formed such as for cardiac support, dialysis and renal support, pancreatic support, etc. within the individual medical specialties. In one sense this diminished the emphasis on ASAIO and the other artificial organ societies as the fields grew and organ specific societies were formed and grew. But it also deemphasized the importance of the interrelationships among the organs and the importance of innovation that for some organ support systems depended on common needs (i.e. vascular assess, energy requirements, pumping means, biomaterials, sensors, etc.). Certainly, the artificial organ societies should remain focused on the broader goal of supporting the sum of organ support technologies and encouraging innovation.

From the early days of ASAIO, the efforts were very much United States focused. As the field grew the international interests flourished (Table 1). The ASAIO held its first meeting in Atlantic City in 1955. As its publication it published the *Transactions* and later the *ASAIO Journal*. In 2024 it celebrated its 70th Anniversary. In 1957 the Association of Artificial Internal Organs was founded in Japan and in 1962 the Japanese Society for Artificial Organs (JSAO) was founded with its *Journal of Artificial Organs* (English version of its Japanese language journal). In 1974 the European Society for Artificial Organs (ESAO) was founded along with its journal, the *International Journal for Artificial Organs* (Int J AO). The ESAO celebrates its 50th Anniversary in 2024. As was the general rule in the late 70s, to be a full member of the national

TABLE 1 Major artificial organ organizations/publications.

1955 ASAIO holds first meeting in Atlantic City; *Transactions*, *ASAIO Journal;* **70th anniversary**
1957 Association of Artificial Internal Organs founded in Japan
1962 JSAO founded; *Journal of Artificial Organs* (English)
1974 ESAO founded; *International Journal for Artificial Organs;* **50th anniversary**
1977 ISAO founded with 1st meeting in Tokyo; *Artificial Organs*
1979 ICAOT opened in Cleveland; AO Collection; web site icaot.org
1998 LSAO, Latin American Society for Artificial Organs, Biomaterials, & Tissue Eng.
2004 ISAO transitioned to IFAO
2013 APSAO formed, Asia-Pacific Society for Artificial Organs

societies one had to be living in the area. As a result, in 1977 the International Society for Artificial Organs was formed and accepted as full members those that applied. It held its first meeting in Tokyo and introduced its journal, *Artificial Organs*. In 1979 the International Center for Artificial Organs & Transplantation (ICAOT) was formed to house an artificial organ collection and educational center. For two decades it operated a museum in Cleveland and then the Collection was moved to Houston in 2000 where artifacts were on display until 2011. The Artificial Organ Collection presently is in storage and the ICAOT is looking for a permanent home.[5] In 2021 the ICAOT formed a web site on which it describes its history and lists key milestones in the fields of artificial organs & transplantation and has a Virtual Collection where institutions, companies, and individuals may post its historical collections. In 1989 the Latin American Society for Artificial Organs, Biomaterials, & Tissue Engineering was formed. In 2004 the ISAO transitioned to a federation, the International Federation for Artificial Organs (IFAO) consisting of ASAIO, ESAO, and JSAO where *Artificial Organs* is its official journal. In 2013 the Asia-Pacific Society for Artificial Organs was formed. It behooves the IFAO and the major national societies to reach out and support the early formed and developed societies.

Over the course of several years I organized the International Apheresis Registries. In its 2007 Registry[6] one conclusion was that regional differences continue to exist as the local economics dictate reimbursement and costs, disease treatment demographics, technology availability and physician training and education. Such is true for other artificial organ technologies. It is very important to view the field for a broad perspective and to learn from what others are doing. Some years ago, a group from the International Federation for Artificial Organs (IFAO) reported on long-term survival for hemodialysis patients and how it might differ in Japan versus Europe and the United States.[7] They concluded: the differences in comorbid characteristics among hemodialysis patients do not fully explain the superior survival seen in the Japanese hemodialysis patients. Differences in practice likely contribute (i.e. greater prevalence of arterial–venous fistula, longer treatment times, and slower ultrafiltration rates in Japan), and cultural differences (Japanese patients stay for full treatment times per prescription and have greater adherence to dietary recommendations). We must continue to review and compare international results, such as through the IFAO, and to reach out to the developing world to support their needs.

Our experiences with the evaluation of dialyzers and their clinical evaluations strongly suggested that their performance can be variable and that clinical performance was reduced compared to in vitro performance such as by variations in blood and dialysis flows during the dialysis period, dialyzer clotting and variations of dialyzer characteristics. We developed the procedure of Direct Dialysis Quantification (DDQ)[8,9] that involves the collection of the spent dialysate and the direct quantification of the solute losses. The information produced by DDQ was clinically reliable, and reproducible, and provided an effective tool to guide the routine nutritional and dialytic therapy in addition to improve the technical competence of the staff.[9,10] It was shown that elevated blood urea nitrogen (BUN) was multifactorial and that protein intake was not a frequent cause of elevated BUN as suspected by the dialysis team and, in fact, a person with a high BUN may be even undernourished.[11] In comparison with the computerized urea kinetic model (UKM) in 40 simultaneously modeled patients, statistically significant differences were found in pool volume, protein catabolic rate, and dialyzer clearance with UKM yielding a higher mean in each case. In studies of new and reused dialyzers, DDQ showed that there were no significant differences and that dialyzer clearances were shown to be 30% lower than manufacturer's data.[12]

3 | LESSONS LEARNED FROM RENAL SUPPORT TECHNOLOGIES AND THEIR APPLICATION TO TREAT OTHER DISEASES

The rationale for the application of the use of extracorporeal therapies in a disease is the abnormal chemistries in the disease state. Excess solutes may be detrimental and therefore the rationale for removing them. It is hypothesized that the removal of the excesses will improve the symptomology and possibly effect a cure. Critical to their removal is defining the removal means. In renal failure, for example, there are abnormal chemistries that build up in the blood including metabolic toxins (i.e. urea, creatinine, uric acid), electrolyte imbalances occur, and water is retained. Various removal means have been evaluated including forced diuresis, sauna bath treatments, edible sorbents, gut microbiome modifications, blood and plasma exchange, dialysis of the gut, peritoneal, and blood. Of these means dialysis is the most practical.

We have investigated the use of bacteriotherapy for renal support.[13,14] The concept of using living microorganisms as substitutes or replacements for physiologic functions is to bring the patient into more intimate contact with the appropriate organisms capable of treating the metabolic deficiency/abnormality, reducing the time sequence of events, and facilitating mass transfer. For renal support,activated sludge from a wastewater treatment plant was reacted with normal urines aerobically for months. Removals of urea nitrogen, creatinine, uric

acid, organic acids, inorganic phosphorous, chloride, and sodium were shown. Starting with mixed organisms and strains, three dominant organisms were cultured: (i) *Pseudomonas alcaligenes*, (ii) *Diptheroid bacilli*, and (iii) *Alpha streptococci*. The concept of applying the appropriate microorganisms for health is well known in the field of probiotics today to improve our microbiome. With today's knowledge of modifying the microbiome, gene editing, and cloning this field offers promise for not only treating renal failure but other diseases.

From our study of renal failure and its treatment by dialysis, we recognized that the non-selective approach (i.e. dialysis), although not perfect, it proved to be life sustaining. Excepting successful transplantation, dialysis, either hemodialysis or peritoneal dialysis, is the most cost-effective treatment modality for end-stage renal disease and at present over 820 000 patients survive with it. We assessed the possibilities of extrapolating lessons learned to other diseases. We recognized that standard dialysis has molecular size removal limits. Many disease states, both metabolic and immunologic, exhibit abnormalities of high molecular weight solutes or protein-bound solutes in blood and plasma. Our approach was to identify the appropriate separation/removal means (i.e. sorption, plasma exchange, plasma filtration, or other blood and plasma treatment methods). In 1980 we submitted the abstract to ASAIO "On-line removal of immune complexes from blood by double step membrane filtration"[15] that was rejected. In the following year our abstract on "Macromolecule removal from blood" was approved for presentation and the full article accepted for publication.[16] This publication outlined over 40 specific disease states and their increased factor(s) or chemical abnormalities in blood that be amenable to treatment by plasma membrane filtration and/or sorption and we reported on our early experiences to use cooled plasma filtration (cryogelpheresis). This publication was recognized in the ASAIO Gold, the 50th Anniversary Special Edition, June, 2004, recognizing the 25 landmark papers in its 50-year history. Decades later this author updated our experiences in the publication "Therapeutic Apheresis: Why?"[17] At that time over 100 disease states from the general disease categories as neurology, rheumatology, nephrology, pulmonary, gastroenterology, endocrine, cardiology, hematology, transplantation, dermatology, cancers, ophthalmology, obstetrics, otolaryngology, and others and the most probable causative agents were shown. The potential benefits of therapeutic apheresis were discussed and concluded "therapeutic apheresis: why not"?

As a starting point for our research to develop technologies for the treatment of diseases other than by dialysis we collected discarded plasma from our hematology group treating patients by plasma exchange. These

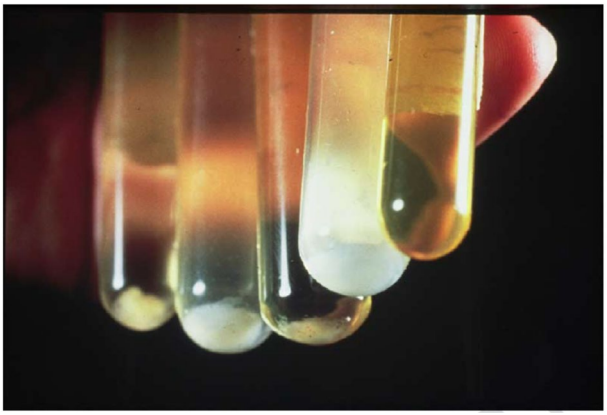

FIGURE 1 Cryoprecipitable proteins in patient plasmas with various autoimmune diseases. From the right: Normal person's plasma not showing cryoprecipitable proteins, rapidly progressing glomerulonephritis, rheumatoid arthritis, myasthenia gravis, and Sezary syndrome. (Permission requested from Schattauer.) (Colors are visible in the online version of the article: https://doi.org/10.3233-120729.) [Color figure can be viewed at wileyonlinelibrary.com]

plasmas were refrigerated until used for studies. One very observable finding was that most of the refrigerated plasmas had precipitates. Recognizing that the precipitates were likely agents associated with the diseases treated and our need to process these plasmas at near physiological temperatures we warmed the plasmas and found that the precipitates dissolved. With further research[18] we realized that these precipitates were cryoprecipitable proteins and while not commonly analyzed for they are pathologic. As our research continued our lab was requesting from our laboratories more assays for cryoproteins than the whole institution. We showed that the presence of cryoproteins was not limited to cryoglobulinemias as seen in Figure 1. For disease state treatments we chose membrane plasma filtration the reasons being: the marker solutes in many disease states treated by plasma exchange are of a molecular weight greater than that of albumin, the typical replacement fluid in plasma exchange, and generally greater than about 100 000 daltons; the molecular cut-offs of membranes are not very selective (circa 1980–81); and improved selectivity can be achieved by augmenting molecular separation as by temperature control of the separated plasma; cryofiltration (formerly called cryogelpheresis) for removal of cold aggregating solutes, and thermofiltration for the removal of lipid and higher molecular weight solutes. A limitation for plasma separation is the carry over of some cells with the plasma. Furthermore, while centrifugal plasma collection is most common when carried out in hematology units, dialysis centers are familiar with membrane devices.

In the late '70s and early '80s the procedures for plasma separation were not well defined. One general problem,

based from the experiences in dialysis, was the use of high transmembrane pressures that led to plugging of the membrane filters. Our group took the lead in analyzing the issues and developed clinical operating procedures to achieve stable plasma filtration for up to multiple hours as was required in some treatments[19,20] through regulation of the transmembrane pressure, typically below 50 mm Hg, and controlled plasma flow. With continuous membrane plasma separation, the plasma can on-line be processed for treatment with membrane filtration or sorption as with resins and activated charcoal as we carried out. Furthermore, the separated plasma can be temperature regulated (i.e. cooled to near about zero degrees Centigrade in cryofiltration, or warmed to about body temperature in thermofiltration) to improve the selectivity of removing the pathological solutes in plasma without the need for plasma replacement products. The treated plasma can then be warmed and returned to the patient in a continuous fashion.

Prior to initial patient trials I and my colleagues submitted to procedures. As noted in Figure 2, the procedure was uneventful. Heparin was used as the anticoagulant and the blood access was through a veni-puncture with the return on the opposite arm by a veni-puncture. As blood passed through the membrane plasma separator the plasma was drawn, cooled, and filtered through a membrane filter in the cold. Following plasma filtration the plasma was warmed, reunited with the blood, and returned to the patient without plasma product replacement. Cryofiltration has been used to treat patients with dozens of different diagnoses. In addition to the procedures performed at the Cleveland Clinic, studies were performed at the Vanderbilt University and the Department of Veterans Affairs Medical Center in Nashville, Cedar Sinai Medical Center (Los Angeles), Rush Presbyterian St. Luke's Medical Center (Chicago), and Tokyo-Tokatsu Clinic (Chiba). The first clinical application of cryofiltration was carried out on a 62-year-old female with functional class IV rheumatoid arthritis and presented with prior joint replacements. She was institutionalized and could do very little on her own. She had been diagnosed with rheumatoid arthritis since the age of 15.[21] Her blood chemistries indicated the presence of cryoproteins. Not knowing the frequency to treat, we chose three times in the first week and then she was maintained on a twice weekly schedule for several months without immunosuppressive drug therapy. C1q binding immune complexes were significantly reduced and despite reductions of rheumatoid factor by filtration its level showed only a slight decrease in the patient's blood. Clinical signs correlated with the immune complex level and the volume of plasma treated. We treated her for months, gradually decreasing the frequency of treatment over 4 years. In time she regained some functions. Important to note, treatment frequency decreased over time. A concern in the application of apheresis treatments in disease states is the lack of understanding of the biological changes. While there is a need for control trials, the design must be very carefully evaluated and on-going assessment are critical and pre-controlled trials carried out where appropriate.

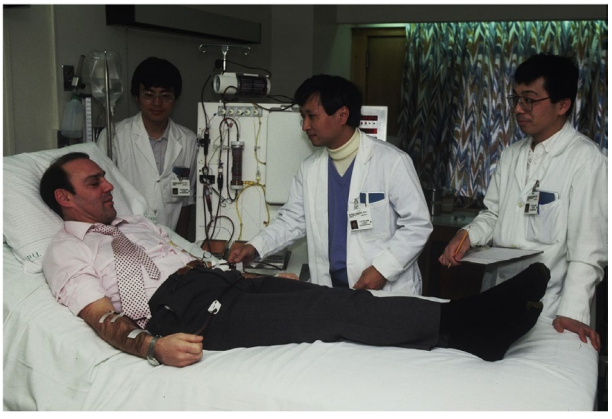

FIGURE 2 Author undergoing a cryofiltration procedure performed by his colleagues preliminarily to patient clinical trials. [Color figure can be viewed at wileyonlinelibrary.com]

From our investigations and studies of cryoprecipitable proteins from cryoglobulinemia patients,[22–24] cryoprecipitable proteins inhibited the blastogenesis on normal mononuclear cells and inhibited neutrophil phagocytosis with suppression concentration dependent; lymphocytes showed increases in proliferation pre- to post-cryofiltration to the mitogens phytohemagglutinin, concanavalin A, and pokeweed mitogen showing prior suppression of both T and B cells; and cryoprecipitable proteins had a suppressive effect on normal lymphocyte proliferation; patients' plasmas with cryoglobulinemia were inhibitory to normal granulocyte chemotaxis per the Agarose method. In disease states, just what are the short-term and more importantly the long-term effects of such toxic macromolecules in the blood and tissues in chronic diseases? As demonstrated in these studies of cryoglobulinemia patients, the biology has been modified and the effects are seen also in the various cells. While the treatments are designed for removal of macromolecules, the effects are seen also in the cell populations.

Our research extended to the study of lipid abnormalities. As noted in Figure 3, the size differences between the low density and very low-density lipoprotein (LDL-VLDL) (so-called bad cholesterol) and the high-density lipoproteins (HDL) (so called good cholesterol) fractions in plasma are quite significant and we were able to identify membrane filters that could separate the “bad” and allow the “good” to pass. In this scheme of thermofiltration, we warmed the separated plasma to about body temperature

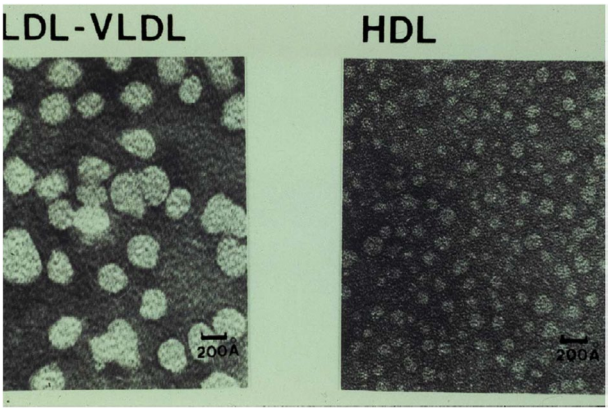

FIGURE 3 Microscopic visualization of the sizes of the low density and very low-density lipoprotein (LDL-VLDL) and the high-density lipoproteins (HDL) fractions in plasma. [Color figure can be viewed at wileyonlinelibrary.com]

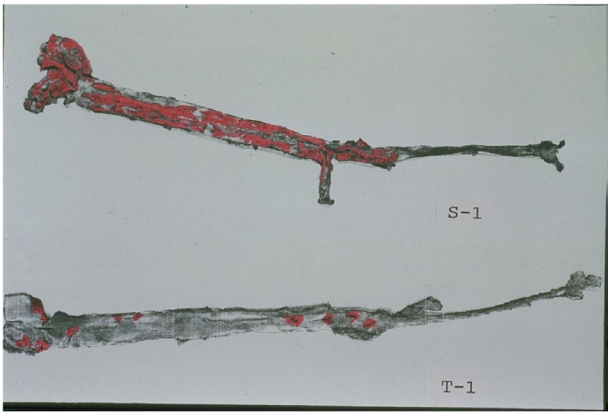

FIGURE 4 Visualization of aortic atherosclerotic plaque from homozygous Watanabe heritable hyperlipidemic rabbits. The study showed 44.2% coverage (top, S-1) in the untreated animals compared to the thermofiltration treated rabbits with 15.0% coverage (bottom, T-1). [Color figure can be viewed at wileyonlinelibrary.com]

which allowed larger plasma volumes to be processed. and more compared to ambient temperature.[25] In studies on hypercholesterolemic dogs, lower LDL/HDL ratios were maintained for up to 2 weeks.[25] Initial clinical thermofiltration procedures were performed on a secondary hypercholesterolemia patient. The procedures were well tolerated and without adverse reactions.[26] In rabbit and dog hyperlipidemic models, magnetic resonance imaging investigations using the chemical shift selective 1-3-3-1 imaging sequence allowed the noninvasive imaging of plaques that were confirmed by investigations of aortas at autopsy.[27] Figure 4 visually shows the results. The thermofiltration treated rabbits show that the progression of aortic atherosclerosis was stopped with treatment.[28] Studies by others show that regression is possible with therapeutic apheresis.

In the various clinical studies with plasma treatment for the removal of macromolecules, the beneficial effects of solute reductions last longer than would be expected from the physical removal of these large solutes from the circulation, for example, such as improved phagocytic activity. We referred to this as the "X-effect". In a sense, these macromolecules are like "smoke in a fire". Clearing the smoke may activate the biological system to return to normalcy and allow pharmacological agents to work more effectively. We have seen in cryoglobulinemia and rheumatoid arthritis patients treated with cryofiltration that the removal of cryoprecipitable proteins improved cellular functions as noted above. In biliary cirrhosis patients treated with charcoal and an anion exchange resin improved cellular functions.[29] In hypercholesterolemia patients treated by thermofiltration, LDL cholesterol remained lower for an extended period.[30]

4 | ARTIFICIAL ORGAN TECHNOLOGIES FOR THERAPEUTICS, HEALTH, AND WELLNESS

Most, if not all, diseases develop over time. Cryoglobulinemia is associated with liver, renal, musculoskeletal, and neurological diseases.[18] Renal tissue losses can begin in the teens. Symptoms of Parkinson's appear only after 60–80% of the nerve cells that make dopamine are lost. In a report from the University College Cork, note is made that inflammatory molecules in blood are seen in the 40s and 50s and maybe aging our brains.

The normal detoxification processes are lacking in disease states. "Factors" accumulate leading to pathological processes,[17] at times in response to the disease processes. Normal removal processes become deficient. The uptake of "factors" by cells leads to impairment. Aggregation of proteins occur in some cases with enrichment of other factors.[31] One approach is to remove the degraded and aggregated "factors" as by therapeutic apheresis that can improve cellular functions and stimulates biological processes to restore the norm.

When a cell begins to turn cancerous, it can become senescent and not divide but secrete signaling molecules that stimulate regeneration and repair; but can over time, as more cells turn senescent, the levels of these secreted molecules stop positively influencing their neighbors and begin to cause inflammation. With the accumulation of abnormal proteins there is impairment of cellular functions. An approach is to reprogram senescent cell.[32] In addition, there is the formation of degraded proteins in the cytosol. Protein accumulation results from impaired protein degradation with age. Misfolding of proteins lead to their non-function

and aggregation and accumulation that increases with age[33]; many diseases are driven by protein aggregation (i.e. Parkinson's, Alzheimer's, Huntington's ALS).[34] Human cells intentionally collect aggregates to prevent other cellular damage, which can spill over to the plasma.[35,36]

With age and disease there is a loss of cellular protein quality control.[33] There is an increased production of toxic protein clumps and aggregates. Genetically changed worms are used to study the aging process; it has been shown that proteins change in abundance impairing their functionality leading to surplus protein contributing to death.[33] Longer-lived worms deposit surplus and harmful proteins in insoluble aggregates that are enriched with helper proteins (chaperones) that prevent the toxic effects by aggregates.

Some approaches proposed to address senescent cells are to develop therapeutic pharmacological agents to target them, reprogram them,[32] or deactivate them. Furthermore, an "artificial organ" approach would be to remove the "toxic" compounds where there is a role for therapeutic apheresis. Can therapeutic apheresis serve as an artificial senescent cell? We have seen that the accumulation of pathological molecules can lead to various chronic disease states including autoimmune, cardiovascular, and cancers of varying types.

5 | FUTURE PROSPECTS

Looking back at the progress made and with present development, the future is bright for dealing with chronic and debilitating diseases. Where will the next break throughs come from: artificial intelligence, xenotransplantation, data collecting wearables, brain implants, etc. How will national regulations and budgets impact development, innovation, and clinical applications? What will be the continuing impact on healthcare of artificial organ technologies? What will be the approach? With better diagnostics and earlier treatments, can end-stage diseases be delayed?

Can artificial organ technologies be applied more so for therapeutics? As I recall Dr. Yuki Nosé's remark "we are developing "pre-priest" devices", that is to say that before the medical team calls in the priest to provide the last rites for the patient, they call in the artificial organ team to give it a try. On several occasions I recall that was the case to support liver failure patients, some of which were in a coma. Imagine earlier treatments with systems designed for intermittent needs for therapeutics to avoid end-stage diseases and systems designed for health and wellness. To reach such goals, I propose a prescription for success: develop deep friendships in your field, build strong collaborations for cooperation, embrace lively competitiveness, and seek out the best technologies and medical truths.

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