The Multidisciplinary Approach to Develop Artificial Organs

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Key Words

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Abstract

This paper presents the author's perspective of how artificial organ development has evolved in the past 35 years into a multidisciplinary effort. Examples are taken from the fields of hemodialysis, oxygenators, and affinity immunoadsorption devices. Development of the multidisciplinary approach to develop dialysis and oxygenation membranes has been significantly advanced by private and governmental collaboration and conferences that gathered together chemists, physicians, engineers, and fluid dynamics experts. Lengthy delays occurred in artificial organ development when such interdisciplinary collaborations did not take place.

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I want to draw your attention to a trend in science that has great benefits not only to society as a whole, but also to the science practitioner. It is the increasing collaboration between experts in different disciplines to solve difficult technical problems. There is an analogy in the practice of medicine where referrals to subspecialists has been com-

mon practice for years. But in the physical sciences, the practice has been slow to develop. In this paper I want to share some examples from my past experiences that illustrate both the benefits of such collaboration – and the price in development time we pay when we fail to do so.

Graduate students of my generation who finished at Tulane University were classified as specialists in one of four fields of chemistry: inorganic, organic, physical, or analytical. Biochemistry was considered a medical school discipline and was not taught in the 'higher halls' of learning. Engineering was considered an applied art, not yet a science. But this discrimination was prevalent not only in those subjects that were part of an Arts and Sciences curriculum; even in the accepted specializations, there was a sense of superiority, an aloofness, with respect to new disciplines. The fastest growing segment of chemistry at the time dealt with polymeric products, but polymer chemistry was not yet considered a 'science'. Many of us had to learn polymer science by experience. And it was polymer science that made possible the membrane developments we now depend on for preparing ultrapure water, dialyzers, oxygenators, and even such mundane things as catheters.

This compartmentalization was not unique to chemistry: engineers were working in similar isolation. Chemical engineers were jokingly referred to as 'boilermakers' and received little or no training in the chemical side of their discipline. If you are less than 50 years old, I do not think

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you can imagine what it was like to do research in those isolated environments. But by some strokes of luck, my early career in fiber chemistry put me in close contact with organic chemists, with physicists, and with some of the early polymer chemists. So I had the benefit of some interdisciplinary training. I am convinced these collaborations helped my career.

It is the benefit of interdisciplinary cooperation that I want to illustrate in this presentation with a few examples and recommend to you. Let me compare those days to my current position. I work in a nephrology division which has ten physicians on the faculty, two of whom have PhDs in biological sciences. There is also a PhD pharmacokineticist on the faculty, who can teach us statistics and kinetics, as well as a PhD chemical engineer who has been busy quantifying hemodialysis process, heparin dosage, and pure water production. One of the physicians is also the director of the proteome analysis center for the university. I am the lone chemist, but in this environment I can contribute to almost all of their projects.

This change in interdisciplinary effort over the years can be used to illustrate how collaboration has benefited the field of medical devices – and more importantly – how its absence has, at times, delayed progress in the field. There are many more examples, but I will use three to illustrate what I mean in this paper:

The first illustration deals with the evolution of early hemodialysis techniques into the sophisticated technology we now offer patients; the second example deals with the improvement in oxygenator performance by the incorporation of some fluid-dynamic principles, and the third discussion is about a technology which has not yet realized a major application, but which will eventually find a niche in the medical device market: immunoadsorption using affinity membranes.

In the early 1960s, after 12 years in government and industrial research, I took a job directing a division of a nonprofit research institute, called Gulf South Research Institute. Then, just as now, the major sponsor of research was the US Government, and my job was to find answers to problems the government was willing to pay for. By then I had quite a lot of experience in polymer and fiber chemistry and two programs attracted me. One was the US Department of Commerce's Saline Water Purification Program to develop better reverse-osmosis membranes. This was just a few years after Loeb and Sourirajan had demonstrated the use of asymmetric cellulose acetate membranes to desalinate brackish water. My group worked on that, but that is a discussion for another time.

Another program of great interest to me was a special project under NIAKDD called the 'Artificial Kidney and Chronic Uremia Program'(AKCUP) This was organized to improve and broaden the application of hemodialysis procedures first demonstrated for acute uremia treatment. The program endeavored ... 'to bring about improvements in artificial kidney apparatus and methodologies, to increase their effectiveness and decrease their costs, and to improve the rehabilitation of patients treated with chronic intermittent dialysis' [1].

To attract the best talent to the AKCUP, its director, Dr. Ben Burton, convinced NIH administrators that they should offer a contract program as well as a grant program and that it should not be limited to nonprofit organizations. The participation of industrial laboratories brought a variety of new disciplines to the hemodialysis field. That helped to create a highly competitive environment: not only did one compete with academic research groups, but many major corporations wanted to participate, perhaps for the prestige of solving a difficult medical problem. This was before Medicare coverage of end-stage renal disease, and there was certainly no commercial incentive yet.

There were several thrusts in the program, and one dealt with the development of improved membranes. I wrote a proposal to develop more selective membranes using polypeptides made via their N-carboxyanhydrides and waited to see how we would score. Before we even got a contract from the NIH, I was invited to the first of two meetings that I think had a significant influence on the development of artificial organs. The first meeting [2] was in 1967 and was held at the Blood Research Institute at Harvard. That was really my introduction to medical device development work. The Boston meeting was a multidisciplinary gathering of surgeons, chemists, nephrologists, engineers, and biochemists. It had a significant influence on my thinking in the coming years, as I focused more on medical devices.

In figure 1a is shown the program cover page for the Boston meeting. I want to use statements from the Boston meeting to illustrate my theme: interdisciplinary collaboration leads to more rapid progress in artificial organ development.

At the Blood Research Institute Meeting in Boston, the talks were about blood oxygenation, hemodialysis, and natural membranes. Let me cite just three statements from the meeting that describe the state of the knowledge then.

The first statement was by Dr. Ben Lipps, a chemical engineer and manager of the Dow Chemical hollow-fiber

Fig. 1. First conferences after establishment of AKCUP. **a** Blood Research Institute, Proceedings of the Meeting at Harvard University. **b** Report of 1st Contractors' Meeting of the AKCUP in Bethesda, Md., USA.

spinning project. Ben's group had already produced cellulose acetate hollow fibers and were attempting to convert them to cellulose hollow fibers before packaging in tube and shell hemodialyzers. Ben wrote in the program:

'To determine the actual fiber permeability, the influence of the dialysate resistance was greatly reduced with the agitated dialysis bath.'

It was known in 1967 that the blood flow in the fiber lumens would be laminar flow, but there was not any experience on how to analyze the shell side flows that influence transport from blood to dialysate. All the related experience was with heat transfer devices not made with soft floppy tubes that could move in the stream. In a section to follow, I will show an easy approach to analyzing shell side flow, now that we understand it better.

The second statement from the Boston meeting comes from Dr. Albert Babb. He was head of the nuclear engineering faculty and a design engineer at the University of Washington. He recognized that a lot of the confusion in comparing dialysis performance with various membranes was caused by the great differences in fluid resistance encountered in different plate and frame designs – the style of dialyzer most commonly used in the late 1960s. In Boston, Dr. Babb suggested that the membrane research community should establish a test dialyzer design with predictable fluid boundary resistances for evaluation of progress in hemodialysis membranes.

His suggestion led to a broad collaboration between scientists of varied disciplines. Evaluating new hemodia-

lyzers involved not only the polymer chemists and engineers, but, as I will show you later, toxicologists, hematologists, and pathologists as well.

At the same Boston meeting that had such influence on dialyzer development, we heard from Pierre Galletti, a surgeon, whom many of us considered the smartest fellow we had ever met. In speaking about oxygenators, he said: '... synthetic membranes per se do not constitute at the present time the limiting factor of gas transfer in blood-gas exchange devices' [3].

His experience at that point had been limited to thin coatings of silicone polymers on supporting membranes and with very thin Teflon membranes. In his future were microporous fibers, where his statement was even more applicable. The problem was not in transmembrane kinetics, it was in the plasma boundary layers. If that had been recognized in 1967, extracorporeal membrane oxygenation would have been in practice many years earlier.

The second meeting that I believe had a significant impact on artificial organ development was the 1st AKCUP Contractor's Conference. It took place in January 1968, just a few months after the Blood Research Institute conference. The cover page of that report, now only available as a microfiche, is shown in figure 1b. These were some of the summary statements from that meeting:

'... Of necessity, the experience of investigators in many disciplines – must be brought to bear on a problem of this complexity ... the Proceedings are published ... to present the results to date of this multifaceted approach undertaken by this Program ...'

Table 1. Some of the contractors reporting at the 1st Annual Contractors' Conference of the AKCUP, January 1968

Contractor	Objective
Aerojet General	High-flux cellulose acetate membranes DEAE-cellulose
Dow Chemical	DEAE-cellulose acetate Cellulose hollow fibers from cellulose acetate
MIT	Daily dialysis; wearable kidney
Monsanto Research	Acrylic hollow fibers; nonthrombogenic surfaces
Gulf South Research Institute	Selective membranes from poly(methylglutamate)
Batelle Research Institute	Heparin-linked membranes
IIT Research Institute	2nd source for cuprammonium membrane

'... hemodialyzers now used can be divided into two designs. The first is the parallel plate, where blood flow on one side ... The second is the tubular, where blood flow in a tube ...'

'... much work has gone into the study of new membrane materials ... with the attempts to control or enlarge pore sizes ... One will be able to increase mass transport and thus reduce the time and membrane area required ...'

but concluded:

'... it is pertinent to add that despite all these accomplishments, further advances are still dependent upon a clearer understanding of the "toxic" substances in uremia ...'

The interdisciplinary structure of the AKCUP made such collaboration simpler and was, I believe, a major achievement of this special NIH effort to improve the treatment of chronic uremia.

Table 1 lists some of the contractors and their topics of research reporting at this 1st Annual Contractor's Conference. At the start of the program, all hemodialysis membranes, in tube and sheet form, were made of regenerated cellulose. One factory in Germany produced nearly all of the dialysis membranes used in the USA, and there was a serious concern that no alternate supplier was available in case of a factory accident. As a result, a number of projects were started to provide alternative sources of membranes, with the added hope that they would produce improved performance when compared to the cellulosic films.

The polymer chemists in one of the earliest membrane research groups, Aerojet General, were successful in preparing cellulose acetate and aminated cellulose acetate

(DEA-CA) membranes with a wide range of transport properties. Even with relatively crude measurement techniques, they showed that higher solute clearances were attainable with these new membranes when compared to the then ubiquitous Cuprophane (Akzo, Wuppertal, Germany). Today we use cellulose acetate membranes, although in fiber form, with similar properties. But when this group produced membranes for clinical trials, they found that only lower clearance membranes could be accepted – because high clearance was accompanied by a high ultrafiltration rate (UFR). And there was no means of limiting patient fluid loss with the then available dialyzers and dialysate control machines.

We experienced the same dilemma with our polypeptide membranes: they had to be made with properties similar to Cuprophane to provide the fluid loss control that came from pulling dialysate through plate and frame dialyzers, such as the Kiil. So for more than 10 years, no really improved membranes could be used clinically, because there was no way to control UFR with highly efficient membranes. Looking back on it, I still cannot understand how we missed such opportunities. The delay of mechanical engineering collaboration to produce a volume-controlled dialysate mixer was a major failure of the AKCUP, and in this instance it reflected the lack of collaboration between dialyzer producers and machine manufacturers.

The solution came in the late 1970s, when Rhône-Poulenc offered a closed-tank reservoir dialysate system, so that their high UFR AN-69 membranes could be used. This was soon followed, in Germany, by the introduction of the Fresenius 2008 controllers which used balancing chambers to control the UFR, no matter how permeable the membrane used. Once the 2008 machine was available, the introduction of new membranes – especially in fiber form – blossomed.

The absence of a collaboration between membrane-producing groups and the machine manufacturers was the basis of this long delay in introducing better devices. Akzo, the major membrane producer of the time, produced only low-flux membranes, had no machine development group, and had no need to introduce volume controllers. The companies making dialysate-mixing and metering equipment did not make membranes, so did not recognize the obstacle facing introduction of new membranes.

Only when Rhône-Poulenc wanted to introduce their higher-flux poly(acrylonitrile) membranes commercially was machine development recognized as a need. The pressurized tank they introduced had a series of operational difficulties and was soon displaced by the Fresenius

Fig. 2. a Water displacement by saline solution in the shell of the dialyzer. The x-axis is the normalized shell volumes; the y-axis is the reduced conductivity. **b** Differential of outflow rate for a well-packed dialyzer.

2008. This machine, in turn, induced Fresenius to enter the membrane production field by introducing poly(sulfone) hollow fibers.

Although polysulfone is an extremely hydrophobic polymer, and not water wettable, it was possible to produce functional hemodialyzers with this material. The fibers were made wettable by the incorporation of poly(vinylpyrrolidone) into the extrusion solution [3], based on research done to produce reverse-osmosis hollow fibers. This polymer allowed the production of very high UFR hemodialyzers. Coupled with precise volume control, the combination has led to dramatic increases in dialysis efficiencies.

The Dow project listed in table 1 was to produce cellulosic hollow fibers by extrusion of cellulose acetate hollow fibers, followed by hydrolysis. Because the resulting fibers had only low UFRs, no volume controllers were needed, and the project could proceed to clinical trials as soon as some mechanical sealing problems were resolved. The Dow group benefited by having a variety of disciplines

working together. Mass transfer was recognized early on as a major problem, especially on the shell side of the fibers. The cellulose fibers were soft and had a tendency to clump together, so characterizing the shell side transport as difficult.

In our laboratories, we recently developed a rather simple way to get an estimate of shell side efficiency. The fibers are filled with an oil, such as olive oil, and the shell is perfused with water. At a designated moment, the perfusion is switched to saline solution, and the conductivity at the outlet of the shell is monitored. If there were pure plug flow through the shell, an instantaneous increase of conductivity would be experienced at the outlet, once the void volume of pure water had been displaced. In practice, we often see an early breakthrough of salinity exiting the shell followed by a retarded flow of water leaving the shell. Taking the differential of conductivity versus reduced volume (i.e., Qt/V_0) gives a distribution of retarded flow. For ideal plug flow, the derivative would be a single line at $\theta = 1.0$. In figure 2 are shown the breakthrough and

Fig. 3. Differential of outflow rate for a poorly packed dialyzer.

Fig. 4. The first hemodialyzer evaluation monograph (a) and its contributors (b).

derivative curves for a well-packed dialyzer. Notice that the derivative is nearly symmetrical about the $\theta = 1.0$ axis, with very little tailing toward the $\theta > 1$ end of the axis. In figure 3, the same plots for a poorly packed dialyzer are shown. Now one sees a very early spike of salinity well before the void volume has been displaced, indicating that the salt solution has reached the exit port before the bulk of the shell water content has been displaced. The test is quick and can easily identify problems with packing density, fiber clumping, and channeling. To illustrate my collaboration point, I have to tell you that a chemical engineering MS student working with us in the Department of Medicine developed this apparatus and the method.

To close this section on collaborative work in dialyzer development, figure 4a shows the cover page of a study group report sponsored by AKCUP 10 years after the pro-

gram began [4]. Dr. Babb had suggested the core portions at the Blood Research Institute meeting in 1967. The report was entitled 'Evaluation of Hemodialyzers and Dialysis Membranes'. In figure 4b are listed the contributors. The authors included two chemists, two nephrologists, a nephrologist/physiology MD/PhD, a toxicologist, four chemical engineers, and a pathologist. It was interdisciplinary collaboration at its best, since it considered not only the efficiency of the device, but also the effects of devices on the patients. The report has served as a guideline for dialyzer development for years, and rare copies of it still appear on some bookshelves.

Another positive example of fruitful interdisciplinary collaboration can be taken from the oxygenator field. Recall that Dr. Pierre Galletti had already concluded that membranes (thin-film silane composites, in his case) were

Fig. 5. **a** Schematic of red cell distribution in laminar flow within a hollow fiber. **b** Schematic of extraluminal flow through fiber mat.

not the major resistance in oxygen transport. In the years following his statement, dense membranes were replaced with even more O_2 -permeable microporous hollow fibers, but his conclusions remained valid. The major resistance to oxygen transport lies in the film of plasma between the surface of the exchange membrane and the flowing red cells. In lumen flow in hollow fibers, the lift forces tended to move the red cells toward the center line of the fiber, away from the fiber wall, thus thickening the plasma boundary layer. Oxygen introduced at the microporous fiber wall must diffuse through the plasma layer to reach the cells. But the low solubility of oxygen precludes high concentration gradients. Thus the solution of the problem requires a closer approach of the cells to the fiber wall. Since the system operates under laminar flow, higher lumen flow rates are not a solution. The eventual solution [5, 6] – provided by engineers with fluid mechanics backgrounds – was to have the blood flow externally to the fibers arranged in a fiber mat. The concepts are illustrated by figure 5. The effect of extraluminal flow (ELF) on gas transfer is seen in figure 6 which plots gas transfer rate versus pressure drop in the blood channel. With the higher specific transfer rates, it was possible to produce oxygenators of lower blood contact area, leading to improvements in hemolysis and thrombosis.

A further advantage to the ELF flow is encountered in the case of thrombus formation. If the flow is intraluminal, the entire fiber is blocked from a single clot. With

Fig. 6. Transfer rates for extra- and intraluminal flow. Blood oxygenation inside versus outside blood flow.

ELF, only the point where the clot shadows the fibers is lost to gas transfer. This is illustrated in figure 7. The net result has been a decrease in the blood contact area required for oxygenation, with a major accompanying decrease in the required extracorporeal blood volume

Fig. 7. Schematic of clot handling with intra- and extraluminal flows.

needed for operation of the exchangers. A number of disciplines contributed to this advance in oxygenation, but the major improvement was the recognition of the fluid boundary problem.

One more example of the benefits of interdisciplinary collaboration in artificial organ development came out of efforts to develop improved apheresis. This story begins in March 1983 at a meeting held in Rottach-Egern, Germany. It was sponsored jointly by the University of Munich and the ISAIO to discuss the then emerging field of therapeutic plasmapheresis. Participation was by invitation only, and the organizers limited attendance to 'experts in cellular immunology, rheumatoid arthritis, or mass transfer, and all shared a common interest in plasmapheresis ...'. The discussions of this eclectic group took place only a few years after it had been demonstrated that removal of immunoglobulins via membrane plasmapheresis could be carried out beneficially for several diseases. A number of techniques were discussed and compared, including cascade filtration (to recover some of the albumin), cryofiltration (to remove selected fractions), and direct microfiltration with plasma replacement. The biochemical objective of apheresis was generally the removal of IgG and/or IgM and their immune complexes. The initial procedures relied just on the separation of plasma from whole blood, with the patient plasma discarded and

replaced either with fresh frozen plasma or albumin solution. Cascade filtration was a two-step process which attempted to conserve patient albumin for reinfusion. The extent of treatment, when plasma was discarded, was limited by the depletion of fibrinogen levels; this, in turn, restricted the fraction of immunoglobulins that could be removed. It was generally agreed that the then available membrane techniques offered some advantages over centrifugal separations, in terms of simplicity; in the case of two-stage filtrations it provided lower costs of replacement fluids. But as one examined possible applications for removal of specific antigens, it was clear that the membrane separations were too crude to achieve selective removal. As a consequence, both in the preface and in one of the final papers of the meeting, the projection was made that it would take development of immunoadsorption techniques to bring true specificity to this therapy.

Preliminary reports on immunoadsorption bead columns had been reported by Terman et al. [7] using a crude DNA ligand adsorbed to activated charcoal. The application problems had not been investigated at that time, so the simple approach was to take the biochemist's tools of bead columns and perfuse with plasma separated using a microfiltration device. By 1993, the field had advanced significantly. Du Moulin et al. [8] reported their work on polyclonal antibodies attached covalently to Sepharose

beads for the removal of low-density lipoprotein and IgG.

In parallel to these clinical applications, the biotechnology industry was wrestling with a similar problem: the purification of biological products from tissue culture or other growth media. Broad-category ligand columns, such as ion-exchange columns, were being used for protein concentration and purification. Like the poorly selective membranes being used in plasmapheresis, the ion-exchange materials were not providing sufficient selectivity. Both fields were heading toward a similar solution: affinity chromatography.

Cuatrecasas et al. [9] had shown 15 years before the Rottach-Egern meeting that it was possible to chemically immobilize a ligand to a porous gel bead and to use this matrix for the selective capture of biologicals from complex mixtures. The method was being developed initially as a laboratory tool, but it soon showed promise for larger-scale applications, such as protein recovery from bacterial fermentations. There were similarities in the two separation problems: both dealt with dilute-soluble targets in a dispersion; both required sterile systems; both had to operate quickly to process volumes up to 5 liters to avoid biological degradation (in the case of bioproducts) or thrombosis (in the case of plasma processing), and both applications needed multiple uses of costly ligand matrices.

Increasing the size of the laboratory affinity columns to adapt them for biotechnical or clinical use is not a satisfactory solution for scale-up. The fundamental problem is diagrammed in figure 8. The solute to be bound by the ligand perfuses the surface of the beads, but must diffuse, often slowly, into the bead interior to be bound. To fully utilize the capacity of the ligand bed, the residence time at the bead surface must be sufficiently long to allow for this diffusion. If it is too short, a significant portion of the solute will remain unbound and exit the column before the ligand sites are saturated. The relationship between the time needed for diffusion to the bead core, t_D , and the residence time of the solution on the column, t_C , was given by Brandt et al. [10] in terms of the Peclet number:

$$Pe = \frac{t_D}{t_C} = \frac{\frac{L^2}{D}}{\frac{V_0}{Q}} < 0.01$$

where L is the length of the diffusion path (bead radius), D the diffusivity of the ligate, V_0 the interstitial volume of the bed, and Q the perfusion rate. To process large volumes, one has limited choices: increasing the bed volume

Fig. 8. Relationships between time needed for diffusion and available residence time for a packed bead column.

allows an increase in perfusion rate, but with an increased cost of expensive ligand. Using smaller beads allows higher perfusion speeds, but is limited by increased pressure drops and compaction of the sorbent bed. The columns that have reached clinical application have made compromises in performance to satisfy both capacity needs and treatment times. In recent years the availability of clinically useful immunosorbent devices has grown, albeit slowly. A summary of the group-specific adsorbents is shown in table 2.

The relatively large column sizes demand corresponding extracorporeal blood volumes and, in the case of expensive ligands, high prices. Those that are regenerable work in pairs, as indicated in table 2. All but the DALI device require preliminary separation of plasma. Sepharose-based bead columns are generally used in pairs, so that they can be cycled between adsorption and regeneration.

About 10 years ago, my laboratory began work on developing immunosorption membranes to overcome some of the limitations cited for the bead geometry. Covalent linkage of immunosorbents to the pore surfaces of microporous membranes produced diffusion paths $< 0.1 \mu\text{m}$, so that the perfusion speeds can now approach the limits of complexation rates. One consequence of this high perfusion rate is that smaller devices can be used, because the recycling time is also very short. A number of papers describe this work [11–18], but here I want to focus on just a few aspects. Our work initially concentrated on immobilizing recombinant protein A onto microporous hollow fibers. Increased capacity for IgG was achieved by the use of selected leash lengths and by the choice of linker chemistry. But a capacity of 30–40 mg ligand/ml membrane appears to be a practical limit. The theoretical bene-

Table 2. Group-specific adsorbent columns available in 2003

Device name	Target	Ligand	Producer	Size, ml
LDL-Therasorb	LDL via apo B	Sheep Ab to apo B on Sepharose	Plasma Select, Teterow, Germany	2 × 300
Immunosorba	IgG w/some IgM, IgA	Protein A on Sepharose	Fresenius, St. Wendel, Germany	2 × 62.5
Prosorba	IgG w/some IgM, IgA	Protein A on silica	Fresenius	300
Globaffin	IgG	Peptide-GAM on Sepharose	Affina Immuntechnik, Berlin, Germany	2 × 60
Ig Therasorb	IgG w/some IgM, IgA	Sheep Ab to human IgG on Sepharose	Plasma Select	2 × 300
Immusorba	Immunoglobulins, fibrinogen, and others	Tryptophan or phenylalanine on PVA	Asahi Medical, Tokyo, Japan	350
Selesorb	LDL and Lp(a)	Dextran sulfate on cellulose	Kaneka, Osaka, Japan	2 × 150
DALI ¹	Lipoproteins	Polyacrylic acid grafts to polyacrylamide	Fresenius	300–1,200

¹ The only beads large enough to handle whole blood.

fit on allowable perfusion rate due to shorter diffusion paths was clearly demonstrated, as shown in figure 9. This compares the effective capacity (i.e., IgG captured in milligrams per milliliter membrane volume before the effluent IgG concentration reached 10% of the inlet) for protein A immobilized on Sepharose beads and on the 0.2- μ m pore size hollow fibers. By the time that the perfusion rate reaches five times the bed volume per minute, essentially all of the IgG will pass the column without capture, but the hollow fibers have lost <10% of their equilibrium capacities. The fiber unit can operate at much higher perfusion rates; it is eventually limited only by the time required for the reaction between protein A and IgG to form a complex.

For therapeutic IgG adsorption the hollow-fiber design is dependent on the equilibrium capacity that can be attained and on the packing density of the membrane in the housing. The latter may seem to be a strange variable; after all, why should the empty space pose a problem? It becomes important because of the need to recycle the capacity of the sorbent, especially when the target molecule in the plasma is as prevalent as IgG. As an example, assume that the IgG capacity of an immunosorbent fiber bed is 30 mg/ml and that the fibers occupy 50% of the space in a 50-ml housing. The capacity of the unit would be 750 mg, and it should clear 75 ml of plasma in a single pass. Two units working together provide continuous removal of 75 mg of IgG per pass. But when the first unit is saturated and the 2nd is placed on-line, the plasma remaining in the exhausted unit (25 ml) together with the last saline in the rinse after regeneration and prior to reuse of the unit will pass back to the patient. Thus, for each 75 ml of plasma cleared, the patient is volume expanded by 25 ml, if the packing density is 50%. If the packing

density is lower, or the IgG capacity is lower, more volume expansion occurs. While this can be dealt with by incorporation of a small ultrafilter into the line, it adds another dimension of complexity. The development of efficient immunosorbents will require improvement in selectivity and specific capacity (a biochemistry problem), better packing configurations (a membrane problem), and clever cycling protocols (an engineering problem). The need for collaboration among several disciplines is obvious.

When more selective ligands are available that target a specific immunoglobulin, the problem becomes easier because the required capacity is less. One such example is the removal of anti-Gal alpha 1–3Gal antibodies which contribute to the hyperacute rejection of xenotransplanted organs. We produced and linked Gal alpha 1–3Gal oligomers (fig. 10) to hydrazide-modified microporous nylon membranes [19] and showed that the immobilized oligomers could achieve complete antibody inhibition at 1 mg oligosaccharide per milliliter normal human plasma. The membranes were linked with >2 mg carbohydrate per milliliter bed volume. In the case of such dilute antibody concentrations, a single-use device with high flow rates would be relatively easy to produce.

Another problem with bead columns (except for the DALI device) and microporous membrane absorbers is the complication of producing particulate-free plasma. With the help of Dr. Ulrich Baurmeister, a very clever engineering colleague, we addressed this for two different applications. One was the removal of IgG, the other was the removal of postoperative heparin. His plasma isolation concept is illustrated in figure 11 [20]. The ligands are immobilized within the pore structure of microporous fibers. As whole blood enters the module densely packed

Fig. 9. Bead columns lose their capacity rapidly with increasing perfusion rate. Membranes can operate at 10 BV/min with 85% capacity retention.

Fig. 10. Galactosyl galactose ligand for binding human anti-Gal antibodies. Membrane-immobilized Gal alpha (1-3)Gal affinity ligand for prophylactic binding of human anti-(Gal alpha 1-3 Gal) antibodies for prevention of hyperacute rejection of pig xenografts [from ref. 19].

with the fibers, there is a pressure differential between the outside of the fibers (the shell side) and the fiber lumens. Plasma is convected through the fiber wall, and the pressure difference between shell and lumen decreases from the entrance point to the module exit. At the end of the fiber, there is no pressure difference, and plasma and concentrated blood are recombined. The ligands bind the target molecules, as the plasma traverses the fiber walls. Fig-

Fig. 11. Schematic for internal cross-flow-induced adsorption.

Fig. 12. Depletion of heparin from a 100-ml whole-blood pool by direct extraction using internal cross-flow modules of three different lengths.

ure 13 illustrates the depletion of IgG from a 100 ml reservoir of whole blood using such an internal cross flow (ICF) device whose fibers were modified with protein A. With an anion-exchange site attached to the pores, heparin is strongly adsorbed from the plasma. If necessary, the bundle can be recycled after a strong salt wash. Similarly, IgGs can be bound, if protein A is the ligand. This design works both with whole blood and simpler dispersions,

Fig. 13. ICF module depletion of IgG. **a** Fractional IgG depletion with urea and total protein as controls. **b** Rate of IgG binding by the fiber module.

such as gene-modified drugs produced in yeast. An example of heparin extraction from a whole-blood reservoir dosed to 5 IU/ml of heparin is shown in figure 12. Three different module lengths were investigated, each at a constant inlet pressure of 40 mm Hg. At a fixed inlet pressure, the resulting flow rate is inversely proportional to the fiber length. As a consequence, the mean residence time in the pool ($t_m = V/Q$) increases with the longer fiber units. The axis of the plot is normalized by expressing it as dimensionless time, t/t_m . For a pool volume of 100 ml and a module containing only 50 fibers, the reservoir was reduced by 90% within 12–20 min, depending on the fiber length.

I have tried to illustrate the benefits of interdisciplinary collaboration by selecting some experiences from well-developed technologies, such as dialysis and oxygenation, and from a new technology, immunosorption, that does not yet have wide applications. It is clear that medical devices are so complex that their conception and development require the work of many disciplines. And as they become more sophisticated, the need for early integration of the various scientific disciplines becomes more urgent. One of the great added benefits of these collaborations is the enjoyment that comes from learning about other aspects of science. My recommendation to you is to find a

smart colleague in another discipline who has the same interests as you do. Work will become more stimulating and bring much more fun for both of you.

Acknowledgments

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