SYNTHETIC POLYMERIC MEMBRANES: PRACTICAL APPLICATIONS— PAST, PRESENT AND FUTURE

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Abstract—The past decade has seen the rapid development of important laboratory and industrial applications of permselective, synthetic polymeric membranes, the majority of which involve molecular separations which in earlier times have been costly, difficult, or impossible to accomplish by other means. The hydraulic-pressure-activated treatment of aqueous solutions and process streams via the techniques of reverse osmosis and ultrafiltration, making use of controllably permselective, asymmetric membranes, constitutes the most advanced application of membrane technology today; such processes are now in widespread use for water-demineralization, waste-water treatment, food by-product recovery, and for isolation and purification of biologicals. Membrane ultrafiltration has also revolutionized preparative and analytical methods in experimental molecular biology and biochemistry, and has led to significant improvements in diagnostic laboratory practices for the assay of biological fluids such as urine, plasma and cerebrospinal fluid.

Hemodialysis continues to be the most important extracorporeal membrane-separation process in medical practice. Recent membrane developments promise at last to permit efficient dialytic removal of "middle-molecule" impurities from blood, and to utilize ultrafiltration as a safe and improved alternative to dialysis for blood purification. Novel membranes with high O_2/CO_2 permeability are being evaluated for use in efficient hemoxygenators or "artificial lungs".

Synthetic polymeric membranes are now embodied into novel pharmaceutical products called Therapeutic Systems, which deliver drugs to specific body sites at precisely controlled rates for prescribed periods of time, for safer, more effective, and more reliable disease treatment.

Separation of gaseous and volatile liquid mixtures by membrane permeation continues to be a subject of intensive research, although practical large-scale separation processes of this type remain to be developed. Permselective gas-separation membranes are being used to increase the sensitivity and accuracy of gas-chromatographic analytical instrumentation.

Ionically permselective membranes (of the classical ion-exchange, or diffusible ion-carrier type) are being used industrially in such processes as electrodialysis, and as the detecting elements of potentiometric ion-analyzers. The relatively new concepts of "facilitated diffusion carrier membranes", of immobilized-enzyme-containing membranes, and of "ionic mosaic membranes", whose origins stem from our increasing awareness of the structure and function of biological membranes, are today receiving intensified research and development interest, with potential application to gas- and electrolyte- separation and recovery, to detection and analysis of biological substances, to new methods of electric power generation, and the like. Pressures on human survival relating to environment, energy, nutrition, and health are certain in coming years to evoke applications of membrane science and technology which will make current progress in the field look primitive by comparison.

I. DISCOVERY AND EARLY HISTORY

The use of membranes to effect the separation, purification, identification, or fractionation of molecules or particulates in multi-component gaseous or liquid mixtures has a long and noteworthy history in science. Among the earliest observers of membrane-semipermeability was Thomas Graham[1] who in 1861 coined the term "dialysis" to describe the transmembrane diffusion process, and at the same time first differentiated between "colloid" and "crystalloid" (his terms) via membrane permeation. In the ensuing half-century, the use of then-available natural membrane materials (mainly animal tissue and vegetable (cellulosic) parchments) to carry out rather crude dialytic separations and purifications, using very primitive equipment and tedious procedures, became established laboratory procedure.[2–4] Even electrodialysis (using parchment membranes) was identified as a useful (albeit inefficient) technique for facilitating separation of electrolytes from non-electrolytes in aqueous solution.[5] Ultrafiltration as a process concept was first utilized on a laboratory scale near the end of the last century, employing hydrogel-impregnated porous ceramics as "membranes".[6] Hartman[7] devotes several pages to discussion of the evolution of ultrafiltration as a separation/purification procedure during the period 1896–1933.

II. EARLY SYNTHETIC MEMBRANES AND MEMBRANE PROCESSES

Probably the first synthetic polymeric material to be evaluated and developed for use as a semipermeable dialysis/ultrafiltration membrane was cellulose nitrate in the form of collodion,[8] whose discovery was almost contemporaneous with Graham's work. Collodion represented the first major breakthrough in applied membrane technology, since it allowed the preparation of stable, reproducible membrane structures which could be fabricated with relative ease into a variety of configurations. The finding that the permeability of collodion membranes could be controlled by adjusting the degree of nitration of the polymer[9] was reported in 1907; the effects on membrane permeability of such fabrication variables as casting solution composition, drying, and washing history is the subject of several publications dating from 1907 to 1927.[10–14] It is astonishing that the art of microstructure—control in nitrocellulose membranes for the purpose of controlling semipermeability was developed to a high degree of sophistication long before there was much understanding of structure/properties relationships in membranes, and long before the widespread utility and power of membrane separation processes in the laboratory, industry, and medicine had begun to be recognized.

III. CELLOPHANE AND CLASSICAL DIALYSIS

The viscose process for solubilizing and regenerating cellulose, discovered in 1892, was developed commercially in the early nineteen twenties, primarily for the manufacture of regenerated cellulosic textile fiber (Rayon); cellophane was (and continues to be) an important byproduct of that development, destined primarily for use as a packaging film. Curiously, cellophane tubing developed for use as sausage casing rather inadvertently found its way into the laboratory as a dialysis membrane; today—fifty-plus years later—cellophane remains the dominant membrane for laboratory and industrial dialysis, and continues to be the principal membrane-material in the oldest (and still most widely practiced) medical application of membrane-separation: hemodialysis.

That dialysis, being the earliest-discovered membrane-separation process, should have been the first such process to find industrial application, is probably not surprising; that 75 yr should have intervened between discovery and industrial use of the process may be puzzling. The explanation, of course, is simply that during that time interval there existed no industrial operation for which dialysis was perceived to be necessary or desirable. Earliest large scale use of dialysis (employing cellophane membranes and rather simple equipment) appears to have been in the mid-1930's for the purification (via removal of electrolytes and other microsolutes) of aqueous solutions of biologicals (vaccines, serum proteins, etc.) and recovery of caustic soda in the processing of soda cellulose and its derivatives (principally viscose, from which—paradoxically—cellophane is derived). Discovery of the Cohn process for the fractionation of human blood-plasma proteins in the 1940's carried dialysis to a new level of sophistication and importance in the field of biologicals processing during, and in the years immediately following, World War II.

IV. GAS PERMEATION THROUGH MEMBRANES—EARLY HISTORY

The discovery of vulcanization by Goodyear in 1839 transformed natural rubber from a virtual curiosity into an essential world-wide commodity before the end of the century; the development of pneumatic rubber products (balloons, then bicycle tires, and ultimately the automobile tire) led to the puzzling observation of air-loss from inflated rubber containers in the absence of detectable wall-defects. It is a curious coincidence of scientific history that the earliest reported observation that rubber is permeable to different gases in different degrees, and that permeability does not correlate with gas viscosity, or density, is that of Thomas Graham in 1866[15]—only 5 yr following his classic paper on dialysis. Many additional studies of gas- and vapor-permeation through rubbers (whose principal objectives were to understand the causes of gas-leakage and find means to eliminate it) were conducted between 1877–1945.[16-22] This research not only established that rubber was both gas- and vapor-permeable and selectively so; even more importantly, it laid the groundwork for our understanding of the mechanisms and kinetics of molecular transport processes in polymers, and of the factors influencing permeability and perselectivity in natural and synthetic polymer membranes. Thus, the ability of membranes to selectively permeate and effect separations between *molecules*, as well as between "crystalloid" and "colloid", was established rather early in the evolution of membrane science.

V. MICROPOROUS MEMBRANES AND PARTICULATE SEPARATIONS

Yet, oddly enough, the most important, widely utilized, and lucrative practical application of membrane technology to emerge from pre-World-War-II research—one which even today continues to dominate the laboratory and industrial scene—is the use of controlled-pore-size microporous polymeric membranes for micron- and submicron-particle removal from gases and liquids. The techniques of manipulation of collodion to produce controlled-permeability cellulose nitrate membranes developed in the mid-nineteenth century were greatly refined and scaled up for commercial production of laboratory and industrial membrane-filters in Germany in the 1930's and 1940's, and these fabrication techniques adapted to other more durable and chemically resistant polymers (cellulose acetate, polyvinyl chloride, fluorocarbon polymers). These processes (which are commercially practiced today in the U.S., Germany, Japan, and many other countries) permit the production of highly reproducible, uniform particle-filters of high hydraulic permeability and rather narrow pore size distribution, pore sizes being controllable over the range of *ca.* 0.1–2.0 μm. Specific applications of these microporous membrane filters are far too numerous for citation here; suffice it to say that they are principally used for industrial and laboratory scale clarification of liquids; sterile filtration of gases and liquids; isolation, identification, recovery, and/or analysis of micro-organisms or other particulates; and culturing and harvesting of bacteria and other living cells. Worldwide annual sales of microporous membrane-filters and attendant filtration equipment are probably in excess of $75 million today, and continue to increase each year.

VI. LARGE SCALE GAS SEPARATION BY SELECTIVE PERMEATION

It is also a matter of historical interest that the first major industrial application of staged gas-mixture separation with membranes was born in profound secrecy during World War II, employed neither natural nor synthetic polymeric membranes, and even now constitutes the most immense, costly (in capital outlay as well as operating expense) and complex separation process ever to have been (and probably also ever to be) designed, constructed, and operated. This, of course, is the gaseous diffusion plant in Oak Ridge, Tennessee for isolation of U_{235} from uranium hexafluoride. The design-concepts embodied into this impressive installation[23] provide the basis for all "cascaded" multistage membrane gas- or vapor-separation processes which have subsequently been proposed; yet to this day (to the best of this writer's knowledge) no such process has ever been reduced to commercial practice for any other large-scale gaseous separation. The reasons for this will become apparent later in this review.

VII. ELECTRODIALYSIS

In the mid-1940's, the techniques of polymer synthesis and manipulation utilized in the preparation of particulate ion exchange resins were first modified and adapted to the industrial fabrication of strong, durable, highly ion-permeable, cation- and anion-selective ion exchange membranes. This development led promptly to the development of equipment and processes for demineralization of water and aqueous solutions of non-electrolyte-containing process streams by electrodialysis. (The process of electrodialysis was, it should be mentioned, first reduced to industrial practice in Germany in the late

1920's, utilizing natural "animal" and "vegetable" membranes of poor durability.) Electrodialysis continues today to be an important industrial process for economic desalination of brackish water-sources and for electrolyte removal or reconcentration from aqueous liquors in the food, pharmaceutical, and metallurgical industries; it has, however, yet to achieve the level of world-wide commercial importance as a large-scale desalination method originally forecast by its early developers. Economic factors (high capital investment, coupled with high operating and maintenance costs), and problems with "poisoning" of anion-exchange membranes by trace organic or inorganic impurities, have been in the main responsible for the relatively slow growth of industrial electrodialysis.

VIII. REVERSE OSMOSIS (HYPERFILTRATION)— THEN AND NOW

In the years immediately following the end of World War II, the United States Government became actively interested in novel methods for producing potable water from saline water sources, and through the Office of Saline Water of the U.S. Department of Interior, committed substantial financial resources for over two decades (1950–1973) to the development of membrane separation processes for water-desalination. Out of this program emerged an essentially new technology for electrolyte removal from water and aqueous solution— reverse osmosis or hyperfiltration—which has now become established as one of the most promising large-scale processes for the economical removal of salts from sea and brackish water, and for the removal and recovery of valuable electrolytes from waste chemical process streams. Key discoveries during this period were (1) the finding that cellulose acetate was highly permselective to water relative to salt under pressure-driven permeation,[24] and (2) special membrane casting methods made it possible to produce "asymmetric" cellulose acetate membranes displaying extraordinarily high permeabilities to water while retaining impressively low permeabilities to salts.[25] For the first time in history, it became possible (in the laboratory) to remove salt from water with a membrane by pressure-filtration at pressures of 50–75 atm, with yields of *ca.* 10–15 gal product water per day/ft^2, with about 95–98% salt removal efficiency, making a *single-step* membrane purification of brackish water practical. Initial efforts to design equipment and systems utilizing such asymmetric cellulose acetate membranes for efficient water-desalination were plagued by a problem which has been anticipated but not heretofore encountered in membrane separation process design: viz., the separation kinetics were no longer membrane-limited, but were instead limited by "concentration polarization" of salt at the upstream membrane/solution boundaries. Thus, the decade 1955–1965 was devoted to detailed analysis and treatment of the polarization phenomenon, and development of membrane module designs which minimized it. Today, reverse osmosis systems based on both tubular and "spiral-wrap" membrane modules are in established commercial and industrial use for moderate- to large-scale demineralization of brackish water, recovery of valuable electrolytes from electroplating wastes, removal of objectionable microsolutes from chemical plant effluents, and the like. Compact, low-output (less than 20 gal/day) reverse-osmosis systems are also being manufactured and marketed for desalination and/or removal of taste- or color-impurities in water delivered to drinking fountains, soft-drink dispensers, etc.

The development, in the late 1950's, of techniques for spinning small-diameter, thin-wall tubes (hollow fibers) from cellulose acetate and other reverse-osmosis-membrane-forming polymers[26,27] made possible the fabrication of very high specific-surface-area, relatively inexpensive, membrane modules comprising cylindrical fiber bundles externally fed with feed liquid under pressure, with product permeate being produced via the fiber-lumens. First-generation hollow-fiber RO module systems were based on 6–6 nylon fibers, and displayed but marginally-acceptable demineralization capability. Substantial improvement in salt rejection was accomplished by the use of aromatic polyamide fibers, and several rather large-capacity experimental water-treatment systems have been installed utilizing these membrane modules. However, hollow-fiber reverse osmosis systems have so far failed to compete significantly with tubular or spiral-wound sheet-membrane modular systems in most industrial applications. The reason appears to be an inherent limitation of "shell-side-feed" hollow fiber modules: accumulation of particulate and/or precipitated colloidal contaminants present in the feed liquid within the interfiber spaces, which greatly reduce module separation efficiency and capacity, and which can be removed from the fiber bundle only with great difficulty. Whether improvements in module design and fiber-development can ultimately circumvent this problem remains to be demonstrated. The basically high throughput capacity per unit module volume, long useful service lifetime, and potentially low cost of hollow fiber RO modules continue to make this approach to large-scale water treatment very appealing.

Until relatively recently, the practical production of potable (less than 500 ppm salinity) water via reverse osmosis was limited to brackish feed waters, since the salt-rejection efficiency of the best available membrane was too low to permit effective desalination of more saline water in a single membrane-stage. Now, however, techniques have been developed[28,29] for producing "ultra-thin membrane" laminates comprising *ca.* 500 Å thick films of highly salt-rejecting polymers (e.g. cellulose triacetate, polyethylenimine) on durable, highly water-permeable microporous polymer supporting-membranes, which now make it possible to produce potable water from sea water in a single pass at reasonable pressure. Spiral-wound RO modules containing these laminate membranes are now being made and incorporated into small-scale seawater demineralizing systems[30] (see Fig. 1). In view of the superior performance, reliability, and apparent durability of these new membrane-laminates, and the fact that they can be manufactured in quantity to rigid specifications economically, it is probable that these improved membranes will soon dominate the field of industrial reverse osmosis.

While reverse osmosis was initially developed for the large-scale production of potable (or industrially usable) water from saline water-sources, it remains doubtful to this writer whether the process will ever become firmly established for these applications; indeed the enormous increase in the cost of energy which has taken place over the past eighteen months (and which seems unlikely to abate or be reversed in the foreseeable near future) had made all energy-consuming means for water production less appealing. However, the future for reverse osmosis in recovery of values from industrial waste water streams (e.g. metal salts from hydrometallurgical and electroplat-
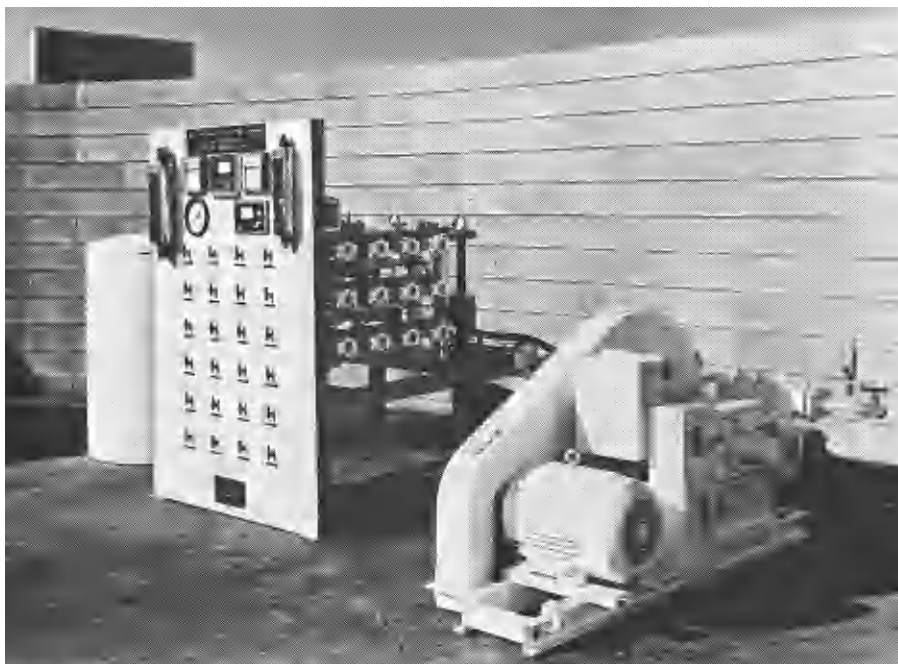
Fig. 1. Pilot-scale, single-stage seawater reverse-osmosis desalination plant utilizing spiral-wound "ultra-thin membrane" laminate. (Courtesy ROGA Division, Universal Oil Products, Co., San Diego, California.)

ing wastes; sugar, other edible microsolutes from food-processing wastes); for the removal of ecologically objectionable contaminants from plant-effluents; and for in-process concentration and or purification of valuable chemical products or intermediates, appears to be bright in a world of rapidly-depleting natural resources.

IX. ULTRAFILTRATION: LABORATORY APPLICATIONS

In the early 1960's, the techniques utilized in the fabrication of asymmetric reverse osmosis membranes were discovered to be applicable to the production of asymmetric microporous membranes whose "skin" layers contained pores in the 10–200 Å range.[31,32] This for the first time allowed the production of ultrafiltration membranes with excellent macrosolute retentivity, yet astonishingly high hydraulic permeability. With such membranes, it thus became possible to carry out, by filtration at modest (3 atm and less) pressures, macromolecular separations, concentrations and purifications rapidly, easily and economically.

In the past 10 yr, ultrafiltration has become as widely recognized, and nearly as widely employed in laboratory analytical and preparative procedures, as is particle filtration with microporous membrane filters. Besides facilitating the concentration, purification and fractionation of biological macromolecules (where it has in large measure supplanted dialysis, vacuum-evaporation or freeze-drying, and precipitation methods), it has also greatly facilitated the study of macrosolute-microsolute interactions in solution by permitting speedy assay of the macrosolute-free solution phase.[33] The availability of a variety of sheet-membranes covering a broad spectrum of solute retentivities (Molecular weight "cut-offs" as low as 500, and as high as 300,000), and of an array of micro- to medium-scale batch- and continuous-flow ultrafiltration equipment and accessories,[34] has made aqueous polymer solution- and colloidal dispersion-processing in the life-sciences and chemical laboratory versatile, convenient, and routine.

More recently, small-scale ultrafiltration has gained prominence in the field of medical diagnostic procedures, where it has greatly increased the sensitivity of detection and assay of abnormal proteins in such body fluids as blood plasma, cerebrospinal fluid, lymph, and urine (by the techniques of radioimmunoassay, immunodiffusion, and immunoelectrophoresis) by allowing rapid, selective concentration of these substances without altering their structure or reactivity.[35] Exquisitely sensitive techniques for early cancer detection, for detection of residual neoplastic disease in patients under treatment, and for diagnoses of viral disease, may soon become feasible via the use of ultrafiltrative concentration of microsamples of biological fluids. Development of an extremely simple, disposable ultrafiltration membrane concentrator for small liquid volumes, which utilizes capillary imbibition into a porous pad to provide the driving pressure for transmembrane flow, has rendered ultrafiltrative processing in the diagnostic laboratory a clean, fast, and highly convenient procedure (see Fig. 2). More widespread use of this technique in diagnostic practice is almost certain to follow increased reliance on immunochemical methodology for disease detection and treatment.

In the late 1960's, techniques were developed for the continuous fabrication of asymmetric, microporous ultrafiltration membranes in hollow-fiber form, with the ultra-thin barrier- or "skin"-layer on the lumen side of the fiber (see Fig. 3). Since ultrafiltration can be carried out at quite low pressures, it thus became possible to fabricate a hollow-fiber membrane module to which feed solution could be delivered under pressure to the *inside* of the fibers, filtrate or permeate being collected on the exterior (shell-side) of the fiber-bundle. This design provided, for the first time, a means for minimizing solute-accumulation on the feed side of a membrane (with its attendant interference with solvent-permeation and solute-
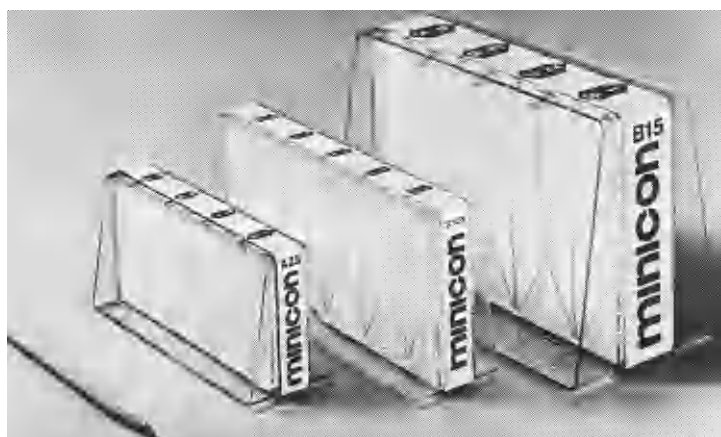
Fig. 2. "Minicon concentrator"—a small-volume ultrafiltration concentrator employing capillary imbibition for water-removal. (Courtesy Amicon Corp., Lexington, Mass.)
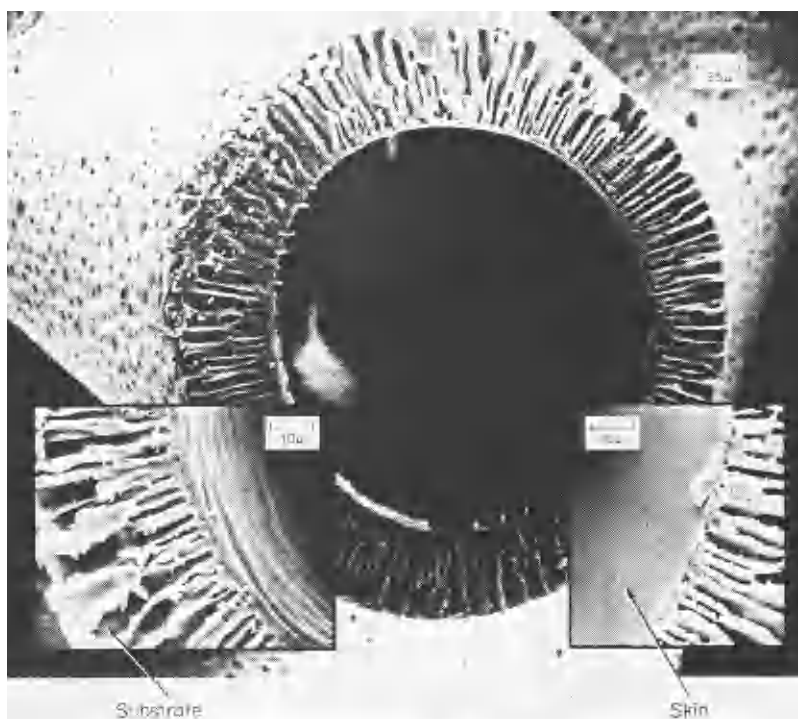

Fig. 3. Scanning electromicrograph of the cross-section of an asymmetric ultrafiltration membrane hollow fiber (Lumen Diameter $ca.$ 200 μm). (Courtesy Amicon Corp., Lexington, Mass.)

retention), while utilizing the advantages of high specific capacity, simplicity, and potentially low cost of hollow-fiber module geometry. While hollow fiber modules are particularly attractive for moderate- to large-scale continuous ultrafiltration, they are also available in laboratory-scale systems for high-speed dewatering (concentration) of, and microsolute-removal from, protein solutions (see Fig. 4).

A recently-conceived, novel laboratory application[36] for hollow-fiber ultrafiltration membranes, whose utility is now under evaluation is the chromatographic separation of macrosolute mixtures (in aqueous solution) by "selective polarization". If a solution of mixture of solutes of differing molecular weights (none of which is membrane-permeable) is fed under pressure to the lumen of a hollow-fiber membrane so that solvent permeates the membrane wall while the solution moves in laminar flow down the fiber-lumen, the solutes will be concentration-polarized near the inside wall of the fiber, the higher molecular-weight (lower diffusivity) species being concentrated the more highly. Thus, with a "step-input" of solution to the fiber, followed by continuous flow of pure solvent, the lower molecular weight solute species will move more rapidly down (and out of) the fiber than the higher. The effluent from the fiber (or fiber-bundle) will therefore contain a time-varying concentration of each solute species, yielding a reverse chromatogram from that usually found by gel-partition chromatography. Since such a separation process is completely independent of the selectivity of the membrane, and solely dependent on
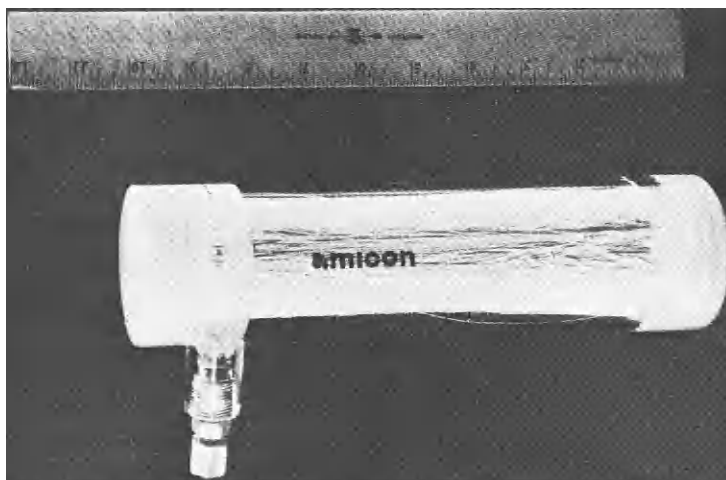
Fig. 4. Hollow-fiber ultrafiltration module containing *ca.* 12,000 fibers. (Courtesy Amicorn Corp., Lexington, Mass.)

solute diffusivity in solution (as well as on flow-hydrodynamic parameters), it is potentially more versatile and adaptable to a wider range of macrosolutes than is conventional chromatography.

X. ULTRAFILTRATION—INDUSTRIAL APPLICATIONS

The development of moderate- to large-scale industrial applications of ultrafiltration has been paced by efforts to develop membrane modules of reasonable cost and durability, which employ fluid management techniques designed to minimize concentration polarization.[37] Several such modular designs are now commercially available: these include (1) tubular membranes, with high velocity, turbulent feed flow inside the tubes (Abcor, Inc.); (2) tubular membranes with low velocity, laminar feed flow in a narrow annular ring inside the tubes (Romicon, Inc.); (3) sheet-membrane "plate and frame" stacks, with turbulent feed-flow between parallel membranes (Dorr Oliver, Inc.); (4) sheet-membrane, "plate and frame" stacks, with low velocity laminar feed-flow in thin channels adjacent to the membrane surfaces (Amicon Corp.); and, most recently, (5) hollow-fiber membrane modules with laminar feed-flow in the fiber-lumens (Amicon, Romicon).

An early industrial application of ultrafiltration, which continues to gain in frequency of use, is the purification and concentration of biologicals—vaccines, plasma proteins, polypeptide hormones, enzymes. Principal advantage of ultrafiltration in biological processing is minimization of loss in biological activity of the product arising from denaturation or deterioration.

A major outlet for larger-scale ultrafiltration process equipment and systems is in connection with the electrocoating process for applying paint to automotive- and appliance-components.[38] The functions of ultrafiltration in this application are (1) to recover colloidally dispersed paints from rinse liquors, (2) to selectively remove water (and unwanted electrolytes) from the electrocoating bath, and (3) to reduce water-consumption in the entire electrocoating process. Virtually every electrocoating plant currently in operation has an ultrafiltration system as an integral part of the process.

Application of ultrafiltration to food processing is now beginning to be practiced on a large scale. Major area of activity is the concentration and recovery of pure protein from cheese whey.[39] This process not only yields a product of significant nutritive and economic value, but also mitigates a serious water-pollution problem associated with dairy processing operations around the world. Edible-protein-containing waste streams are also encountered in many food processing operations outside of the dairy field (e.g. meat packaging and processing, vegetable canning, fat and oil-rendering); opportunities in these industries for ultrafiltration to provide food values and abate pollution remain to be exploited.

Ultrafiltration of tap water yields sterile, colloid-, virus- and pyrogen-free water. Pharmaceutical and biological manufacturers are thus using ultrafiltration systems to produce high-purity water for preparation of parenteral solutions. When combined with deionization, ultrafiltration yields "ultra-pure" water from available water supplies. Large ultra-pure water systems are today commonly encountered in semiconductor and integrated-circuit manufacturing industries, where such high-purity water is essential to the production of high-quality electronic solid state devices and components.

The advent of small, compact, high-capacity hollow-fiber ultrafilters which can process a few liters of water per hour at pressures of only a few pounds per square inch has recently aroused interest in the production of a lightweight, easily portable drinking-water purifier for military-, camping-, or travel-use. In all probability, a unit of this type (about the size of a small campstove) will be commercially available within the next year, and should greatly reduce the risk of disease and misery so commonly associated with contaminated drinking water in areas of poor sanitation.

XI. GAS/VAPOR MIXTURE SEPARATION WITH MEMBRANES

Despite the early demonstration that gaseous and/or liquid mixtures can be separated into their components by membrane-permeation and pervaporation,[40,41] and the elaboration of process-techniques for multistage gas- or liquid-mixture resolution via membranes,[42] there exist today (to the best of the writer's knowledge) no industrial scale membrane processes for gas, or vapor separation. The major reasons for this are that (1) the energy costs and capital investment requirements for *multistage* membrane separation of gases or liquids are substantially greater than those encountered with traditional separation methods and as fractional distillation, absorption and

extraction; and (2) the perm-selectivity of synthetic membranes to most commercially important gas/liquid mixture components is too low to make *single stage* mixture resolution feasible. Probably the only gas-phase mixture-separation of industrial consequence which is amenable to one-stage membrane separation is the recovery of helium from natural gas;[40] nonetheless, cryogenic techniques for effecting this separation are sufficiently reliable and economic to discourage interest in the development of a membrane process to perform this task.

The prospects for useful and economic practical applications for gas/vapor mixture separations via membranes have been significantly brightened in recent years by three important membrane developments: (1) the development of "ultra thin" gas-permselective membranes (submicron films deposited on microporous substrates) which have substantially increased through put at low pressure-gradients, and thus much reduced energy requirements for permeation; (2) the development of "immobilized liquid membranes"—microporous membranes containing a selectively gas-permeable liquid phase retained by capillarity within the pore-spaces;[43] and (3) the development of "facilitated transport" membranes based on the immobilized liquid membrane structure, wherein selective gas-binding solutes dissolved in the liquid phase augment substantially the permeability of one permeating species by serving as a "carrier" of that species through the membrane.[44] The latter two developments have yielded membranes with impressively high specific permeabilities (relative to most polymeric membranes), and astonishingly high permselectivities to certain reactive gases (e.g. SO_2, H_2S, CO_2), thereby rendering single-stage enrichment with low power-demand feasible.

Now commercially available[45] is a reasonably compact, electric-motor-driven, oxygen-enriched-air membrane permeator, utilizing "ultra thin" supported polypropylene oxide membranes, for inhalation therapy (see Fig. 5). This device produces continuously a *ca.* 40–48% O_2 gas stream from air in a single membrane stage. Cost analyses for other industrial needs of oxygen-enriched air indicate[45] that, as fossil fuel (gas, oil) costs escalate, the costs of oxygen enrichment by traditional (cryogenic) methods become increasingly closer to those of membrane-enrichment, making the latter a serious contender for this application in the near future, if fuel costs continue to rise.

XII. BIOMEDICAL APPLICATIONS OF MEMBRANE SEPARATIONS

The treatment of acute and chronic kidney-failure (as well as poisoning) by hemodialysis has, since the procedure was first attempted on humans in the late 1940's, become the best established, safest, most effective, and most widely practiced extracorporeal life-support procedure in world wide use today. A wide variety of hemodialysis systems is now commercially available, virtually all of which utilize regenerated cellulose membrane, incorporated into presterilized, disposable membrane cartridges. An important, relatively recent step forward in hemodialyzer design has been the development and commercialization of a regenerated cellulose hollow-fiber dialysis module of large membrane area, small size, and low blood priming volume.[46] Mass transfer dynamics of this dialyzer (blood flowing in the fiber-lumens, dialysate in radial flow around the fibers) are significantly better than those of more conventional (sheet-membrane) design, permitting shorter dialysis times and/or better urea-clearance from the patient's bloodstream.

Much effort has been expended in recent years toward

Fig. 5. Oxygen-enriching membrane permeator for inhalation therapy. (Courtesy General Electric Co. Research Laboratories, Schenectady, New York.)

development of improved membranes for hemodialysis which would eliminate or minimize thrombosis at the blood–membrane interface. (In conventional hemodialysis, thrombosis is avoided by preheparinization of the patient—a potentially dangerous procedure.) To date, however, nothing is in immediate prospect that would permit safe hemodialysis without heparin pretreatment.

Nephrologists have also voiced increasingly the belief that, since the normal kidney glomerulus is freely permeable to quite large molecules, while cellophane is virtually impermeable to molecules of molecular weight much above 500, the inability of hemodialysis to restore the anuric patient to normal health may be due to the accumulation in the bloodstream of intermediate molecular weight metabolic wastes. This has aroused growing interest in development of a dialysis membrane displaying high permeability to larger molecules as well as to urea (the "reference" solute for evaluating dialysis efficiency).

The development of the asymmetric hollow-fiber ultrafiltration membrane module has provided a means for accomplishing this, since a membrane substantially impermeable to albumin and other plasma proteins, yet freely permeable to all lower molecular weight solutes is available in hollow fiber form. When used as a dialysis membrane, an ultrafiltration membrane behaves (with respect to all solutes of molecular size small enough to pass through the barrier-layer pores) as an immobilized liquid membrane, and the permeability of any solute through the membrane is determined solely by its diffusivity in water. Because of the high hydraulic permeability of ultrafiltration membranes, however, careful control of the hydrostatic pressure difference between the blood and dialysate sides of the membrane must be accomplished to prevent excessive hemodilution or hemoconcentration. A dialyzer based on this principle is currently under development and evaluation,[47] and its clinical performance should answer questions about the importance of removal of "middle molecules" in uremia.

Since the kidney glomerulus functions as an elementary blood-ultrafilter, it was recognized some years ago that direct ultrafiltration of blood through a synthetic ultrafiltration membrane retentive for plasma proteins would provide an alternative means to dialysis for blood purification. By prediluting blood with isotonic gluconesaline solution, followed by ultrafiltrative reconcentration to the same predilution volume (a process called "hemodiafiltration", illustrated schematically in Fig. 6), it is possible to reduce all plasma impurity-concentrations by a constant fraction, irrespective of their molecular size. This process has been the subject of intensive development and clinical evaluation for several years,[48]

particularly following development of the hollow-fiber ultrafilter;[49] current clinical experience suggests that hemodiafiltration may prove to be superior to hemodialysis as regards the general health of the chronic uremic patient.[50]

An interesting and beneficial consequence of research on hemodiafiltration has been the realization that a very small area of ultrafiltration membrane and a small pressure-drop across that membrane can be used to remove water (i.e. protein-free-plasma) rapidly from a patient's body. Since fluid-retention is a frequent complication of kidney malfunction, and since careful control of fluid balance an important aspect of maintaining patient stability during hemodialysis, a small "in-line" ultrafilter in series with a hemodialyzer can provide a safe and convenient means for adjusting fluid balance. Such a device has recently become commercially available, and its utility as an adjunct to hemodialysis demonstrated in the clinic.[51]

One other membrane-transport process which has gained prominence in extracorporeal life-support is hemo-oxygenation, primarily in connection with extracorporeal circulatory (heart/lung) support during cardiac surgery. Sheet membrane oxygenators, utilizing either poly (dimethyl siloxane) elastomer or fluorocarbon elastomer membranes, are in clinical use today. In this application also, the recent advent of hollow-fiber membrane devices with high area/volume ratio and good boundary-layer-resistance control has sparked development of hollow-fiber blood oxygenators, which offer promise of greater O_2–CO_2 transport efficiency and less blood-damage than is encountered with existing membrane- or bubble-oxygenation systems.

A very interesting new extracorporeal application for a membrane separation device which hollow-fiber technology has made feasible is the "artificial placenta". In such a device, the blood from one subject or patient is passed over one side of a membrane, while that of another subject is passed over the opposite side. If the membrane is impermeable to formed blood elements and macrosolutes, but freely permeable to microsolutes, then any low-molecular-weight toxins (or essential biochemicals) can be transmitted between subjects without cross-contamination of elements of the immunochemical systems of each subject. By this means, a patient in acute (but reversible) kidney-, hepatic-, pancreatic-, or endocrine-failure could be sustained over the critical period with minimal risk by cross-dialyzing his blood with that of a healthy human (or animal) donor.

A particularly exciting recent development of membrane process technology, which may have a major impact upon medical practice in the treatment of degenerative and deteriorative diseases, is the discovery that mammalian cells can be cultured, nurtured, and maintained viable for long periods by confinement within the interstitial spaces between fibers of a hollow fiber ultrafiltration module, while nutrient solution is flowed continuously through the fiber-lumens[52] (see Figs. 7 and 8). It has recently been demonstrated that (1) insulin-producing pancreatic cells can be so cultured and will elaborate insulin in response to glucose-challenge;[53] and (2) hepatic cells can be similarly cultured, and will metabolically convert bilirubin in much the same fashion as the normal liver.[54] The possibility that such membrane systems can be used to culture and maintain secretory *human* cells (e.g. pancreas, pituitary, adrenal, etc.) and to produce in commercial quantity *human* hormones,
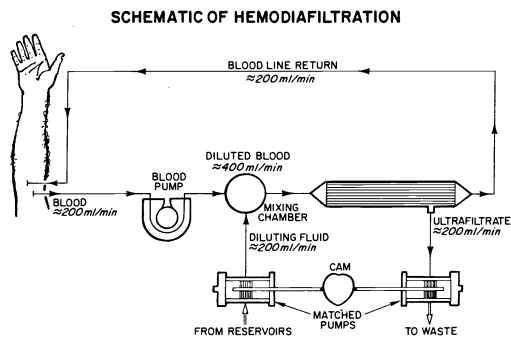
SCHEMATIC OF HEMODIAFILTRATION

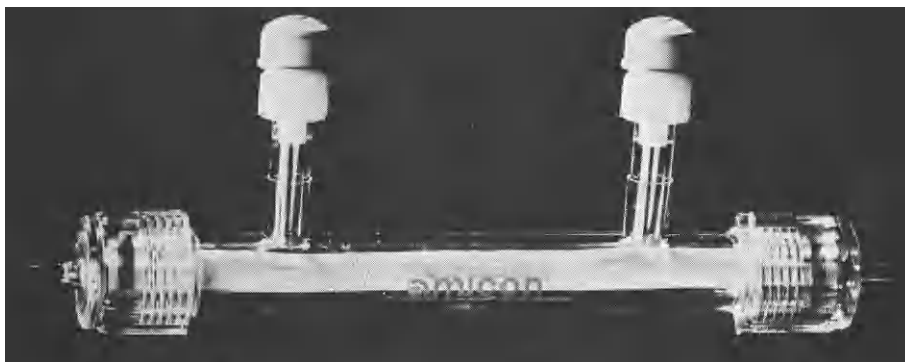Fig. 6. Flow diagram for hemodiafiltration—see Ref. 50.

Fig. 7. A hollow-fiber module designed for cell-culturing; cells are confined to the "shell side", while nutrient flows through the fibers. (Courtesy Amicon Corp., Lexington, Mass.)
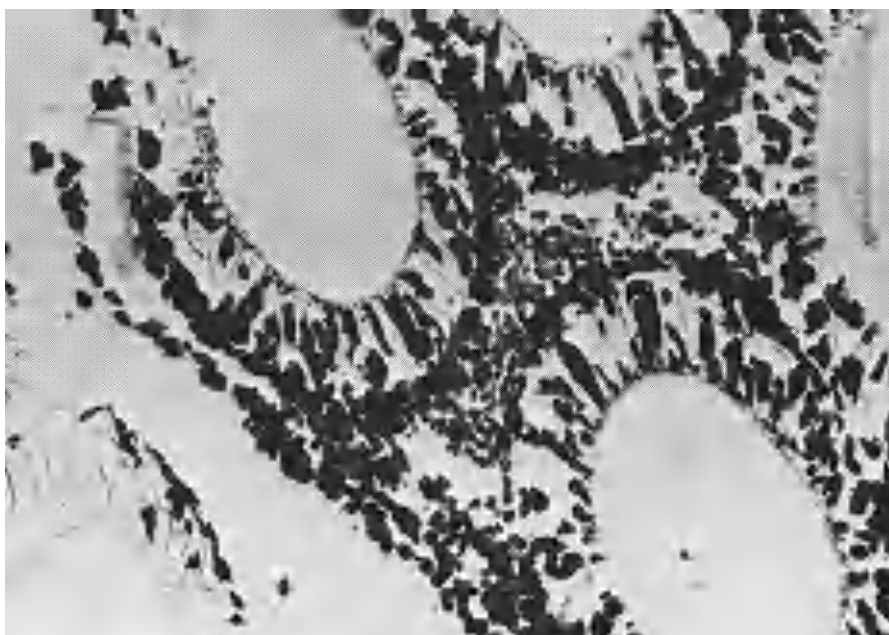

Fig. 8. Cross-section of a hollow-fiber bundle containing growing mammalian cells. Note cell population-density, and penetration into the annuli of the fibers.

growth factors, and the like (instead of our having to rely on limited supplies of animal-derived substances which present immunological problems) seems to be very great. Moreover, the possibility also exists of developing a family of "semi-artificial" external organs containing homogeneous cell-cultures designed to secrete specific regulatory substances, or to detoxify abnormal substances in the circulation, which can be connected to the patient's bloodstream and left in place until the patient's own organs are again able to perform their normal functions. Ultimately, it may be possible to develop an *implantable*, membrane-moderated human-tissue-containing organ which will function as a secretory (or metabolic) organ for the life of the host, and thus free the patient with permanent organ-disfunction from chronic medication, or frequent extracorporeal device-treatment.

XIII. OTHER IMPORTANT CURRENT OR EMERGING APPLICATIONS FOR MEMBRANES

The growth in interest, over the past several years, in the use of enzymes for the conduct of specific chemical synthesis or conversions of importance in the food-, pharmaceutical-industries, has created a new opportunity for beneficial use of membranes to effect separations between enzyme, substrate, and product, and thus improve the efficiency and economy of the conversion process. Continuous recirculatory ultrafiltration of an enzyme-containing solution has been used to both conserve enzyme and increase reactor conversion-capacity, when both substrate and product are membrane-permeable.[55] When the substrate is polymeric (e.g. cellulose or amylose), and the product of low molecular weight (e.g. glucose), continuous conversion with recycle-ultrafiltration yields pure product without substrate or enzyme contamination.[56]

Recently, a new and simple technique for enzyme "immobilization", and conduct of enzymatic conversions of micromolecular substrates into micromolecular products (e.g. lactose to galactose and glucose) has been proposed and tested, utilizing asymmetric hollow-fiber ultrafiltration membranes:[57,58] Concentrated enzyme solution is allowed to saturate the external annular porous

shell of the fibers, and substrate solution passed through the fiber lumens (see Fig. 9). Radial diffusive transfer of substrate and product into and out of the annulus, with retention of the enzyme in the annular space, permits efficient enzymatic conversion and high capacity per unit volume, with excellent retention of enzyme activity over long time periods. This technique circumvents most problems and limitations of chemical enzyme-immobilization methods (the enzyme is easily removed and replaced as well as introduced, and there is virtually no loss in activity associated with immobilization), and promises to have considerable advantage for large-scale enzymatic conversion operations.
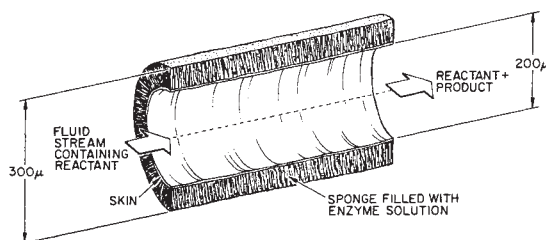

Fig. 9. Schematic cross-section of an asymmetric hollow fiber membrane used to "immobilize" an enzyme for a continuous enzymatic conversion. (See Refs. 57, 58).

Fig. 10. A pilocarpine-releasing membrane laminate placed in the lower cul-de-sac of the eye: The OCUSERT[R] ocular therapeutic system for treatment of glaucoma. (Courtesy ALZA Corp., Palo Alto, California.)

Over the past 5 yr, a new dimension has been added to human and animal therapeutic practice via the development of programmed drug- or biologically-active-substance-releasing systems utilizing semi-permeable synthetic membranes for the treatment of disease.[59] Representative Therapeutic Systems based on this concept include (1) a pilocarpine-containing membrane laminate placed under the eyelid (Fig. 10), which provides constant release of medication for one entire week, for treatment of glaucoma; (2) a progesterone-containing, membrane-moderated intrauterine module (Fig. 11), which administers a constant, low dose of the natural hormone to the uterine lining for one year, thereby
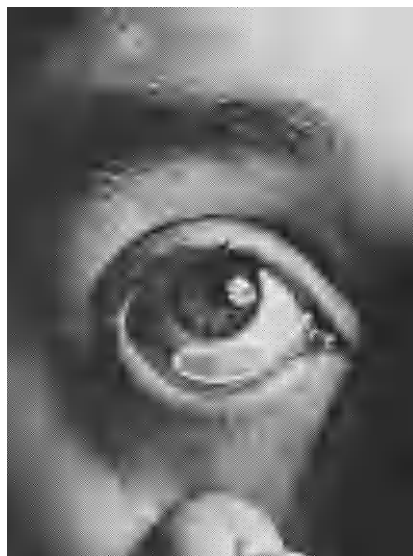
producing safe and effective contraception; and (3) a scopolamine-containing, skin-applied delivery system (Fig. 12), which administers drug to the systemic circulation at a constant rate for ca. 24–36 hr, and provides continuous protection against motion-sickness. The potential for these Therapeutic Systems in the treatment of a host of chronic and acute diseases, where temporal and spatial control of drug administration can maximize therapeutic benefits while minimizing side-effects, and at the same time provide improved comfort for the patient as well as security and convenience to both the patient and physician, is undoubtedly great.

Obviously, the concept of precision-control of release

Fig. 11. Intrauterine progesterone-delivery system (PROGESTASERT™) designed to provide one year of contraceptive protection. (Courtesy ALZA Corp., Palo Alto, Calibornia.)

Fig. 12. A transdermal drug delivery system designed to provide 24–36 hr constant administration of scopolamine for protection against motion-sickness. (Courtesy ALZA Corp., Palo Alto, California.)

of medication via membrane transport has important implications in the controlled release of biologically active substances for such other applications as insect control, plant- and animal-growth control, and the prevention of water-, air-, and ground-pollution. The next decade will, almost certainly, see a major surge in the development of controlled release pharmaceutical-, food-, agrichemical-, and ecological-control products, which will constitute a large and important new outlet for polymeric membranes and membrane technology.

Viewed in perspective, the evolution of membrane science spans more than a century, but membrane *technology*—the practical application of membrane phenomena—is only about 30 yr of age, and still in its childhood. That it has been a very vigorously-growing and prolific child during this period is a tribute to the mutual support and close cooperation among the physicists, chemists, and engineers who have participated in its early development. Continuing cooperation among these contributing disciplines will ensure that membrane technology will even better serve society's needs in the years ahead.

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