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By the mediation of Dr. Carl W. Walter, who introduced one of his brain children, a thermoswitch, to Toray Industries, Inc. (Tokyo, Japan) in the 1950s for the spinning of synthetic fibers such as polyamide, the Harvard-Toray joint research project on two subjects was started in 1974. One of them concerned an ocular insert for the slow release of antibiotics into the conjunctival sac to cure trachoma. The other was the development of a new artificial kidney system in collaboration with the Peter Bent Brigham Hospital, Harvard Medical School. I was dispatched to Boston at that time, and that transfer was the beginning of a new era of cooperation between Harvard and Toray through the intermediacy of Dr. Walter.

The year 1974 was the 50th anniversary of the first case of human hemodialysis conducted by Dr. G. Haas in Germany, and almost the 25 year anniversary of the first clinical trial with the Kolff-Brigham artificial kidney at the Peter Bent Brigham Hospital [1,2]. The Kolff-Brigham kidney, actually a rotating kidney machine, was constructed by Dr. Walter based on the blueprint lent by Dr. W. J. Kolff, the father of hemodialysis therapy who was born in the Netherlands and immigrated to the United States after World War II. Dr. Walter was present at the first hemodialysis trial with this kidney in 1948 together with the late Dr. J. P. Merrill, who was the physician-in-charge.

Based on such a long historic background, our program for the development of a new artificial kidney was thus launched under the guidance of Drs. Walter and Merrill. The purpose of the program was to develop an improved artificial kidney system of the second generation for "feel better" treatment and improved rehabilitation utilizing a new, noncellulosic hollow fiber membrane made from polymethyl methacrylate (PMMA) devised by Toray [3]. At first, more versatile and better-controlled removal of fluid and middle molecules than the conventional method

was clinically tried, and an ultrafiltration rate controller was designed.

While the joint program has continued and been expanded to include a plasmapheresis study, a few evolutions originating from this program have been made. First, intensive investigation of the biocompatibility of the hemodialysis membrane was started with support from the National Institutes of Health. Second, new modified membranes with different permeability profiles of various solutes, including electrolytes, were produced, and behaviors of a few electrolytes in chronic hemodialysis patients were also examined. In addition, various control modules were developed. This report describes the outlines of these consecutive research projects and developments.

PMMA Hollow Fiber Membranes

The membrane made from PMMA, which is the same material as that of plastic lenses and hard contact lenses, was carried to the Peter Bent Brigham Hospital in 1974. It was the first noncellulosic hollow fiber hemodialysis membrane in the world. This membrane was spun by utilizing a characteristic phenomenon of PMMA stereocomplex gel formation, which originates from stoichiometric and thermoreversible crosslinking by hydrophobic bonding [3,4]. By manipulating this unique characteristic, various kinds of membranes with different performance levels have been produced. At first, a high-flux PMMA membrane, called the B1 series, was developed and was clinically demonstrated to be applicable to new therapies, such as hemofiltration, because of its higher hydraulic and middle molecule permeability, as compared with commercially available cellulosic membranes, while maintaining perfect albumin retention [5]. Type B1 membrane was also shown to have a comparable permeability of small molecules, such as urea, to that of cellulosic membrane and, therefore, simultaneous combination of hemodialysis with hemofiltration (later called hemodiafiltration) was theoretically and clinically evaluated to make the best use of the potentials of the

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B1 membrane [6-8]. A convective process, as found in hemofiltration, yields much higher clearance for middle molecules than hemodialysis, whereas the high rate of small molecule removal, easily attainable in hemodialysis, is sacrificed in hemofiltration. It was demonstrated that clearance is linearly enhanced as the increase in the ultrafiltration rate (convection) and that the magnitude of this effect is greater with larger molecular species. Validity of the one-dimensional mathematic model developed by Dr. S. M. Ross [9] was also proved. Change in small molecule and middle molecule levels in the body fluid accompanied by a switch from conventional hemodialysis to hemodiafiltration was then estimated based on the simulation with a two-pool kinetic model [7].

Responding to the advent of the high-flux membrane and being stimulated by the aforementioned calculations, a new kidney machine that could be used for such diversified therapeutic modes was devised [7]. Its flow schema is shown in Figure 1. This system is composed of three parts: a high-flux PMMA dialyzer; a dialysate flow control module; which provides single-pass dialysis from a closed flow equalizing system; and a balancing system, which proportions the substitution fluid to control the net weight loss in the patients. In this system, independent control over the three variables, small molecules, middle molecules, and fluid removal, has been achieved. Through preliminary clinical evaluations with this system, validity of rapid dialysis, with a 20 to 40 percent reduction in dialysis time by combining the high rate of controlled ultrafiltration with optimal diffusion, was demonstrated [7].

It is noteworthy that the recognition of hemodiafiltration as a most efficient and tolerable therapy has been renewed at recent scientific meetings, such as the annual meetings of the American Society for Artificial Internal Organs and the European Dialysis and Transplant Association.

The B2 series of PMMA membranes with reduced hydraulic permeability for conventional hemodialysis were successively developed and intensively evaluated at Harvard, mainly from the viewpoint of biocompatibility.

Blood and Membrane Interaction

An important investigation of blood and membrane interaction, namely, biocompatibility of the hemodialysis membrane, has evolved from our joint research program. Although transient leukopenia during hemodialysis with cellulosic membrane, which had long been the only commercially available dialysis membrane, has been pointed out since the 1960s, few quantitative and analytic investigations on this phenomenon have been carried out. However, the advent of noncellulosic membranes, including our PMMA dialyzer, the spread of the multiple use of a cellulosic dialyzer, and the development of the vari-

ous sensitive biochemical assay systems have accelerated the study on biocompatibility. Furthermore, and most importantly, the sincere desire of the end-stage renal disease patients, who can survive once hemodialysis is introduced, to have better quality of life has forced physicians and researchers involved to find a new clue toward "feel better" treatment and to eliminate the long-term complications, such as anemia, renal osteodystrophy, and various infections.

At Harvard Medical School, Dr. R. M. Hakim, as principal investigator, and his colleagues have performed detailed and systematic investigations on this subject with the help of a grant from the National Institutes of Health. In their controlled and crossover evaluations [10-12], it has become evident that the decrease in neutrophils during hemodialysis strongly depends on the type of membrane, being more pronounced with the cellulosic membrane than with either of the two noncellulosic membranes (the PMMA membrane and the polyacrylonitrile [PAN] membrane [AN69,® Hospal Ltd., Switzerland], and that no "overshoot" is demonstrated with the two noncellulosic membranes. In addition, a decrease in the arterial oxygen tension, activation of the alternative pathway of the complement system, especially generation of anaphylatoxin C3a, and then the interrelation of these phenomena were carefully analyzed by the investigators. Another important study recently performed by Dr. Hakim [12] concerns the intermediate and long-term effects of chronic activation of complement during hemodialysis. Again, the significant and consistent difference between cellulosic and noncellulosic membranes was confirmed.

My view of the present state of biocompatibility study is shown in Table I. Accumulation of case reports on anaphylaxis-like symptoms and demonstration of a transient increase in pulmonary arterial pressure in an animal model with sheep have enriched the investigation of this subject. Since the clinical significance of blood and membrane interaction has thus been recognized, we cannot discuss extracorporeal blood circulation therapies further without taking into consideration biocompatibility of the system.

Based on the results of the biocompatibility study thus obtained, the optimal procedure to reuse PMMA membranes when needed, with sodium hypochlorite as a rinsing and sterilizing agent, is being established. Blood components adhered on the membrane are completely removed and the originally biocompatible membrane surface is thus regenerated.

Membrane Permeability of Ionic Solutes and Homeostasis in Chronic Hemodialysis Patients

As a second evolution of the joint research program, studies on the behaviors of electrolytes in blood purification therapies have been carried out. Al-

TABLE I Extended Studies on Biocompatibility

	Short-Term (each treatment)	Intermediate-Term (weeks to months)	Long-Term (years)
Clinical symptoms	New dialyzer syndrome (first use syndrome) Hypersensitivity and anaphylaxis Allergic reaction	? Infection ? Anemia Increased adverse symptoms	? Immunodeficiency ? Increased morbidity and mortality ? Carpal tunnel syndrome
Biochemical data	Leukopenia Decreased phagocytosis Hypoxemia Complement activation Platelet activation	Eosinophilia Antiethylene oxide antibody Change in neutrophil Change in C ₃	Change in immunoglobulin G and E
Animal models	Increase in pulmonary arterial pressure		

though it has long been recognized that correction of impaired electrolyte balance, even if transient, is one of the most important purposes of hemodialysis, little attention has been paid to membrane permeability of ionic solutes and their manipulation, except for the selection of a dialysate buffer system, namely, the switch from bicarbonate to acetate in the late 1960s, and the recent and partial return from acetate to bicarbonate. The first outcome in these studies was the development and evaluation of the anionic PMMA membrane, TK-201 (B3 series) [13].

In the natural kidney, the first step in urine production is glomerular filtration. As demonstrated through the exquisite research of Dr. B. M. Brenner and his colleagues [14], this filtration is skillfully controlled by not only pore size, but also the charge of the membrane. Incorporation of the charge into the artificial membranes was, therefore, intended to improve the permselectivity in the membrane separation and, as the first trial, the anionic hemodialysis membrane has been developed to lessen an amplitude of the fluctuation in acid base balance, especially during rapid hemodialysis with a large-surface-area dialyzer combined with acetate dialysate. In this study, it was proved not only in an *in vitro* setting, but also clinically, that the anionic charge of the dialysis membrane reduces permeability of the bicarbonate ion while preserving the removal rate of nonelectrolyte solutes, such as urea and creatinine. It was also demonstrated that the anionic membrane, TK-201, prevents rapid loss of the bicarbonate ion from blood into dialysate, especially at the initial phase of rapid hemodialysis and excessive accumulation of acetate ion into blood during the latter part of the treatment, thus resulting in significantly reduced symptoms compared with rapid hemodialysis with noncharged membranes.

The second outcome of the electrolyte study was the discovery of a few characteristic phenomena of phosphorus compounds, including inorganic phosphate in patients with end-stage renal disease, which may be a new clue to correcting their impaired inor-

ganic phosphate homeostasis. Renal osteodystrophy is one of the most severe long-term complications among these patients that remains to be solved. Although involvement of inorganic phosphate in renal osteodystrophy has long been suggested, few systematic studies on this subject have been performed. During our clinical evaluations and supporting laboratory experiments, rapid outflow of inorganic phosphate from its reservoirs during hemodialysis was observed [15,16], and repeated transient hypophosphatemia and probable negative balance of inorganic phosphate in the present hemodialysis therapy were suggested. At the present time, more individualized and optimal guidelines for inorganic phosphate level control are being established. During these investigations, the impaired glycolytic process in uremic red blood cell was also discovered [16,17], and methods to correct this impairment are now being tried.

New Membranes and Control Units

In addition to the anionic PMMA membrane, TK-201, the protein-leaking PMMA membrane, TK-401 (BK series), was produced. It has similar solute permeability as that of the peritoneum. Whereas PMMA membranes for hemodialysis, hemofiltration, and hemodiafiltration developed earlier retain albumin, TK-401 leaks small amounts of albumin just as the peritoneum does and is used for continuous ambulatory peritoneal dialysis. Utilizing this membrane, for example, removal of the complex of aluminum and desferrioxamine, a chelating agent for chronic hemodialysis patients, is being evaluated, as more attention has been paid to the accumulation of aluminum in patients with renal failure as one cause of bone disease. Another new product is the continuous hemofilter, TK-601, which is used without a blood pump for the treatment of acute renal failure. With the same polymer material (PMMA), the small module is made for this purpose and, in some cases, it was clinically used for 7 consecutive days without interruption. Although I will not discuss

it in depth here, a plasmapheresis module made with PMMA (Plasmax®) has been developed [18] and clinically evaluated at Harvard Medical School. On the other hand, more versatile machines have also been devised. The prototype of the machine for hemodiafiltration already mentioned (Figure 1) was refined through in vitro and clinical evaluations and fully developed as TR-700, which can be employed for hemofiltration, hemodialysis, and hemodiafiltration. From the functions that TR-700 possesses, the ultrafiltration rate control mechanism was extracted and commercialized alone as an ultrafiltration rate controller for conventional hemodialysis (TR-200). Furthermore, the single-patient dialysis machine, TR-320, which can supply both acetate and bicarbonate dialysate, is also available. In addition to these series of products, an ion-exchange fiber column employed as an adsorbent for some specific solutes, such as bilirubin, and polymyxin-B-immobilized module, employed as an endotoxin trap, are now being developed.

Future Prospect in Blood Purification Procedures

As mentioned herein, the strong association of medicine and industry during the past 10 years has made a great contribution toward the progress of extracorporeal blood purification procedures, mainly in hemodialysis and related fields. Numerous membranes with different characteristics and performances (pore size and its distribution, electric charge, affinity, biologic activity, and so on) and various control modules with different functions have become available. Important data on blood and membrane interaction have also accumulated. In addition, if the target is pinpointed, immobilization of biologically active substances, such as enzymes or monoclonal antibodies, into the extracorporeal circuits is now possible. On the other hand, many suggestions and preliminary clinical trials regarding new applications of these extracorporeal procedures to diseases other than chronic renal failure, such as acute renal failure, hepatic failure, tumor, and various autoimmune diseases, have been made during the 10 year period.

These new trends strongly suggest that we are now at the beginning of the blood purification procedure of the second generation in the sense of its combination with medication or the incorporation of the concept of biologic response modifiers in this field. However, looking at the extracorporeal blood purification therapies from another angle, the present state can be considered a kind of disappointment and frustration, especially to the industry. Recent strict government policies that aim to suppress the treatment cost of hemodialysis are discouraging both medicine and industry from making a breakthrough in the field. Plasmapheresis, which appeared as a postdialyzer a few years ago, does not seem to thoroughly meet our expectation. However, I believe that

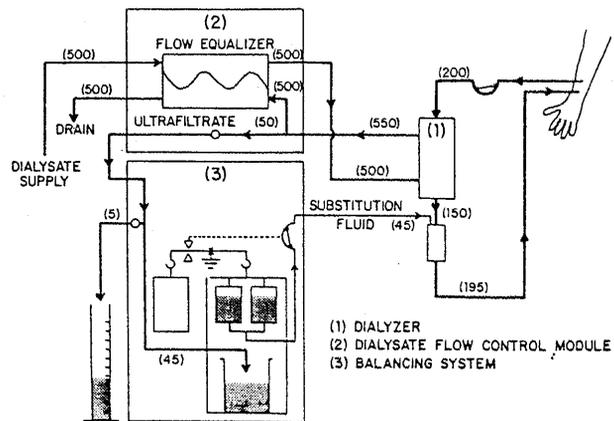


Figure 1. Flow schema of hemodiafiltration. Examples of representative flow rates (ml/min) under standard operating conditions are shown in the parentheses.

extracorporeal blood purification procedures still have great potential, which calls for future judging on the basis of recent progress in technology and medical science. For the full development of medical products and the establishment of therapies with these products to occur, a close association between medicine and industry is essential. Dr. Walter has been playing a triple role as a distinguished surgeon, engineer, and entrepreneur. Now we are at the crossroads of extracorporeal blood purification procedures and, therefore, it is just the time when we truly need Dr. Walter.

References

- Merrill JP, Thorn GW, Walter CW, Callahan EJ III, Smith LH Jr. The use of an artificial kidney. I. Technique. *J Clin Invest* 1950;29:412-24.
- Merrill JP. The legacy of 'Pim' Kolff. *Nephron* 1984;36:153-5.
- Sakai Y, Tsukamoto H, Fujii Y, Tanzawa H. Formation of poly(methyl methacrylate) membranes utilizing stereocomplex phenomenon. In: Cooper AR, ed. *Ultrafiltration membranes and applications*. New York: Plenum Press, 1980:99-107.
- Sakai Y, Tanzawa H. Poly(methyl methacrylate) membranes. *J Appl Polymer Sci* 1978;22:1805-15.
- Kunitomo T, Lowrie EG, O'Brien M, et al. Performance and clinical use of a convertible hemodialysis (HD)-ultrafiltration (UF) system. *Proc Clin Dial Transplant Forum* 1976;6:120-7.
- Kunitomo T, Lowrie EG, Kumazawa S, et al. Controlled ultrafiltration (UF) with hemodialysis (HD): Analysis of coupling between convective and diffusive mass transfer in a new HD-UF system. *Trans Am Soc Artif Intern Organs* 1977;23:234-42.
- Kunitomo T, Kirkwood RG, Kumazawa S, Lazarus JM, Gottlieb MN, Lowrie EG. Clinical evaluation of postdilution dialysis with a combined ultrafiltration (UF)-hemodialysis (HD) system. *Trans Am Soc Artif Intern Organs* 1978;24:169-76.
- Kirkwood RG, Kunitomo T, Lowrie EG. High rates of controlled ultrafiltration combined with optimal diffusion: recent advances in hemodialysis technique. *Nephron* 1978;22:175-81.
- Ross SM. A mathematical model of mass transport in a long

- permeable tube with radial convection. *J Fluid Mech* 1974;63:157-75.
10. Hakim RM, Lowrie EG. Hemodialysis-associated neutropenia and hypoxemia: the effect of dialyzer membrane materials. *Nephron* 1982;32:32-9.
 11. Hakim RM, Lowrie EG. Effect of dialyzer reuse on leukopenia, hypoxemia and total hemolytic complement system. *Trans Am Soc Artif Intern Organs* 1980;26:159-63.
 12. Hakim RM, Fearon DT, Lazarus JM. Biocompatibility of dialysis membranes: Effects of chronic dialysis with complement and non-complement activating membranes. *Kidney Int* (in press).
 13. Ono T, Iwamoto N, Kataoka H, Taniguchi Y, Kimura M, Kunitomo T. Anionic poly(methyl methacrylate) (PMMA) membrane for rapid dialysis. *Trans Am Soc Artif Intern Organs* 1982;28:38-42.
 14. Brenner BM, Hostetter TH, Humes HD. Molecular basis of proteinuria of glomerular origin. *N Engl J Med* 1978;298:826-33.
 15. Sugisaki H, Onohara M, Kunitomo T. Dynamic behavior of plasma phosphate in chronic dialysis patients. *Trans Am Soc Artif Intern Organs* 1982;28:302-7.
 16. Sugisaki H, Onohara M, Kunitomo T. Phosphate in dialysis patients. *Trans Am Soc Artif Intern Organs* 1983;29:38-43.
 17. Kunitomo T, Onohara M, Nishiumi S, Inagaki F, Sugisaki H. Phosphate in chronic hemodialysis patients. *Artif Organs* (in press).
 18. Idezuki Y, Hamabe S, Sonoda T, et al. A new PMMA plasma separator: Its application in the hepatic assist system. *Trans Am Soc Artif Intern Organs* 1982;28:220-4.