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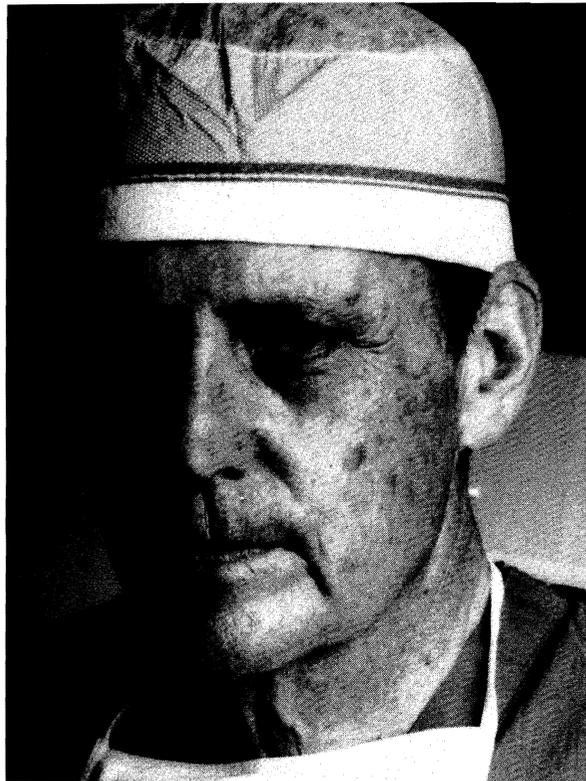
**MY THIRTY-FIVE YEAR VIEW OF
ORGAN TRANSPLANTATION**

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In my earlier historical reassessments (1-3) and those of Calne (4,5), Murray (6), Moore (7), and Groth (8), the dawn of transplantation was defined as the turn of this century, in part because these reviews emphasized kidney transplantation. Kahan has exposed the incompleteness of this perspective by tracing the roots of transplantation into antiquity (9). Notwithstanding the early traces, evolution of the modern field is a phenomenon of the last 40 years. During the first part of this time, I picked up the trail of renal transplantation and started a new one with liver replacement. From 1958 onward, liver transplantation played an increasingly prominent role in generic advances that were applicable to all organs.

The first known attempts of kidney transplantation in humans were made in France and Germany between 1906 and 1923 using pig, sheep, goat, and monkeys or apes for donors (10-12, translation for 11,12 provided in 10). The first human-to-human kidney transplantation was reported

in 1936 by the Russian, Yu Yu Voronoy (13, translation provided in 10). The technique of renal transplantation which became today's standard was developed independently by three different French surgeons, Charles Dubost (14), Rene Kuss (15), and Marceau Servelle (16) and reported in 1951. A number of the kidneys were taken from criminals shortly after their execution by guillotine. John Merrill, the Boston nephrologist had seen the French operation while travelling in Europe in the early 1950s as was later mentioned by the surgeon, David Hume (17) in his description of the beginning (in 1951) of the Peter Bent Brigham kidney transplant program. It was adapted later for the historically important identical and fraternal twin cases in Boston. Although immunosuppression was not available, patients of R.H. Lawler of Chicago (18) and Hume and Merrill (17) may have derived some benefit. In Hume's patient, the kidney graft which was placed in the thigh produced urine for five months.

STARZL

PHASE I (1955 to 1958)

Although oblivious to transplantation during most of this time, I began experiments in hepatic physiology which led directly to the first efforts in 1958 to replace the liver in dogs. These were stimulated by a clinical observation while I was an assistant resident in training at the Johns Hopkins Hospital in Baltimore (1952 to 1956). In 1955, I helped Dr. Alfred Blalock (Chairman of Surgery) perform a splenorenal shunt on a mildly diabetic rum manufacturer from Jamaica whose diagnosis was cirrhosis of the liver. Afterwards, the patient no longer needed insulin to control his blood sugar.

I wondered if this was because the patient's natural insulin coming from his pancreas into the portal vein had been bypassed around the liver and was therefore made either more effective or more available. The idea became irresistible when I. Arthur Mirsky, a biochemist from the University of Pittsburgh, suggested at about the same time that insulin action was regulated by a hypothetical liver enzyme which he called insulinase. Mirsky speculated that diabetes was a disorder caused by too much insulinase and the consequent need for insulin overproduction.

The idea was tested by animal experimentation at the University of Miami where I finished my general surgical residency in 1956 to 1958. Because there was no large animal facility at this new medical school, I set one up with homemade metabolic cages in an empty garage across from the Emergency Room of the Jackson Memorial Hospital. We obtained dogs from the city pound, made them diabetic with alloxan, calibrated their insulin requirements after they became diabetic, and eventually performed portacaval shunt. To my dismay, the insulin requirements after operation increased drastically instead of diminishing as I had hoped (19). In addition, the animals quickly developed the previously well-known syndrome of "meat intoxication." Now, I became convinced that a different metabolic relationship than I had envisioned must exist between the pancreas (by virtue of its insulin) and the liver. In further experiments, various kinds of blood were used for portal venous inflow. Everything we tried then (19) and for a long time later (20-22) failed to unmask the kind of insulin-liver relationship which I was looking for.

The questions about sugar and insulin metabolism raised by these still primitive thoughts and investigations would require better models, including one of total hepatectomy in large animals. While still in Miami, I developed an improved method of total canine hepatectomy (23) which soon replaced previously used techniques in other laboratories. A fringe benefit was my realization that a new liver for the pursuit of metabolic studies could be installed (I

thought easily) in the empty space from which the normal liver had been taken. Work on this possibility was begun in earnest after I relocated in Chicago in June 1958.

While I wasted time in Miami during 1956 to 1958 doing physiologic experiments, efforts in transplantation were going on elsewhere. There was no way of preventing rejection and without such treatment, clinical transplantation could succeed only between monozygotic twins. This step was taken two days before Christmas 1954, with a kidney transplantation from an identical twin donor by Murray et al (24). It was the first example of successful transplantation of a vital whole organ and had a major impact on the field as described elsewhere (2). However, further progress in all other situations would require immunosuppression.

Peter Medawar's appreciation that rejection was an immunologic phenomenon (25,26) made inevitable the efforts to alter the immune system to prevent this process. As early as 1951, Rupert Billingham, working with Medawar and Peter Krohn, showed that corticosteroids delayed skin graft rejection in animals (27,28). Then, W.J. Dempster of Hammersmith Hospital, London, showed that steroids ameliorated established acute rejection after kidney transplantation in dogs (29), presaging the clinical response to this kind of "rescue" therapy that later would soon be seen in many thousands of patients. Dempster also was the first to show the immunosuppressive effects of total body irradiation (30).

PHASE II (1958 to 1961)

The ostensible purpose of returning to Northwestern Medical School (where I had graduated in 1952) was to become fully qualified to do thoracic surgery. This was going to be another passing fancy. I had already foregone a promising career in

neurophysiology in which I had obtained a Ph.D., only to abandon this field and to work for a year and a half in heart physiology preparatory to work in cardiac surgery. Now, I was training to be a thoracic surgeon, after having already lost interest in

this field. Because the thoracic surgery load was light, I immediately resumed the canine hepatectomy experiments and during July 1958, the first liver transplantations were performed at the VA Research Hospital. This was a project to which I paid more and more attention as time went by after hearing from John Lewis, my thoracic surgery chief at Northwestern, that Norm Shumway, Lewis' previous cardiac surgery fellow at the University of Minnesota, had begun attempts to replace the dog heart at that institution.

A four-page application was sent to the National Institutes of Health and resulted in funds of about \$30,000 a year for five years. An unexpected further boost came during the summer of 1958 when Dr. John A.D. Cooper, Associate Dean of Northwestern Medical School, asked me if I wanted to be the school's candidate for a Markle Scholarship. It was an unusual honor because there could be only one nominee from each of the 100 or so medical schools in North America. From the pool of nominees, 20 to 25 would be chosen. Those selected committed themselves to academic careers as opposed to private practice.

The criteria by which the candidates were chosen was not obvious. Fortunately, the judges who were not scientists were insufficiently informed to know how bizarre my proposed career plan was. It is amusing to recall that the committee at the Markle interviews from February 2 to 5, 1959, saw no reason at all why my proposal of liver transplantation could not be accomplished. I was given the Markle scholarship and a few months later began a junior faculty appointment.

Free from patient responsibilities for the first time in four and one-half years, I started on July 1, 1959 to work in the laboratory full time. With grant money in hand, the liver transplant project was transferred from the VA laboratory to the University surgery laboratories in the Montgomery Ward Building at 303 Chicago Avenue. Two senior

medical students named Bob Lazarus and Bob Johnson and a third year surgical resident named Harry A. Kaupp Jr., joined the team. Within a few weeks, liver transplantation, which I had been doing alone for the preceding year, including anesthesia management, was perfected enough to have the dogs live through the operation on a regular basis. The secrets were simple.

First, the liver was preserved by core cooling with cold saline or lactated Ringer's solution which was infused into the portal vein at the same time as the liver blood supply was interrupted in much the same way as practiced clinically today except for the solution (31). The second key requirement was a veno venous bypass system during the anhepatic period when the native liver was being removed and the vessels of the new organ were being anastomosed to those of the recipient. Otherwise, the consequence of simultaneously obstructing both the portal vein and inferior vena cava for the necessary 30 to 60 minutes was irreversible injury to the intestines and other splanchnic viscera. With the use of plastic bypass tubes which effectively decompressed the obstructed venous beds, the main blood vessels supplying and leaving the liver could be anastomosed with less urgency. The vascular anastomoses were sophisticated ones but well within the grasp of trained surgeons. Biliary reconstruction also was a conventional procedure.

Thereafter, liver transplantation could be done with a reasonable expectation of short-term survival until rejection occurred. By the end of the summer of 1959, we were confident that this operation was not only feasible, but could someday be applied for the treatment of human disease. We had heard by now that a similar project, which also was begun in the summer of 1958, was underway at the Peter Bent Brigham Hospital under the direction of Francis D. Moore.

Our work on canine liver transplantation and that by Moore's Boston team was not generally known until the annual meet-

ing of the American Surgical Association (ASA), held at White Sulphur Springs, West Virginia on April 5, 1960. A paper on the Boston results was read by Moore and published the following autumn in the *Annals of Surgery* (32). As a guest of the society, I discussed Moore's paper (33), based on our impending publications in *Surgery, Gynecology, and Obstetrics* (31,34), the journal of the American College of Surgeons. Moore had presided over the early trials of kidney transplantation at the Brigham. He expected that what was being learned with the kidney model would be applicable to other organ transplants and vice versa. So did I.

Moore was reporting on 31 liver transplant experiments. Seven of his animals lived for more than four days, with a maximum of 12 days before death from rejection. From these seven animals, he had pieced together a very complete picture of the postoperative course after liver replacement in the untreated dog. In my discussion, I described how in more than 80 experiments we had systematically tested different ways of restoring the transplanted liver's blood supply including the omission in some dogs, and the augmentation in others, of portal venous inflow. This was a reflection of my original interest in interorgan metabolic relationships. Livers which were given a normal portal venous inflow performed better than those which were not. The important practical achievement for the moment was that we had 18 dogs with survival greater than four days, with one animal living for 20 and one-half days.

During this meeting, two friendly young men whose faces I recognized introduced themselves in the lobby of the Greenbrier Hotel. One was Dave Hume, the former Harvard surgeon who had started the Peter Bent Brigham Hospital kidney transplant program but who now was at the Medical College of Virginia. With him was Dick Egdahl, and after a few minutes we were joined by John Mannick, who would soon move to Richmond with Hume. In 1978,

Mannick would succeed Moore as Chief of Surgery at the Brigham. Although they expressed interest in my work, I was far more intrigued by theirs.

Just before Moore's presentation, Hume, Egdahl, Charlie Zukoski and three other colleagues had given a paper on kidney transplantation in dogs which had been conditioned with total body irradiation (35). The work provided a remarkable insight into the difficulties to be overcome if there ever was to be clinical value of any whole organ transplantation procedure. When Hume's dogs were given more than 1000 rads, rejection of the kidneys could be prevented, but they all died of overwhelming infection. With smaller doses, the grafts were rejected. There was no margin of safety.

It seemed to me that Hume's paper (which Moore discussed) had the same negative implication for clinical use. Hume agreed and told me that he and two of his coworkers (Charlie Zukoski and H. M. Lee) were experimenting with a new drug called 6-mercaptopurine as a substitute for x-ray therapy. Six weeks earlier they had sent an abstract with encouraging results to the Surgical Forum committee of the American College of Surgeons, to be considered for the annual meeting in San Francisco the following October.

This was the first of many personal or phone conversations with Hume, of which the last was at the American Surgical Association meeting at the Century Plaza Hotel, Los Angeles, in April 1973, a few weeks before he was killed in an airplane crash. He always reminded me of a human buzz saw, constantly advancing but with such precision and beauty of motion that it was a masochistic thrill to realize that the cutting pathway was directed straight to you. Few people passed through the veneer and were allowed to see behind. A very friendly and generous man was hiding there.

Both Zukoski's abstract and one of mine were accepted for presentation at the

1960 fall meeting of the American College of Surgeons to which Hume had referred. I had gone beyond simple liver transplantation in that other organs were being transplanted with the liver in what was called multivisceral transplantation (36). Instead of facing its new recipient environment alone, the liver was accompanied by the donor stomach, intestines, and pancreas. Since these were the organs which drained into the portal vein, the transplanted liver could bring with it its own supply of insulin, food, and the other substances which a few years hence would be called hepatotropic factors.

Only five animals survived the difficult operation, but in each one rejection of the individual organs was less than would be expected if they had been transplanted by themselves. Because the large grafts contained lymph nodes, spleen, and other elements which are part of the normal immune system, it was not surprising to find cells throughout the recipient's own tissues which were thought (but not proved) to have migrated from the graft, reflecting graft-versus-host disease (GvHD) (37). It would be another 13 years before the extent of GvHD, even with transplantation of the intestine alone, would be worked out in rats by the Massachusetts General Hospital surgeons, G.J. Monchik and Paul Russell (38).

My enthusiasm about the multivisceral transplant project was put into the deep freeze by the discussion that followed my talk. William Longmire of UCLA deflated any illusions I might have had about its importance. He asked wryly if it might be easier than performing this complex operation to simply anesthetize the dog and have a laboratory assistant carry the animal from one table to another. The ripple of laughter from the audience completed the humiliation.

Longmire was implying what I already knew, that any such research, including that involving liver transplantation alone, was a

technical exercise unless a means could be found of controlling rejection. Stimulated by Hume's report earlier in the year (35), I had already tried to depress the immune system with x-ray therapy before liver transplantation. Irradiation of liver grafts had no beneficial effect and irradiation of the recipient was overtly harmful (39).

The faint hope that remained was the 6-mercaptopurine Hume had mentioned to me earlier and which Calne had described the previous February in two dogs which had survived for 20 and 47 days after similar kidney transplant operations (40). At another Surgical Forum session on the same day as my presentation, Zukoski reviewed the evidence from Hume's Richmond team that kidney graft rejection was weakened and delayed by this drug (41). His results, along with those from earlier skin graft experiments in rats (42,43), and the independent observations by Calne provided hope where there had been none before.

The hope was dim because only a small minority of animals could be kept alive for as long as one month, and none of the kidney recipients had truly long survival. In principle, the dilemma was not different than with x-ray therapy, although the possibility remained that there was a better therapeutic margin. It was also obvious that liver transplantation was much too complicated an operation to use for studies of immunosuppression. The road to the liver would have to lead through the kidney.

Knowing that Joe Murray's Brigham research team was screening immunosuppressive drugs in Frannie Moore's surgical laboratory (Calne would be coming there in 1961), I approached Moore as we walked down the street after one of the forum sessions. I asked him if he would accept me for a research sabbatical in Boston, effective immediately if possible. The fact that I was a Markle scholar gave me a small financial hedge since these funds (\$6,000/year for five years) could be trans-

ferred between universities. I had not discussed the matter with anyone for the simple reason that leaving Northwestern had not occurred to me until that day.

I can remember how firm Moore was, but also how kind, as he denied my request. I became (and still am) indebted to Moore for his decision which, because it was negative, moved me on to an entirely new level of development and responsibility. Fourteen months later, I left Chicago to be an Associate Professor of Surgery at Colorado. On March 27, 1962, less than three months after arriving in Denver, I performed our first human kidney transplantation on a patient who is still alive 29 years later. Eleven months after that on March 1, 1963, came the first attempt at human liver replacement. As I had concluded in San Francisco, the road to the liver would lead through the kidney, but I would have to find a pathway myself by becoming involved in the renal field.

Deciding to leave Chicago in the space of one day in San Francisco was easier than actually doing it. I had no place to go nor any prospects because I had not been planning to move. However, it seemed to me that the next step in transplantation would not be possible where I was. After a year of exclusively experimental work, I had begun to see private patients in the summer of 1960. The practice grew uncontrollably but almost all of it was being done in private hospitals rather than the Northwestern University hospitals. Overnight, I had become a commercial surgeon and by so doing had freed myself from debt for the first time in more than 10 years. But the time and energy to accomplish this had been stolen from the research program which was the justification for my Markle scholarship.

A way out was found for me by Ben Eiseman, who was Chairman of the Department of Surgery at the University of Kentucky. William R. Waddell, the newly appointed Chairman of Surgery at the

University of Colorado, was looking for someone to fill the position of Chief of Surgery at the Denver VA Hospital, an appointment held by Eiseman until his departure for Kentucky. This was one of the best nonchairman jobs in the United States. Eiseman recommended me to Waddell who subsequently came to Chicago in the summer of 1961 to discuss the possibility. Waddell wanted transplantation to be an imprint of his new department. Although he had no experience in the field, his long stay in Boston had exposed him to the much publicized activities at the Brigham. His own affiliation at Harvard always had been at the Massachusetts General Hospital, but he was friendly with Dave Hume, Joe Murray, and Frannie Moore.

We agreed on the goal of bringing liver transplantation to clinical use. However, we also realized that it could not be attempted until kidney transplantation, an operation which had almost universally failed until that time, could be made to work. I told him that no single agent or drug, would allow us to accomplish anything more than had been done by the pioneers whose efforts in the kidney field are described in other contributions to this volume.

To avoid a false start, we would follow the tracks of Joe Murray and John Merrill (24) by beginning with an identical twin case in which immunosuppressive treatment was not necessary. Waddell, whose move to Denver in July 1961 preceded mine by almost six months, knew of a 27-year-old patient who had a potential identical twin donor. The potential recipient was being cared for at a Denver private clinic. The attending physician had promised to hold his patient for transplantation until my arrival, instead of sending him to Boston as he originally planned.

Waddell and I placed a high priority on duplication of the Northwestern transplant laboratory at the VA animal facility which was essentially unused by surgeons following the mass exodus of Colorado faculty

during the preceding year. The laboratory had been cannibalized by other departments, and nothing was left for us except for a small operating room with a kennel across the hall that could accommodate 30 or 40 dogs.

What we aspired to seemed like lunacy to some of the people whom we recruited to the transplant team from the existing faculty

in January 1962. In spite of these doubts, the identical twin transplantation went forward in March 1962. Both the donor and recipient teams had practiced the operation many times on cadavers in the morgue, and by the time of its performance there was little reason for anxiety. The result was perfect (44). Both the patient and his donor remain well more than 29 years later.

PHASE III (1962 to 1963)

At the time of our identical twin transplantation, artificial kidney machines had appeared in the United States but were used primarily to tide patients over during an acute but reversible bout of renal failure (7). Transverse incisions to insert the plastic tubes into the patient's vessels for connection to the machine would start at the wrists, moving upward every few inches to find new access sites until the axillae were reached. Each site was used three or four times. When the arms were used up, the incisions would start at the feet and move up to the groins. Once the leg vessels were exhausted, the string had played out.

This was changing after the introduction in 1960 of the Schribner shunt for chronic dialysis at the University of Washington. However, blood vessel access was not the only problem. In 1962, very few artificial kidneys were available. The problem was dramatically publicized in *Life* magazine, November 9, 1962, by pictures of a tribunal in Seattle deliberating on which six patients among many candidates should be selected for entry into the only artificial kidney unit in the world equipped for chronic care (45).

Dr. Joe Holmes, the Chief of Nephrology at the University of Colorado, had the equipment, skill, and experience to use the new technology. Approaching 60 years, he became the oldest member of the transplantation team. Chronically fatigued by overwork and lung disease which he aggravated by constantly smoking cigarettes,

he fought to treat or hold back the tide of desperate patients who flocked to Colorado General Hospital after the publicity of our identical twin transplantation.

One of these patients with renal failure was a 12-year-old Black boy named Royal Jones. His arrival was too early, because we were not ready to treat him and would not be for another half year. Holmes agreed to try to hold Royal Jones on dialysis and the countdown began. The VA transplantation laboratory for which we had been slowly acquiring equipment and personnel sprang into action. It was possible within a few weeks to perform eight or 10 dog kidney transplantations in a day or twice this number if necessary. A supply of the 6-mercaptopurine or its derivative BW 57-322 (Imuran), which was receiving its first trials at the Brigham, was obtained from George Hitchings of the Burroughs Wellcome drug company.

We were particularly interested to see if x-ray therapy could be combined with Imuran since the only genuinely promising results of which we had knowledge in other than twin cases were those of the French teams of Rene Kuss (46) and Jean Hamburger (47). They had used irradiation. However, in our dogs given total body irradiation at the same levels planned for Royal Jones a disquieting effect was seen. Many of the canine kidneys quickly became enormously swollen and cyanotic, seemingly worse than in untreated animals. Only an occasional animal had prolonged survival.

The results were the same as Hume had reported in dogs (35). Our pessimism was reinforced by the discouraging results in the clinical irradiation trials at the Brigham (48,49).

The best results were with Imuran. Some of these dog recipients lived on for years, long after discontinuance of therapy. It was demonstrated unequivocally that prednisone therapy could reverse rejection but caused death from its own side effects of which ulceration and bleeding from the intestinal tract were almost invariable (50). These observations were not published until long after the clinical steroid trials were underway (51). Our conclusion by the autumn of 1962 was that survival for 100 days or more with any single agent could be achieved in only one of every four or five mongrel dogs. There had been no time to test all of the treatment combinations.

What to do with this incomplete information, and with similar observations reported by Calne and Murray from the Brigham laboratories at the Surgical Forum in October 1961 (52), was our quandary. Adequate hemodialysis for Royal Jones was becoming more difficult daily because of exhaustion of his access sites. The transplantation with a kidney from his mother went forward on November 24, 1962, with combination treatment by irradiation, Imuran, and prednisone.

To protect him from infection, he was kept in one of the Colorado General Hospital operating rooms for a month afterwards during which he had a moderately severe rejection which was reversed easily with large doses of prednisone. A few weeks following this, he returned to school. The transplant lasted until 1968, and then was replaced with a second graft. Many years later, the second graft also failed. Royal is still alive awaiting his third kidney nearly 29 years later.

The success could have been a fluke. During the next 12 weeks, three more kidney transplantations were performed but

omitting total body irradiation. Two of these patients who were treated with Imuran and prednisone also are alive, both with their original grafts from a brother or sister. The third patient named Bill Sinclair died of infection 113 days postoperatively. After the transplantation, a large thrombus in one of his leg veins migrated to his pulmonary artery from where the embolus was removed at an emergency operation by Dr. Tom Marchioro, now Professor of Surgery at the University of Washington. Sinclair never fully recovered but his new kidney, which had been donated by his wife, functioned well until the end. It seemed to us that the immune barrier now had been surmounted repeatedly. The stage was set for liver transplantation. It never would be this easy again, in part because our strategy in the kidney program had emphasized the use of related donors and in part because liver transplantation was a vastly more difficult operation.

The first attempted liver transplantation on March 1, 1963, ended in tragedy. The patient was a 3-year-old child with biliary atresia which had brought him to the miserable last days of his life in a condition which today might be considered beyond help by transplantation. The donor was another child who died during an open heart operation. In looking back, one can ask why the liver recipient, who himself was on life support with a ventilator, should not have donated a heart to the other child instead of receiving his liver.

The question did not come up because the first heart transplantation in Capetown was four years in the future. Instead, the donor who already was on a heart-lung machine was cooled while the artificial circulation was maintained. Although we had performed nearly 200 liver transplantations in dogs, nothing could have prepared us for the difficulties in the recipient which were caused by portal hypertension, scarring from previous operations, and a complete lack of clotting. The patient bled to death.

During April and May 1963, more kidney transplantations were performed. Of the first six nontwin recipients, four were destined to survive for the next quarter century. By now, research in the laboratories turned back to the more difficult operation of liver transplantation. The main lesson that had been learned from the first liver case was that the defective blood clotting found with terminal liver disease would have to be controlled. A German coagulation expert named Kurt von Kaulla who was working in the Department of Surgery was recruited to the team. Von Kaulla recommended strategies to shore up defective clotting factors with infusions of purified blood products and to control fibrinolysis with epsilon amino caproic acid (EACA).

In 1962 and early 1963, the University of Colorado did not have the high visibility in the national media which it later enjoyed, or labored under. Only when Bill Waddell announced it while discussing a paper given by Hume in April 1963 at the American Surgical Association in Phoenix, Arizona did the existence of the Colorado kidney program become generally known (53). Before then, Waddell was in contact with Joe Murray and his other friends at the Brigham in Boston. Dave Hume called me almost daily from Richmond for information about the course of our patients. Both Murray and Hume seemed interested only in the kidney cases. The failed first attempt at liver transplantation went unnoticed by the press.

At the 1963 American Surgical Association meeting, I met Will Goodwin, one of the world's foremost urologists and a pioneer in transplantation in his own right. Several years earlier, Goodwin had attempted several kidney transplantations at UCLA. From these cases, a number of important observations were made which would be of great help to later workers. The death of all his recipients had discouraged him and caused him to stop clinical trials.

In one of Goodwin's patients, he had seen reversal of kidney rejection by steroids

in a woman who also was treated with the anticancer drug, cyclophosphamide (54). She survived for 160 days and was the first example of long survival of a human who was treated with drugs only, using a drug combination that was extensively evaluated a decade later (55). Goodwin's historic kidney transplantation was in September 1960. However, the observation of steroid responsiveness was not published until 1963 and was unknown to me. After talking to Goodwin in Phoenix, I added a discussion of Goodwin's case to our paper but failed to annotate the basic literature on steroid immunosuppression (27-29) and the clinical observations on steroid therapy previously made by Kuss (46) and Hamburger (47). This was unintentional neglect.

Beginning in 1962, we had been using Imuran plus prednisone, and our conviction was that prednisone was the dose maneuverable component of this first version of modern day immunosuppression. The Imuran-steroid combination was the secret of our unexpected success and in our manuscript containing this message (51), we emphasized two other points: the reversibility of kidney rejection with high dose steroid (prednisone) treatment, and the "tolerance" which allowed lightening of maintenance immunosuppression in the weeks and months after a successful kidney transplantation.

While we talked in Phoenix, Goodwin told me of an impending meeting on renal transplantation in Washington, DC, scheduled for September at the National Research Council. He said that he would arrange invitations for me and for Bill Waddell. A few days later, Goodwin came to Colorado. I learned later that his habit was to glean information from these informal visits and to report it in memoranda to the UCLA transplant group which included Paul Terasaki. More than 27 years later, in November 1990, a urologist named Jacques Poisson of Nice, France gave me a yellowed copy of a six-page single-spaced

intramural letter from Goodwin which Poisson had saved from his fellowship days with Goodwin in Los Angeles. Dated May 11, 1963, the in-house document started:

"Dear Friends: On May 5 and 6, I visited Denver to learn what I could of the homotransplantation effort of the group there (Tom Starzl, William Waddell, Tom Marchioro, Oliver Stonington, and about a dozen others). The visit was most impressive to me, and I should like to share some of my impressions with you.

When I arrived on the evening of May 5, I went to the Veterans Hospital where I visited the completion of what must surely be the world's first technically successful homotransplantation of the human liver. The recipient, a patient of Dr. Waddell's, was a man with a primary hepatoma involving the whole liver. He had had two explorations, 7 days and 1 day before the transplant. He was a non-veteran admitted to the VA Hospital in order to receive the transplant from a VA patient dying there of a brain tumor. The surgical team was waiting alerted for 48 hours, one of the drawbacks of cadaver donor transplantation.

When the white donor (the recipient was Afro-American) finally died, Dr. Marchioro and his team promptly introduced a catheter via the femoral vessel and began perfusion (up into the aorta) at a slow rate with a heart-lung machine that was primed with refrigerated oxygenated glucose solution plus procaine. Later they opened the chest and also perfused the lower aorta and abdominal organs from above.

Preparation of the sterile donor liver took about 2 hours. Approximately, another 2 hours were spent in transplanting the liver, performing all the necessary anastomoses. When I saw the homotransplant in place, it had a good color and looked like a normal liver. A cholecystectomy was done and the gall bladder bed bled in a healthy normal way. A T-tube was placed in the common duct below the anastomosis and shortly thereafter, it began to drain clear bile. The

above surgical procedures were done . . . with great skill and careful speed. . . . They had tried this some weeks or months ago in a child with congenital atresia of the bile ducts. The procedure failed because the recipient bled to death under their eyes. There was lack of blood clotting. Because of this awesome previous education, they were prepared in the present case, and gave large amounts of human fibrinogen intravenously during the operation.

The next day, I saw and talked with the patient. His new liver was making large amounts of clear bile and he seemed to be in good immediate postoperative condition. It seemed to me that the patient was in better shape than the surgeons on the day after this monumental effort."

The rest of Goodwin's letter was concerned with the kidney recipients, many of whom he interviewed. As it turned out, the patients to whom he talked are still alive. Goodwin went on:

"The Denver team has either 8 or 9 successful kidney transplants (2 or 3 since dead) Another patient I was privileged to see is a 35 year old male who had come from Virginia to the Denver VA because he was told that the Denver and Los Angeles VA Hospitals were "centers" for kidney transplantation. Denver was closer than Los Angeles, but somehow he got past Richmond and Hume. He received a kidney from his 32 year old sister in January, 1963. Before that, he had dialysis in Virginia (at the VA Hospital), and in Denver in preparation for the transplant. He appeared to be in excellent health. He had a moon face and ruddy cheeks. He confessed to an interest in sex and erections but evaded the question of whether or not he had intercourse (he is a bachelor). He apparently is presently a ward of the VA, and is being rehabilitated. I think that he takes Imuran and prednisone and I believe that he formerly had chronic glomerulonephritis. He was a truck driver."

This patient also is still living with his graft which is the longest surviving nontwin kidney transplant in the world. It is interesting that there was an ABO blood group mismatch. He was B blood type and his sister donor was A.

A cadaver organ procurement program was a necessary condition for the Denver program and particularly interested Goodwin. Brain death and the concept of the heart-beating cadaver were five years away. Consequently, all donors were without a heart beat and circulation for five to 30 minutes before an artificial circulation could be restored with a heart-lung machine (56,57). Goodwin had not heard of this method and wrote:

"Tom Marchioro has worked out and is the driving force behind an active and intelligent program to harvest cadaveric organs (especially kidneys) for homotransplantation. . . A very low pressure system is used with low rates of perfusion (aortic) so that the blood inflow (to the pump) matches the output. They feel that this is valuable and useful and have had some good animal experimental data to support them. . . A visit to their dog lab at the VA Hospital was most impressive. It is a well run, active place, air conditioned, and clean. They have plenty of technical help. They keep superb records on their animals, similar to regular hospital charts. They have one doctor in full time charge of records alone. They have a number of excellent kidney transplant experiments going on to test the value if any of splenectomy, thymectomy, etc. They also have an active program with liver transplants."

Goodwin's six-page single-typed memorandum is too lengthy to reproduce in its entirety, but near its end was a comment about the interactions within any multidisciplinary group, showing Goodwin's grasp of human behavior:

"One of the interesting human aspects of this work, not only in Denver but everywhere, is how much each participant

wants to be a part of the team and how each of us speaks so readily of "our experience," while privately considering it "my experience." Everyone with whom I speak is eager and ready to give credit where due, and at the same time wants to ensure his own niche and his own credit."

Reading his report nearly 28 years later, I wondered if Goodwin might have set new standards in journalism had he not committed himself to surgery. He saw everything that was significant. The clotting problem had been dealt with in the liver recipient whom he observed, and the kind of management during operation which he described became standardized over the years. However, the strategy of coagulation control had a delayed backfire in this case and in the next three liver transplant recipients who followed. During the time when the livers were sewed in, the plastic external bypasses were used to reroute venous blood around the area of the liver in the same way as had been worked out in dogs.

In the humans who were being given drugs and blood products to promote clots, these clots formed in the bypass tubing and passed on to the lungs. There, they caused abscesses and other lung damage which contributed to or was the cause of delayed death of not only the patient seen by Goodwin (who died 22 days later) but in three more recipients who had otherwise successful liver transplants in June, July, and October 1963 (57,58). A pall settled over the liver program, and no more patients were entered for more than three years. It was the beginning of a self-imposed moratorium. By this time, single patient trials had failed at the Brigham (59) and in France (60).

When Goodwin left Denver in early May 1963, he realized the regularity with which rejection could be controlled in kidney recipients using the Imuran-prednisone treatment. However, in his lectures, he always warned "Don't promise more than you

can deliver," and illustrated the point with the photograph of an ancient statue of one of the Greek gods who was sparsely clad. Wrapped around the god's leg was a voluptuous maiden, expressing some unfulfilled desire, the nature of which was left to the amused audience's imagination.

Throughout the spring and summer of 1963, our pace of kidney transplantation increased, and the series had reached 30 by the time of the Washington kidney transplant meeting in September 1963. This conference to which Waddell and I were belatedly invited was a small one, with only about 25 contributors. However, almost all of the key workers were there who had brought the field this far. Here, I first met Joe Murray, John Merrill, and other members of the distinguished Brigham group. The French and English pioneers also were there including Ralph Shackman, Ken Porter, and Roy Calne. I was uneasy and felt like someone who had parachuted unannounced from another planet onto turf that was already occupied.

By this time, I had started writing a book, *Experience in Renal Transplantation* (61), which was to be published the following summer. In its introduction which already was in the hands of the printer, I already had summarized the work of these men. After describing the dismal record to date, it went on:

"... Despite these encouraging findings, it was not yet possible to obtain consistent success with homotransplantation procedures, either in experimental animals or man. Like the elusive jigsaw puzzle, in which many of the pieces had been fitted into their appropriate slots, the picture was not yet complete. The pioneer efforts of Murray, Kuss, Hamburger, and Hume had all demonstrated that a renal homotransplant was capable of protracted function in the occasional case. If this could be achieved sporadically, it seemed reasonable to expect that the proper manipulation of a number of small details

might provide a consistently successful solution. Despite this expectation, almost all renal homotransplants had failed when, in the spring of 1963, Goodwin and Martin compiled the known renal transplants from various centers throughout the world. Less than 10 per cent of those cases treated to that time had survived for as long as three months. The courageous and often tragically unsuccessful attempts of the early pioneers provided a vast, although frequently uncatalogued, background of valuable information upon which future progress might be built . . . "

These were the kidney transplant pioneers. What we had done was to complete their story. At the same time, we realized for the first time in Washington that we had more surviving kidney transplant recipients than everyone else combined. Determining the eventual outcome of these patients would be important. This was made possible by the creation at the conference of a worldwide kidney transplant registry, which would be based in Boston. The impetus for this extraordinary compilation came from Joe Murray.

The meticulousness of the registry report (62) made it possible 25 and one-half years later in the summer of 1989 to trace the fate of all 342 nontwin kidney recipients who had undergone transplantation throughout the world from the beginning up to the end of March 1964 (63). There were 24 25-year survivors, of whom 15 were from our original Colorado series. The nine others were still alive at six other centers. These included three of Dave Hume's original patients at the Medical College of Virginia, two from the University of Minnesota (Kelly and Lillehei), and one each from Boston (Murray), Cleveland (Kolff), Edinburgh (Woodruff), and Paris (Hamburger).

In this look-back, none of the world's 24 quarter-century survivors had been given an unrelated donor kidney. Nor was there an example in the world of a 25-year survival of

a cadaver kidney allograft (63). One of Hamburger's cadaver kidney recipients in Paris finally passed this barrier on October 12, 1989. This was not surprising. Inferior results with unrelated donors were evident even at the time of the Washington meeting.

Because liver and heart grafts could be obtained only from cadaver donors, what had been learned so far was not an invitation to go forward with the extrarenal trials. Better antirejection treatment than the Imuran-prednisone combination must be developed or else a means had to be found to better match up the donors to the immune system of the recipient (tissue matching). Apart from the deaths that already had occurred, this was the main reason why the liver program was closed for three more years. Our primary mission of liver transplantation had failed. Instead of introducing a new treatment for liver disease, we had succeeded only in making kidney transplantation practical. Not long after, Waddell remarked that we had climbed onto the wrong tiger and would find it hard to get off. I soon understood how right he was.

After the Washington meeting, several of the conference members came to Denver for a first hand look: Hume, Porter, Shackman, Kuss, and Kuss' young associate, Jacques Poisson. While there, Porter agreed to write the section on kidney transplant pathology for my impending book on renal transplantation. His chapter was a classic which was years ahead of the field. Before long, his interest turned to liver transplantation and stayed there for the next 28 years.

Elsewhere, the kidney gold rush began. At the beginning of 1963, the only active kidney transplant programs in the United States were at the Brigham, in Richmond, and at the University of Colorado. More than 25 new ones sprang up in the United States alone within the next year. We were inundated with fellowship applications, providing a talent pool from which came many of the leading figures in transplanta-

tion of the next generation. Kidney transplantation seemed to have become a clinical service overnight.

This was partly an illusion. It would not be possible for many more years to safely transplant cadaveric organs of any kind, including the kidney. Well into the late 1970's, Terasaki reported a compilation from 105 American programs of nearly 5,000 cadaveric kidney cases in which the one-year graft survival was only 45 percent with an average patient mortality of nearly 20 percent (64). Individual centers tended not to report their own poor results, erroneously believing that everyone else must be doing better.

During the peak of the professional euphoria, many major hospitals had acquired artificial kidney capability, with the result that patients who would have died only one or two years earlier could be kept in reasonable condition while they waited for a transplant. Serving their needs was almost entirely dependent on live donors because brain death as a condition for cadaveric donation was five years in the future. Desperate potential recipients were piling up faster than places could be found for them for dialysis support, a service for which most health insurance agencies refused to pay because it was "experimental."

At the height of the crisis, heterotransplantation was reexplored. On February 16, 1963, Dr. Claude Hitchcock of Hennepin County Hospital, Minneapolis, transplanted the kidney of a baboon to a 65-year-old woman. The organ functioned for four days before its artery clotted (65). The case was not made public until it was learned later in 1963 of a far more encouraging experience by Dr. Keith Reemtsma of Tulane University using the the closer-to-human chimpanzee donor (66). One of Reemtsma's chimpanzee kidney grafts functioned for nine months. Reemtsma also transplanted a Rhesus monkey kidney which was fiercely rejected.

Convinced that his own first failure was due to a defective surgical operation and that the baboon would be an acceptable kidney donor for humans, Hitchcock called me about exploring this possibility for our patients with urgent need. He already had a strong collaboration with the Southwest Primate Foundation, an outstanding primate center in San Antonio, Texas. Baboons were bred there, and their medical records were kept for their life time. Infecting patients with baboon diseases seemed unlikely. An international consortium of primate experts descended on Denver.

Six patients were given the baboon kidneys at Colorado (67). All of the organs functioned promptly and maintained function for 10 to 60 days. However, the necessary doses of Imuran and prednisone were

very high, and eventually the grafts were rejected. As judged by Porter, the rejection was midway in severity between that of the chimpanzee and Rhesus kidneys but not qualitatively different than in some homografts in which there was a humoral component. The same events were recapitulated two decades later in the Baby Fae baboon-to-human heart transplantation in spite of much improved immunosuppression (68). It was clear that the use of animal organs would have to wait for better and possibly fundamentally different immunosuppression. The chimpanzee would be excluded from future consideration because of the threat to its extinction and because its anthropomorphic qualities were increasingly recognized (69).

PHASE IV (1964 to 1966)

After the dust settled, a new era began - this one of consolidation, confirmation, and sober reflection about what had been done. Will Goodwin, whose memorandum of May 1963, was quoted in Phase IV, now wrote another one to his UCLA team, reflecting the amazing events in the intervening 11 months. Like the first document, this one was found in Nice, France, in the memorabilia which Jacques Poisson had saved. After a lengthy description of the papers (many on transplantation) given at the 1964 American Surgical Association (April 1-3, Hot Springs, Virginia), Goodwin concluded:

"... It seems to me that we are now in a kind of "second phase." Many have more confidence than before and are beginning to look for longer range successes. At the same time, we should go slowly to study and observe some of these strange things that are being seen, such as peripheral neuropathies and vascular lesions, etc. I would not be surprised if one of the most interesting things that could come out of all of this will be observations of what may turn

out to be "new diseases" in some of these long range survivors."

Goodwin was prophetic. The most obvious derivative diseases were those caused by the steroids which were essential for consistent success: redistribution of body fat with moon facies and the typical "buffalo hump," growth arrest in children, damaged and thinned skin with abdominal stretch marks, cataracts, bone demineralization and joint decay, myopathy, peripheral neuropathy, and secondary diabetes. The quality of the recipients' lives as well as freedom from lethal opportunistic infections were inversely related to the amount of steroid therapy needed to retain function of their new kidneys. It was soon learned that low steroid dose requirements could be expected only if the donor was a family member.

Even under these circumstances, it was tempting to bring to conferences or symposia only those patients who had been recently operated upon, before the stigmata of steroid treatment became visible. A further specter emerged when several of our

earliest recipients developed a malignant tumor (then called a reticulum cell sarcoma, later classed as B-cell lymphomas) in the brain, liver, or elsewhere (70). It was soon apparent that these and other cancers would be seen in increased numbers in these patients (71,72). Israel Penn, now Professor of Surgery at the University of Cincinnati, began a worldwide registry of these cancers in transplant recipients; at the end of 1990, more than 5,000 had been entered. The complication was attributed to the loss of immunologic surveillance, but evidence supporting this hypothesis was at first marginal (72). Years later, after the demonstration that the Epstein-Barr virus caused the B-cell lymphomas, it was shown that these lymphomas usually involuted when immunosuppression was stopped (73).

Appreciation that kidney transplantation was a still imperfect new form of treatment was a powerful stimulus to find better ways of immunosuppression, or else to find ways to improve tissue matching and thereby reduce the amount of immunosuppression which was needed. Strategies to achieve both objectives were put in place during a half year moratorium on new kidney cases which was decided on in Colorado, beginning in the spring of 1964. Ripples from these strategies can still be seen almost three decades later.

The first step was a trial of tissue matching. What to measure, and how, were unanswered questions. We already had shown the importance in kidney transplantation of compatibility of the ABO blood group antigens. About half of the ABO incompatible kidneys were rejected within minutes or hours, presumably because of binding of the isoagglutinins to ABO antigens in the cells and blood vessel endothelium of the kidney grafts. From this experience came the rules of ABO compatibility for kidney transplantation (74), which later were shown to apply to the liver, heart, and other solid organs (75).

Beyond ABO matching, it was predicted by many of the Washington conference participants of 1963 that tissue matching would improve the reliability and predictability of rejection control. Felix Rapaport, one of the conference members, already was a star in transplantation because of his work in histocompatibility. Paul Terasaki's name was frequently mentioned in such discussions because he recently had developed his microcytotoxicity technique which he thought detected histocompatibility antigens in the lymphoid cells. The concept was the same as that advanced earlier by Dausset (76) using a different antibody detection system and subsequently supported by collaborative investigations with Rapaport.

Workers in Holland, Italy, Denmark, England, and the United States began to search for other antibodies, believing that by back tracking the antibodies, they might be able to identify the tissue antigens which had evoked them. If this were possible, the practical next objective would be to match up these antigens in donors with the antigens of prospective recipients. This was the beginning of human histocompatibility research, a new field of indescribable importance and complexity which made intelligible many previous mysteries of the human immunologic system and certain aspects of immune rejection of transplants.

By 1963, the list of antibodies which seemingly reacted with different human tissue antigens was long enough to convince Terasaki that matching efforts in future cases might be worthwhile. However, he wanted to begin by studying the antigens in

O to non-O*	Safe
Rh- to Rh+	Safe
Rh+ to Rh-	Relatively safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB	Dangerous
*O is universal donor, AB is universal recipient [Reproduced from (74)].	

patients bearing successfully transplanted kidney grafts, comparing those with the antigens in their donors, and seeing if there was any relation of the fit of the antigens with the clinical outcome. A positive correlation of good matching and good outcome would establish that the antigens being studied second hand through their reaction with the antibodies were the crucial ones involved in rejection. This was Terasaki's hypothesis and that of Dausset and Rapaport.

Knowing from Goodwin's report from the Washington conference that most of the kidney transplant survivors were in Denver, Terasaki came to Colorado after the meeting, rounded up the recipients and their donors, drew blood samples, and estimated the antigen match with his still impure and incompletely classified antibody panel. To everyone's delight, many of the most trouble-free recipients were those whose white cell antigens closely matched those on the donor's white cells. The clue was tenuous because there were so many exceptions and also because most of the successfully transplanted kidneys came from sibling donors or from parents who had donated to their children (77).

The retrospective study was finished by autumn and when our kidney program was reopened in October 1964, it included the first effort ever made at prospective matching (78). At the time, kidney donation in Colorado was still being accepted from volunteer convicts at the Canon State Prison who were numerous enough in many cases to allow a choice amongst as many as 50 or 60. In spite of the size of the unrelated donor pool, it was difficult to find a perfect or even good match whereas very complete matches were encountered frequently if there were multiple potential donors within a family.

The results when the transplantations were actually performed were disappointing. The matching in unrelated cases, although never complete, was better than that pre-

viously achieved by chance when no such efforts had been made. However, no difference could be seen in the recovery of patients who received kidneys from these relatively well-matched versus completely mismatched donors or in the histopathology of the grafts which were graded by Porter after biopsy.

The results were reported as "preliminary" in 1966, but by 1969, I was alarmed by the continued lack of correlation between clinical outcome and quality of matching in unrelated cases (by now largely cadaver donors) and concerned about my role in starting these epidemic efforts at matching five years previously and spurring them on subsequently. We collected clinical data on all of our patients in whom we had tissue typing information from the beginning of our Colorado program in 1962 until the present and arranged the first of several grueling work sessions at Terasaki's laboratory. The conclusion was that typing was not a discriminating instrument of donor selection using unrelated donors, that it could be used to select ideal donors within families, and that short of perfect matches, it was only equivocally helpful even within families.

Reports of these results at nephrology and surgery meetings (79) created a furor in the typing fraternity. The evidence was that the antigens being matched were transplant antigens which followed classical genetic (Mendelian) laws (witness the sibling results) but that the system was so complex (more than we were measuring) that matching would not be the boon we had predicted. Terasaki suspected that there might be a "center effect" in which experience and skill with immunosuppression covered up a typing effect or that the sample size was too small to test the original hypothesis.

He set out to collect 1,200 cases from multiple centers. The original conclusions were validated and the new analysis was presented by Terasaki to the Transplantation Society in The Hague on September 8,

1970. Anxious and looking smaller than I remembered him, Paul walked resolutely to the podium and read his message to a huge and it seemed to me hostile audience. When he finished, there was little applause.

Within a few weeks, the federal agency funding Terasaki's UCLA laboratory paid it an emergency site visit and discontinued its support. Terasaki's heretical report was not welcome, and now the messenger must be killed. Before long, others came forward with evidence that Terasaki's conclusions were correct. Terasaki had been right not only about what typing could do, which was considerable for intrafamilial transplantation, but what it could not do in less than perfectly matched cadaveric cases. Twenty years later, the only controversy is whether matching under all other circumstances means enough to be the primary determinant of cadaver kidney distribution. Shorn of his government contract, Terasaki saved his laboratory by other means. Full of honors now, he has remained to haunt the perpetrators of the inequity for the next two decades (80).

By exposing the truth, Terasaki had made it clear that improvement in clinical transplantation would depend primarily on better drugs and other improved treatment strategies, not by vainly hoping that the solution would be through tissue matching. Although it was not appreciated at the time, Terasaki's conclusion breathed life into the still struggling fields of liver and heart transplantation since patients needing these organs did not have recourse to artificial organ support analogous to the artificial kidney while they waited for a well-matched donor. It was a relief to know that the selection of donors with random tissue matching would not result in an intolerable penalty.

Ironically, the supreme practical contribution of tissue typing proved to be the detection of those cytotoxic antibodies which attracted Terasaki's attention in the first place. At the First Histocompatibility Tissue Matching Conference (June 7-8,

1964, in Washington DC), Terasaki described how these antibodies if directed against the cells of the donor can cause hyperacute kidney rejection in the same way as with blood group mismatches (81).

He recommended the cytotoxic crossmatch test which is carried out today before every kidney transplantation anywhere in the world. The credit for this major contribution often is given to someone who was in the 1964 audience and reported the same thing almost two years later. When the details of hyperacute rejection were worked out later, including the similarity of this catastrophe to the Schwartzman reaction (82), Terasaki was a collaborator, and in the late 1970s he defined the kinds of antibodies which were dangerous and which were not.

The tissue matching strategy was played out in the clinics. In contrast, improvement of immunosuppression was a laboratory project from 1963 until the first clinical trials of ALG were begun in 1966. However, the first order of business was an Imuran project with liver transplantation. Our original premise of developing a kidney transplant program as a pathfinder for the technically more difficult liver procedure (83) came into question. When no one was able to obtain truly long survival in dogs, or even survival beyond 30 days after liver replacement, there was growing suspicion that there might be some fundamental difference in rejection of the liver which made this organ more difficult to protect.

After Porter's visit to Colorado in September 1963, 150 canine liver transplantations were performed at the rate of four per week at the Denver VA research laboratories with weekly or twice weekly shipments of the resulting tissues to London. One of the liver recipients from the series (84) lived for almost 12 years before dying of old age. Half of the animals treated with Imuran lived for 25 to 50 days and about one in five survived three months or longer. The results were better than with

dog kidney transplantation, using Imuran alone. At a greater frequency than after kidney transplantation, it was possible to stop treatment after three or four months without evidence of subsequent rejection (85).

The possibility was raised for the first time that rejection of the liver might be easier to control than that of other organs (84,85). Subsequently, much stronger evidence that this was true was provided from pig experiments by Garnier (86), Peacock (87), and Calne (88). The pathologic studies by Porter filled in other missing information (89). He redefined the features of acute rejection, delineated those of chronic rejection, and laid the basis for needle biopsy interpretation which became a cornerstone of modern management of liver transplant recipients.

These liver transplant experiments settled the issue of feasibility but not of practicality. For human cases, all livers would have to come from cadaveric donors. These nonrelated organs would be more difficult to protect from rejection than the "easy" intrafamilial human kidney transplantations that had fanned our enthusiasm in 1962 and 1963. The next project was the development of ALG.

Ken Porter was the person who suggested the ALG project. He knew of work in progress on antilymphocyte serum (ALS) in rats by Michael Woodruff and Keith James of Edinburgh and by other workers in Britain. The principles of ALS therapy had been known since the time of Metchnikoff who immunized guinea pigs with rat lymph nodes or spleen cells and then demonstrated that the guinea pig sera lysed rat monocytes (90). With a flash of clairvoyance Metchnikoff suggested the use of such sera to eliminate the cell lines guilty of causing certain human diseases (later shown to be autoimmune). Sixty years later, the pursuit of this fantasy would take a detour through transplantation.

In modern times, ALS preparations to prevent experimental skin graft rejection

were first used at Yale University (Byron Waksman) (91), Edinburgh (Michael Woodruff) (92), and at Harvard (Tony Monaco and Paul Russell) (93). A tidal wave of publications followed including those from Medawar's laboratory (94). In these experiments, rabbits were immunized against the lymphocytes of mice, guinea pigs, or rats. The rabbit serum was injected intraperitoneally in the treated animals. Skin grafts placed between mice, between guinea pigs, or between rats survived for prolonged periods.

The infusion or injection of raw animal serum into humans was not a particularly palatable idea, especially when the dosage into the abdomen would be several gallons if the experimental information was applied to clinical practice. In addition, a larger animal than the rabbit would be preferable in which to raise the antibodies against human lymphocytes. The horse was a candidate. Finally, there was no reason to give the whole animal serum to patients when the antibody activity was presumably limited to some small fraction of which the location was suspected but not proved.

By the end of 1965, we were far along in research on ALS but with a different purpose than the purely scientific ones being pursued in most other laboratories. We were gearing up for clinical trials. We had selected the horse as a serum donor, identified the gamma globulin as the target for refinement of the antilymphocytic antibodies in the horse serum, learned how to remove and purify this fraction which we called antilymphoid globulin (ALG), and devised test tube analyses which would allow us to estimate its potency. The leader of this research team was Yogi Iwasaki, a Japanese surgeon who today is Chairman of the Department of Surgery at Tsukuba University near Tokyo (95). When he returned home, he sent another surgeon, Noburu Kashiwagi to take his place (96). Kashiwagi now is Professor of Experimental Surgery at Kitasato University.

Every step in the process and its totality were tested in the dog with both kidney and liver transplantation (97). For these animal experiments, dog ALG was prepared using dog spleen and lymph nodes to immunize the horse. For human ALG, the spleens and lymph nodes were taken from fresh cadavers, and the lymphocytes for injection into the horse were removed from these tissues in much the same way as must have been used by Metchnikoff two-thirds of a century earlier.

In June and July, 1966, the first patients in the world to be treated with ALG could be picked out of a crowd of their transplant peers at the Colorado General or Denver Veterans Administration Hospitals. The ALG was given into the muscles of the buttock and caused such severe pain and swelling that the patients constantly walked the floors trying to rid themselves of what felt like a charley horse. They sat crookedly on chairs and formed their own support group to exchange tall tales and especially complaints.

The trial was a success (97,98). Rejection was practically eliminated during the period of ALG therapy if treatment was started at the time of transplantation. If ALG treatment was delayed, it could be used effectively to reverse established rejection. The amounts of Imuran and prednisone (especially the latter) were reduced. This was the beginning of the triple-drug immunosuppression (Imuran-prednisone-ALG) which was the new plateau from which liver transplantation could start again. Not far behind would come the heart.

Later, improvements were made in ALG therapy. Purer preparations of human lymphocytes could be obtained by collecting them from the thoracic duct during thoracic duct drainage (Traeger of Lyon), from the thymus, or by culturing them. The technique of lymphocyte culture was developed by George Moore of Roswell Park Hospital, Buffalo and applied by John Najarian, Richard Condie, and Richard Simmons at

the University of Minnesota. Also, the ALG could be given intravenously, eliminating the intramuscular injection pain which for some patients was almost unendurable.

The limitations of ALG were defined almost immediately (97-99). It was not a drug like Imuran or prednisone which could be used for chronic treatment because of immune reactions against the injected horse protein. A penalty for the use of ALG was a higher incidence of virus infections including those (Epstein-Barr) associated with lymphoma formation. What we had accomplished was a significant but not a quantum improvement in patient care.

Ben Cosimi, one of our Colorado medical students, assisted with the development of ALG for human use before leaving for the Massachusetts General Hospital in July 1964 to begin his surgical training. His dream of producing a more practical and safer ALG came within reach when Kohler and Milstein developed the hybridoma technology (100). With it, Gideon Goldstein and Cosimi produced OKT3, a modern version of ALG, and began its clinical use in 1980 (101).

Improved immunosuppression and a better understanding of tissue matching were justifications for resumption of clinical liver transplant trials. There remained the problems of the liver donor and liver preservation. Preservation technology for all organs began with liver transplant research in the late 1950s. The first innovation of core cooling by infusion of chilled lactated Ringer's solution into the portal vein was the most important (31). This was the first time hypothermia was induced by the intravascular infusion of cold fluids. Earlier it had been appreciated by cardiac surgeons that hypothermia protected ischemic tissue below the level of aortic-clamping (102). Hypothermia to protect human renal homografts was first accomplished with total body hypothermia of living volunteer donors (44), but before long we replaced this cumbersome and potentially dangerous method

with infusion of chilled fluid into the kidney immediately after its removal (103). It was a simple and overdue transfer of technology from the laboratory.

Today, core cooling is the first step in the preservation of all whole organ cadaver grafts and this is most often done in situ by some variant of the technique observed by Goodwin (see earlier) in May 1963 during his visit to Colorado (56,57). This method for the continuous hypothermic perfusion of cadaveric livers and kidneys was used clinically long before the acceptance of brain death conditions. Later Ackerman and Snell (104) and Merkel, Jonasson, and Bergan (105) popularized in situ cooling of cadaveric kidneys with cold electrolyte solution infused into the distal aorta. Two decades later, in situ cooling was refined to allow removal of all thoracic and abdominal organs, including the liver, without jeopardizing any of the individual organs (106,107). When the final versions of these so-called flexible techniques of procurement were published in the 1980s, they quickly became a worldwide standard.

Extension of the safe period beyond that provided by initial cooling and avoidance of warm ischemia has followed one of two prototype strategies. The approach of providing a limited and continuous hypothermic circulation was refined to isolated organ perfusion by Ackerman and Barnard (108) who used a perfusate containing blood. The perfusate was oxygenated within a hyperbaric oxygen chamber. The same method with slight modifications also permitted the successful preservation of dog livers for as long as two days (109) and was applied clinically with remarkable success in several human cases in the pre-brain death era after preliminary total body cooling with extracorporeal perfusion (110).

The isolated liver perfusion project was headed by Larry Brettschneider, a 30-year-old surgeon and Lieutenant Commander in the United State Navy who was detached to Colorado for two years, beginning in early

1966. The technique was ready for clinical use by the end of the year. It may be that this was the best method of liver preservation used to the 1990s. However, the hyperbaric chamber was cumbersome and extremely heavy. The pilots who flew us in small planes to donor cities on the other side of the Rocky Mountains were terrified that it would roll through the side of the aircraft like a lead ball, or explode from its high internal pressure. Later, when brain death was accepted, it never was used again.

Yet, it played a role. This was the technique that was used to preserve all of the first successfully transplanted human livers in 1967 and 1968. Brettschneider died tragically in 1978. When Belzer et al (111) were able to eliminate the hemoglobin and hyperbaric chamber components for kidney preservation, their asanguinous perfusion technique became a worldwide standard. However, efforts to use this modification for livers were unsuccessful (112).

The alternative strategy for the preservation of kidneys, livers, and other organs after initial cooling also had its origin in this era. This was the instillation of special solutions such as that described by Collins, Bravo-Shugarman, and Terasaki (113) or the plasma-like Schalm solution eventually used by Calne (114). The original Collins solution, or modification of it, was used for almost two decades for the so-called "slush" techniques of kidney preservation. The experimental work of Benichou et al (115) and Wall et al (116) with the Collins and Schalm solutions preceded their first clinical use for livers in 1976 which opened up the possibility of organ sharing between cities, but within narrow time limitations.

The introduction of the UW solution was the first major development in liver preservation since then. The superiority of the UW solution to any of previous "conventional" solutions for preservation of liver and extrahepatic organs has been demonstrated in experimental test models (117) and

quickly confirmed in clinical trials (118,119) during the late 1980s. The advance with the liver was then applied to other organs.

One other project of this phase developed a life of its own which continues to expand 25 years later. This was an exploration of the optimum conditions for the transplantation of an extra (auxiliary) liver at some ectopic site, leaving the diseased native liver in place. Reexamination was required of the mysterious Eck fistula (portacaval shunt) and the possible interaction between pancreatic insulin and the liver which had been my entry point into transplantation in 1956 (see earlier). The liver shrinkage caused by portacaval shunts in dogs [and also in rats, baboons, and humans (120)] and the wasting, hair loss and brain damage that follow were ascribed until the mid 1960s to the loss of portal blood flow rather than the loss of exposure to the liver of any specific substance(s) in the portal blood (121-123). This became known as the flow hypothesis of portal physiology. Yet, an uneasiness about this glib explanation could be sensed in an otherwise authoritarian review article written in 1961 by J. L. Bollman of the Mayo Clinic (124) who wrote, "In the 83 years since it was first reported the Eck fistula has been reasonably successful in hiding its secrets as well as giving rise to many additional questions fundamental to an understanding of the functions of the intestine, liver and brain."

The secrets referred to by Bollman finally were unmasked by auxiliary liver transplant studies in dogs which were begun in 1963. This operation was described in 1955 by Welch in what was the first mention of liver transplantation in the medical literature (125). Our experiments eight years later showed that coexisting livers competed with each other for some substrate(s) or nutritional substance(s) (57,126). From 1963 onward, it was clear that when two livers were present, the one with primary access to portal venous flow

would thrive because it consumed something in the portal blood, whereas the other liver would atrophy. This dictated the technical conditions for auxiliary liver grafts. Their portal venous inflow would require blood from the splanchnic venous bed. It was concluded that portal blood contained "hepatotrophic" factors, but the identity of these mysterious substances was unknown at first.

To find out, definitive non-transplant experimental models were designed in which the animal's own liver was divided into two parts, each of which could be given the venous blood that came from different organs or different parts of the body (127-131). Later, experiments were done in which the effect on the liver of removing these organs was tested. All of the testing done from 1971 onward showed that the most potent (although not the only) hepatotrophic factors were from the pancreas. In the end, it was demonstrated that insulin when injected alone into the altered liver circulation could prevent the atrophy and most of the consequences to the liver that were caused by the Eck fistula (132).

This was the death blow to the portal flow hypothesis and the beginning of a new concept about the interactions of the liver with the pancreas and other abdominal organs. The role of insulin as a liver growth control factor was established, as well as a new field of hepatotrophic physiology (133). The concept was that the pancreas (particularly its insulin) and other less important but cumulatively significant substances from the viscera modulated hepatic structure, function, and capacity for regeneration. The metabolic interrelationships of intraabdominal organs was to become a consideration in the technical planning for transplantation of any of these organs and particularly the transplantation of multiple abdominal viscera. Ultimately, the multivisceral operation which had evoked bemusement in 1960 (36,37) became the starting

point for variations which permitted the successful transplantation of bowel for the first time (134-136).

In addition, the original experimental techniques developed to uncover the insulin effects were applied almost two decades later to show that cyclosporine and FK 506 also have hepatotrophic properties including the augmentation of hepatic regeneration (137-139). These drugs and others including rapamycin bind to ubiquitous small molecular weight cytosolic proteins called immunophilins (140,141) and are thought to act by disrupting normal signal transduction pathways (142), but not only in cells with immunologic function (139). Recognition of the pleiotropic function (including growth control) of the immunophilin network (139,142,143) is the latest example of a ripple (or tidal wave) effect in basic science laboratories of clinically directed research in transplantation.

PHASE V (1967 to 1969)

With the support struts of Phase V in place, the time had come to resume the clinical trials of orthotopic liver transplantation (liver replacement). Procurement of livers was from "heart dead" donors. All of the recipients had triple-drug immunosuppression with Imuran, prednisone, and ALG. The seven new patients (all children) passed through the lethal period encountered during and just after liver transplantation in the 1963 cases. Four died after two, three and one-half, four and one-third, and six months. All other complications were trivial compared to the one which caused their deaths. This was the development of gangrene of a portion of the transplanted livers, the other part of which continued to function properly. The dead portion of the liver was infected with bacteria normally found in the intestine.

The other three children remained alive for 13, 15, and 30 months, long enough to demonstrate convincingly the potential

During 1964 to 1966, the Denver VA Hospital laboratory was like Grand Central Station. One visitor, Chris Barnard, was no casual tourist. Barnard spent the better part of a year in the United States at three centers: in Richmond with Dick Lower and Dave Hume who told me later that Barnard had seemed interested mainly in learning how to treat rejection, in Colorado (autumn 1966) where he focused his attention on the ALG project, and in Palo Alto where he visited Shumway whom he had known since their earlier days at the University of Minnesota. I told Barnard candidly that we were planning to go ahead with heart transplantation in Denver but not until we were successful with the liver. I assumed that he was going to start a kidney program in Capetown and so did the others whom he visited.

value of this kind of treatment (144). Two of the three late deaths were caused by recurrence of the hepatomas which had been the reason for the transplantation; the third died of chronic rejection. By the time the last patient died, another child was a half year into a new life that now is well into the twenty-second posttransplant year (145). This recipient had biliary atresia but in her removed liver was found a small cancer which had not been suspected in advance. It never came back.

Carl Groth of Stockholm helped operate on and care for all of these patients. Before he returned to Sweden in March 1968, he helped complete an investigation in dogs (146) which was based on his observations in the children who developed partial gangrene of the liver graft. The study showed that an important factor predisposing to liver infection was under-treatment with immunosuppression with consequent rejection. In turn, a reduction in

liver blood flow caused by rejection previously had been demonstrated by Groth (147), to set the stage for oxygen starvation of the transplanted liver and a consequent lowered resistance to bacteria. Paradoxically, the best way to prevent this was more vigorous antirejection treatment in spite of the consequent depression of systemic resistance to infection (148).

The prolonged survival of the first children in the series became known worldwide by September 1967. The ripple effect went beyond the liver. Penetration of the barrier which had precluded extension of transplantation operations beyond the relatively simple kidney fanned the embers in other organ-defined specialties. By the end of the year, Barnard of Capetown had performed the first heart transplantation (149), followed shortly by the beginning of Shumway's clinical program at Stanford (150). Responding to phone call requests, we became the suppliers of homemade ALG for these and other heart programs which followed.

Within a year, the first successful lung transplantation was performed by Derom of Louvain (151) and the first pancreas and intestinal transplants were attempted by Lillehei and Kelly of the University of Minnesota (152,153). Most of the attempts with all of the extrarenal organs failed. When the rush of enthusiasm was replaced by reality, only a few diehards were left. Further clinical development of hearts would be at Stanford. The pancreas would depend upon Carl Groth in Stockholm, Jean M. Dubernard of Lyon, and Dave Sutherland of Minneapolis. Lung transplantation lay dormant for almost 15 years until Joel Cooper of Toronto finally established its

practicality. Intestinal transplantation was abandoned for almost two decades.

Liver transplantation continued in Cambridge (Calne) and Denver. By early February 1969 we had treated 20 patients since the 1967 reinstatement of the liver replacement trials. For one, a chimpanzee was the donor. Only seven of the patients survived for more than one year. The conclusion was inescapable. Liver transplantation was a feasible but impractical way to treat end stage liver disease. This was the picture presented in a second book, *Experience in Hepatic Transplantation* (154), a companion piece to the earlier *Experience in Renal Transplantation* (61). The liver book was written with Charley Putnam, then a senior medical student at Northwestern and now a Professor of Surgery (in the same department as Charlie Zukowski) at the University of Arizona.

In the new book, every known clinical attempt made at liver transplantation in the world (orthotopic and auxiliary) and every experimental paper written on the subject up to early 1969 were included. The book portrayed liver transplantation more pessimistically than it would actually be during the following 10 years. Yet, more recipients died than lived throughout this time. Altogether, 170 patients were treated between 1963 and the end of 1979 (145). Only 29 (16.5 percent) still survive. Now, they are 11 to 21 and one-half years posttransplantation. In England, Calne maintained the only other sustained liver transplant program which was opened in May 1967 (155). As in Colorado, these efforts created controversy. Calne became a European voice in the wilderness.

STARZL

PHASE VI (1970 -)

If it had not been for the 1960s, transplantation would have remained a fancy, and if it were not for the 1980s, it would have remained a starveling. In be-

tween was the time for those thousands of details to be clarified which had been skipped in the rush to the finish line; a time to explain why the beachhead known as

transplantation had become a slowly eroding revetment; and a time to look for something better. ALG had had a smaller than expected impact on transplantation worldwide because of the necessity for its temporary use only and because of problems with its manufacture, standardization, and testing. Only about 15 percent of cadaver kidney transplantations worldwide were done with ALG treatment.

The results with cadaver kidney transplantation remained fixed at an unsatisfactory level (64,156-158). Trapped now by their own partially successful efforts, surgeons interested in the extrarenal organs brooded in their self-made dungeons, smuggling messages to each other or communicating by secret signals, tapped on their academic cell walls. There were very few left who continued to try. Then the way out of the dilemma came with cyclosporine. The drug was discovered by workers at the Sandoz Corporation and shown by Jean Borel to weaken immunologic responses in a variety of test systems including that of skin graft rejection in mice (159).

In England, Calne and his Cambridge team evaluated cyclosporine for the transplantation of a variety of whole organs (kidney, heart, liver, pancreas) in rats, dogs, and pigs. These experiments led directly to the first human trials in kidney transplantation at Cambridge, beginning in the late spring of 1978 (160,161). At first, it was hoped that cyclosporine could be used as single-drug therapy, but it too was destined to be part of cocktail regimens in which steroids were the most dose maneuverable component (162) and to which azathioprine, ALG, and other agents could be added. Cadaver kidney transplantation finally reached the level of a legitimate clinical service. Transplantation of the liver (145,163) and soon after the other extrarenal organs was revolutionized overnight. For me, most of this new era was at the University of Pittsburgh, where I moved in December 1980. Liver transplantation was made easier by a

modern day version of veno-venous bypass (145,164,165). The liver and heart transplant gold rush dwarfed what had happened with the kidney in 1964.

With the revolution came a downside. In addition to its marvelous qualities, cyclosporine had side effects which had been described by Calne as early as 1979 (161). The most serious were nephrotoxicity and hypertension in the majority of recipients of all kinds of organs. Nephrotoxicity, hirsutism, gum hyperplasia, neurotoxicity, and other less serious side effects were dose-related. When the doses were reduced to relieve them, the risk of rejection increased. Transplant surgeons with an obsession for perfection were less interested in working around these problems than in finding a more fundamental solution. FK 506, a macrolide antibiotic which was discovered in 1984 and first reported in 1987 (166-168) is the most promising new agent. Extensive clinical trials were begun in 1989 (169).

With the advances of the last decade, it has become possible to improve the kinds of transplantation (liver, heart, pancreas) which were feasible but not practical and to succeed with previously "forbidden" transplants of pancreatic islets (170), intestine (171,172), and multivisceral organs containing intestine (134-136). The relative "acceptance" of solid organ grafts in many patients still is not understood, but a recent clue has been the demonstration of post-operative lymphoreticular repopulation of human intestinal grafts with recipient cells.

This means that transplanted organs can become "composites," possibly helping to explain why the need for chronic immunosuppression may recede in successful clinical transplantation of all organs, not just those which are rich in lymphoid tissue. Such cell repopulation was first noted by Porter more than two decades ago in the macrophage system of human liver homografts (89). Thirty years ago, in describing what they called graft adaptation,

Michael and Hazel Woodruff had asked if thyroid transplants underwent some kind of change which explained their acceptance by the host if they could be protected from rejection at the outset (173).

In hepatic grafts whose composite structure has been known for more than two decades (89), it was established in 1964 (58) that the graft metabolic specificity was retained as shown by the replacement of recipient haptoglobin phenotypes with those of the donor. This simple observation was the basis for the treatment with liver transplantation of numerous inborn errors of metabolism, now numbering nearly two dozen (174). The metabolic correction lasts

for the lifetime of the graft. Every few months, a new disease is added to the list.

Now half-forgotten ideas were being reexplored, and burned-out camp sites were being rediscovered, as had occurred with those who arrived in the 1950s. When mountains are climbed by different people, the triumph can be spoiled by asking who took the first step to the summit, who took the longest stride, and most insidiously who did not. All of those who made the clinical transplant journey of the last 40 years found footprints, which like those in the snow in the high mountain reaches, do not melt. No matter how early the transplant explorer's arrival, someone already had been there, at least part way.

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CURRICULUM VITAE**Thomas Earl Starzl****PERSONAL**

Born: March 11, 1926; Le Mars, Iowa
 Marital Status: Married to Joy Denise (nee Conger); 3 Children

EDUCATION

1950 Northwestern University, Chicago, IL, Ph.D.
 1952 Northwestern University, Chicago, IL, M.D.

BOARD CERTIFICATION

1958 General Surgery
 1959 Thoracic Surgery

POSITIONS

1958 Instructor in Surgery, Northwestern University, Chicago, IL
 1959 Associate in Surgery, Northwestern University, Chicago, IL
 1961 Assistant Professor in Surgery, Northwestern University
 1962 Associate Professor in Surgery, University of Colorado
 1964-80 Professor in Surgery, University of Colorado
 1972-80 Chairman of Surgery, University of Colorado
 1981- Professor of Surgery, University of Pittsburgh
 Present Presbyterian University Hospital of Pittsburgh, Children's Hospital of Pittsburgh and Veterans Administration Hospital of Pittsburgh (Oakland)

PROFESSIONAL SOCIETIES

Total: 52
 International Transplantation Society
 1970 Vice President
 1990 President
 American Society of Transplant Surgeons
 1975 Founding President
 Transplant Recipients International Organization
 1987 Founding President
 1987 Permanent Honorary Chairman

AWARDS

1950 Alpha Omega Alpha
 1952 Student Borden Award
 1959 Markle Scholarship
 1965 Alumni Achievement Award, Westminster College
 1965 Prix Société Internationale de Chirurgie

1967	Colorado Man of the Year Award
1968	William S. Middleton Award, Outstanding Research in Veterans Administration System
1969	Merit Award, Northwestern University
1970	Eppinger Prize, Freiburg
1970	Deutsche Gesellschaft fur Chirurgie, Munich
1971	American Academy of Arts and Sciences
1971	Award, Council Creative Research (highest award, University of Colorado)
1974	Brookdale Award (highest award of AMA to person under 50 years)
1975	Josiah Macy Scholar
1976	Robert L. Stearns Award (highest award of Colorado Alumni Association)
1977	Centennial Medallion of University of Colorado
1978	David M. Hume Memorial Award (highest Award of the National Kidney Disease Foundation)
1981	Pittsburgh Man of the Year
1982	Sheen Award, American College of Surgeons
1983	Golden Plate Award, American Academy of Achievement
1983	First Uremia Award, The International Uremia Society
1984	Pittsburgh Man of Year Award by Pittsburgh Academy of Medicine
1984	Honorary Fellow royal College of Surgeons, England (Hon. F.R.C.S., Eng.)
1984	"Membre d'Honneur Etranger" de La Société de Chirurgie de Lyon ("Foreign Honorary Member" of the Surgery Society of Lyon)
1985	Annual Lecturer, Fondazione Giovanni Lorenzini, Italy
1985	Pennsylvania Medical Society Distinguished Service Award
1986	Alumni Medal Northwestern University
1986	Pittsburgh Man of the Year
1986	Biannual Prize of Italiane Hepatology Society presented at Chiaciano, Italy
1986	Distinguished Service Professor of Health Sciences of University of Pittsburgh
1986	Key to the City of Milan
1987	Key to the City of Venice
1987	Jewish National Fund, "Friend of Israel" Award
1987	Ireland (Hon. F.R.C.S., I.)
1987	Honoree International Organ Transplantation Forum
1989	Bigelow Medal, Boston Surgical Society
1989	City of Medicine Award, Durham, NC
1990	Medallion for Scientific Achievement, American Surgical Association
1990	Pittsburgh Surgical Society Annual Award

1990	Glasgow, Physicians and Surgeons (Hon. F.R.C.S., G)
1991	Honorary Member Asian Surgical Association
1991	American Liver Foundation Distinguished Service Award
1991	William Beaumont Prize in Gastroenterology, New Orleans
1991	Recipient Hugh R. Butt Award, American Gastroenterological Association
1991	American Association for the Study of Liver Disease Distinguished Service Award
1991	Designated "Thomas E. Starzl Surgical Ward," Denver VA Hospital
1991	Fondazione Basile Prize World Association of Hepato-Pancreato-Biliary Surgery, Italy
1991	Elu associé étranger (Foreign Member) Academie Nationale De Medecine (French Academy of Medicine), Paris, France

HONORARY DOCTORATES

1968	Westminster College, D.Sc.
1970	New York Medical College, D.Sc.
1971	University of Wyoming, L.LD
1974	Westmar College, D.Sc.
1981	Medical College of Wisconsin, D.Sc.
1982	Northwestern University, D.Sc.
1985	University of Louvain, Belgium, D.Med.
1985	Bucknell University, D.Sc.
1985	Muhlenberg College, D.Sc.
1988	University of Rennes, D.Med.
1988	Mt. Sinai School of Medicine, D.Sc.
1988	La Roche College, D.H.L.
1988	Bologna, D.Med.

EDITORIAL BOARDS AND EDITORSHIPS

Total: 26

PUBLICATIONS

Total:	Scientific Articles	1,400
	Books:	Full Books 4
		Chapters 163
	Presentations at Major Meetings	880