The development of whole organ transplantation

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The success of whole organ transplantation has been one of the least predicted events in the history of medicine. In 1961, the Nobel Laureate Burnet wrote in the New England Journal of Medicine that "much thought has been given to ways by which tissues or organs not genetically and antigenically identical with the patient might be made to survive and function in the alien environment. On the whole, the present outlook is highly unfavorable to success..."[1]. This pessimistic view was published only a year before the avalanche of successful clinical renal transplantations in 1962 and 1963 that extended such procedures beyond the occasional identical and fraternal twin cases of the mid and late 1950s.

Within and outside of the medical establishment, the frenzied pace of developments in 1962 and 1963 dismayed and dumbfounded critics, many of whom were unaware of what had been accomplished already. In the spring of 1964, an editorial beginning with the word 'Cannibalizing' was published in the Annals of Internal Medicine questioning again the inherent feasibility of these efforts as well as the ethical basis[2]. Responses in an ensuing issue including a letter by me reflected a spectrum of views held by basic and clinical investigators[3]. By the summer of that year, I published a detailed account of our experience[4] in which the majority of kidney recipients had achieved long survival with social and vocational rehabilitation. However, these developments were already late in a long, but at first slowly unfolding, story.

The earliest beginnings

Heterotransplantation. – The first clinical efforts at renal transplantation predated the water-shed years of 1962 and 1963 by half a century. The first known attempts at clinical renal transplantation by vascular anastomoses were made without immunosuppression between 1906 and 1923 with pig, sheep, goat, and subhuman primate donors. Jaboulay of Lyon[5] and the German Unger[6] made the first of these foredoomed efforts, but others followed as summarized elsewhere[4, 7]. None of the kidneys functioned for long if at all and the human recipients died from a few hours to nine days later.

Although the trials were carried out with little or no understanding that there was a biologic barrier to success, some principles were clearly delineated. The applicability of vascular suture techniques, and even the possibility of using pelvic implantation sites were either envisioned or actually practiced. No further clinical renal heterotransplantations (animal to man) were tried again until 1963 when systematic and surprisingly successful clinical trials were made with chimpanzee[8] and baboon[9] kidneys. Little noted at the time or subsequently were attempts at chimpanzee to human heart transplantation by Hardy with intraoperative death[10] and transplantation of 3 chimpanzee liver heterografts[11, 12, 13] of which 2 behaved indistinguishably from homografts[11, 13]. The eventual death of all of the recipients of animal organs ended heterotransplantation trials for 15 years until Bailey's baboon to human heart transplantation[14].

Homotransplantation. – The first human to human kidney transplantation (homotransplantation) was reported in 1936 by the Russian Voronoy[15] who transplanted a kidney from cadaver donor of B+ blood type to a recipient of 0+ blood type in violation of what have become accepted rules of tissue transfer[4]. The fact that the donor had been dead for 6 hours further precluded hope of success. The recipient died 48 hours later without making urine. Although the possibility that there would be an immune barrier to success was not obvious to most early clinicians, Voronoy perceived this problem, although imprecisely. A more complete understanding awaited the classical studies of Medawar with rodent skin grafts which established the immunologic basis of rejection[16].

In the 20 years following Voronoy's case, sporadic further efforts at renal homotransplantation were made without effective immunosuppression as documented by Groth[7]. The heterotopic extraperitoneal technique of renal transplantation which became today's standard was developed by the French surgeons Dubost[17], Kuss[18], and Servelle[19] and their associates. John Merrill, the Boston nephrologist, had seen the extraperitoneal operation while travelling in France in the early 1950s as was mentioned by Hume et al[20]. This technique was adapted for the historically important identical and fraternal twin cases in Boston[21, 22]. Variations of the operation shown in Figure 1 are used today worldwide.

As isolated results, none of the foregoing efforts, or even all put together, would have had major significance. The principal ingredients of organ transplantation, namely immunosuppression, tissue matching, and organ procurement (and preservation) were either unknown or so undeveloped that grafting of the kidney at a practical level was only a dream. Extension of transplantation beyond the kidney was beyond imagination. No trace can be found in the literature of transplantation of extrarenal organs until the mid 1950s when Welch described auxiliary (heterotopic) liver transplantation[23], and when Willman and Hanlon[24], and Shumway[25] showed the technical feasibility of heart transplantation. Transplantation of the pancreas which had been used as a physiologic preparation by Houssay[26] was revived in the experimental laboratory in 1960 by Lillehei et al[27].

Thus, the astonishing developments in transplantation of all these organs became a story of the last quarter century. I will provide here some reminiscences of this era and speculate about how the momentum of this progress can be sustained and accelerated. Such hopes derive in part from the seminal contributions already made by the pharmaceutical industry and from the revolutionary changes in drug development that have expedited the search for better drugs to combat rejection, prevent ischemic injury to tissue, and change other pathophysiologic events during or around transplantation. The most specific of these inquiries has been with immunosuppression.

Immunosuppression before SANDIMMUNE® (cyclosporine)*

By 1960, the possibility of weakening the recipient immune system in order to mitigate rejection had been established in animals with corticosteroids[28], total body irradiation[29, 30], and the cytotoxic drug 6-mercaptopurine[31–34] or its imidazole derivative, azathioprine[35]. Sporadic attempts to use these techniques for renal homotransplantation in humans were so unsuccessful[7, 22, 36, 37, 38] that it was widely thought that the immunosuppression requisite to prevent rejection would inevitably lead to immunologic invalidism and lethal infections.

*The editor has replaced the author's references to cyclosporine by SANDIMMUNE, the registered trademark for the cyclosporine product (outside USA, Canada and Holland SANDIMMUN).

Double-drug therapy with azathioprine and steroids

Renal transplantation became practical in 1962 and 1963 with the marriage of corticosteroid therapy (prednisone or prednisolone) to baseline therapy with azathioprine[4, 39]. This synergistic drug combination, the value of which was immediately confirmed[40], permitted fundamental observations to be made, including the fact that rejection was a reversible process (Figure 2). With the passage of time after renal transplantation, a change in the relation between the graft and the host often occurred, permitting eventual reduction of drug doses (Figure 2). Patients who did not require chronic high-dose corticosteroid therapy to retain their grafts have been able to return to useful social and vocational activities for as long as 25 years. The double-drug therapy with azathioprine and prednisone remained the gold standard of transplantation for many years.

However, consistently good results could be obtained only with transplantation from blood relatives, and even then only with good tissue matching (see later). This unsatisfactory situation was a great stimulus to the search for better immunosuppressive regimens.

Triple-drug therapy

Consequently, modifications of or additions to the original double-drug treatment were made as summarized elsewhere[41] during the next 16 years. Most of the modifications were designed to blunt the attack of the lymphocytes, which had been recognized as the mediators of rejection. The most significant addition was antilymphocyte globulin (ALG) which was used as an adjunct to azathioprine and prednisone[42]. The ALG consisted of polyclonal antibodies raised in horses, rabbits, goats, or other animals by immunizing them to human lymphocytes[11]. When thymic lymphocytes were used for immunization, the product was called antithymocyte globulin (ATG). The active gamma globulin was extracted, purified, and made ready for intramuscular or intravenous use. Usually, the ALG was administered during the first few weeks or months after transplantation.

In spite of its great potential value, polyclonal ALG was not universally employed as a part of the anti-rejection armamentarium because of severely limiting features including its inability to be standardized. This latter problem as well as other deficiencies were eliminated with the hybridoma technology introduced by Kohler and Milstein[43]. With hybridoma cells injected into the peritoneum of mice, a homogeneous (monoclonal) antihuman-lymphocyte antibody could be produced. Therapy with monoclonal antibodies was introduced into clinical medicine by Cosimi et al[44], using the so-called OKT3 antibodies which selectively deplete mature T-lymphocytes. Their prime objective was to reverse kidney graft rejection that was non-responsive or poorly responsive to conventional corticosteroid therapy and azathioprine. OKT3 therapy has been proved to be of value clinically, and it was released in 1986 for general use in the United States by the Food and Drug Administration (FDA).

In spite of what had been achieved by 1978 with most of the foregoing drugs and drug combinations, whole organ transplantation remained an unpredictable and dangerous undertaking especially if cadaver donors were used. The margin between effective and toxic immunosuppression was too narrow. Although the feasibility of transplanting the human liver[45, 46], heart[47, 48], lung[49], and pancreas[50] was established in 1967 and 1968, the results were too poor with any of these organs to justify broad application. Consequently, the field of transplantation had a relative growth arrest throughout the 1970s, and there seemed to be little hope of major improvement. The clinical transplant sessions at scientific society meetings had become tedious expositions in which claims of results, counterclaims, and shuffling of details of management filled the programs. The boredom was shattered with the arrival of cyclosporine (SANDIMMUNE).

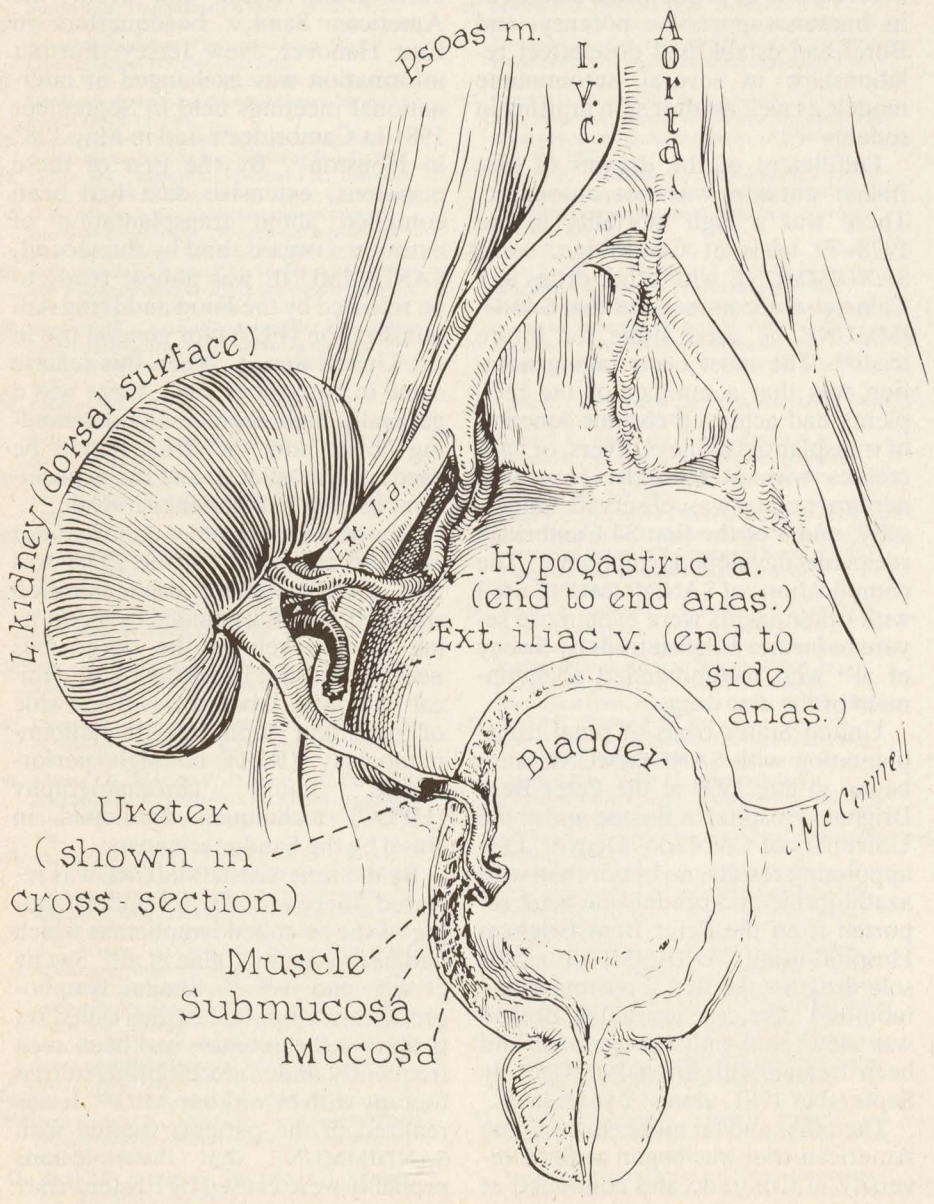

Fig. 1. Renal homograft. (By permission of JAMA *187:* 734, 1964.)

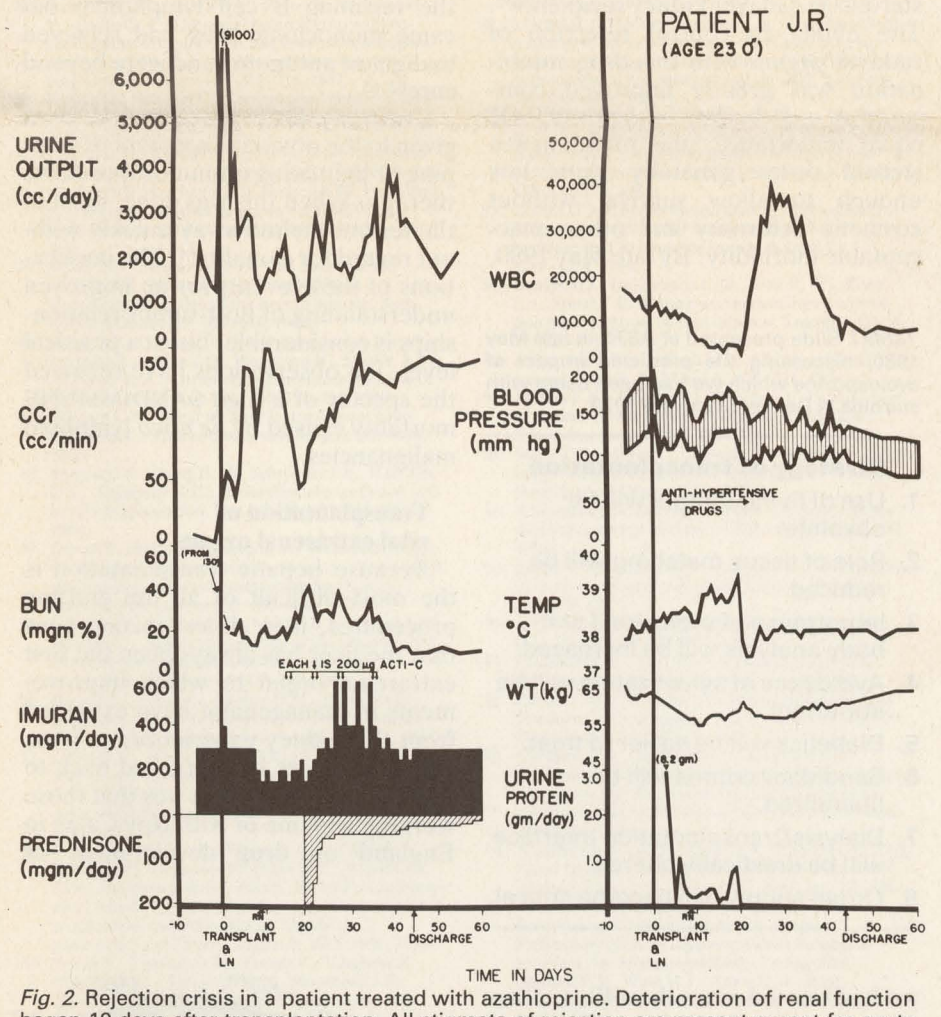

Fig. 2. Rejection crisis in a patient treated with azathioprine. Deterioration of renal function began 19 days after transplantation. All stigmata of rejection are present except for acute hypertension and weight gain, which were successfully prevented by medical treatment. Acti-C-Actinomycin D; LN-Left nephrectomy at time of transplantation; Imuran is synonymous with azathioprine. Note reversal of rejection with what were considered then to be massive doses of prednisone. The kidney is still functioning more than 24 years later. (By permission of Surg Gynecol Obstet *117:* 385, 1963.)

The SANDIMMUNE era

The immunosuppressive qualities of this fungus extract were delineated by Borel et al[51] of Switzerland, and the first clinical trials for solid organ transplantation were carried out by Calne and his associates in Cambridge, England, beginning in the spring of 1978[52, 53].

Renal transplantation

In Rome during the first week of September 1978, the International Transplantation Society held its biennial meeting. The members were granted an audience with the newly proclaimed Pope John Paul I whose short tenure sadly ended little more than a month later. Encouragement of the Catholic church for the transplantation community was forthcoming from Pope John Paul along with a reminder of the attendant social and moral responsibilities. The timing of the support and advice could not have been more appropriate since the first clinical trials with SANDIMMUNE for renal transplantation were reported from Cambridge during that week, along with an impressive array of data from several research laboratories. The magic of a possible new era was in the air. The stages of drug development by the Sandoz Pharmaceuticals

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Division had been a model of scientific accuracy and completeness. The chemical structure and physical qualities of the drug were completed long before Borel et al published studies of its immunosuppressive potency, and Borel had established dose/effect relationships in several autoimmune models as well as after skin grafting in rodents[51].

Fulfillment of the dreams of that Italian autumn was not automatic. There was a high mortality in the 1978–79 trials at Cambridge, using SANDIMMUNE with other drugs and Calne et al recommended that SANDIMMUNE be used alone for future trials[53]. The most encouraging notation was that a number of the recipients had achieved chronic function of transplanted kidneys, livers, or pancreases without steroids. However, nephrotoxicity was observed universally, and 3 of the first 34 Cambridge recipients developed lymphomas. The complications of SANDIMMUNE used with other agents were even more severe in further English trials by Sweny et al[54] who recommended abandonment of the new drug.

United States trials of renal transplantation with SANDIMMUNE were begun in late 1979 at the Peter Bent Brigham Hospital in Boston and at the University of Colorado, Denver. Disappointing results, no better than with azathioprine and prednisone were reported from the Peter Bent Brigham Hospital using SANDIMMUNE as the sole drug for the first 2 postoperative months[55]. The case accrual in Boston was slow, and only 16 patients had been treated with SANDIMMUNE by September 1981, almost 2 years later.

The other and far more encouraging American trial was begun at the University of Colorado and continued at the University of Pittsburgh, systematically combining SANDIMMUNE with steroids in cadaver kidney recipients[56]. The ability to control rejection of cadaver organs with this drug combination was greatly improved compared to any therapy in the past[57]. Of equal importance, the maintenance steroid doses generally were low enough to allow survival without cosmetic deformity and other unacceptable morbidity. By late May 1980, we had treated more than 40 renal recipients, and with this experience, I prepared a slide for a forum discussion at the American Society of Transplant Surgeons about where transplantation was headed. That slide is reproduced verbatim in Table 1. All of the predictions have come true, at least in part.

Table I. Slide presented at ASTS in late May 1980, discussing the predicted impact of cyclosporine which we had been using with steroids in Denver since late 1979.

Strategy of transplantation

1. Use of living donors will be obsolete.
2. Role of tissue matching will be reduced.
3. Importance of preformed antibody analysis will be increased.
4. Avoidance of sensitization will be important.
5. Diabetics will be easier to treat.
6. Candidacy criteria will be liberalized.
7. Dialysis/transplantation interface will be drastically altered.
8. Organ supply will become critical.

The International Transplantation Society next met in Boston on 2 to 5 July 1980, during the American national holiday celebrating independence. The advocates of SANDIMMUNE slightly outnumbered the detractors, but by now two more American trials of SANDIMMUNE and steroid therapy for renal transplantation had just begun or were planned in Minneapolis[58] and Houston[59] exploiting the policy of polypharmaceutical therapy advanced in the Colorado-Pittsburgh trials. With this approach, employing drug combinations with additive or synergistic immunosuppression, the doses of individual agents usually could be kept in the non-toxic range. SANDIMMUNE and steroids also have been combined in later years with azathioprine, and polyclonal or monoclonal ALG (OKT3).

The swift dissemination of all of the information, good or bad, about SANDIMMUNE was done with great responsibility on an almost weekly basis from Basel and from the American Sandoz headquarters in East Hanover, New Jersey. Further information was exchanged at international meetings held in September 1981 in Cambridge[60] and in May 1983 in Houston[59]. By the first of these occasions, extensive data had been compiled about transplantation of extrarenal organs, and by the second, SANDIMMUNE was almost ready to be released by the Food and Drug Administration (FDA) for general use in the United States. When this release came in November 1983, there was a generally high degree of understanding about how the drug should be used, its side effects, and the expectations of graft and patient survival.

One strong recommendation, if not absolute condition, of the FDA was that SANDIMMUNE administration should be carefully guided by monitoring blood levels of the drug. This necessitated the introduction in clinical pathology laboratories worldwide of new and sophisticated radioimmunoassay (RIA) or high performance liquid chromatography (HPLC) techniques developed in Basel by the Sandoz scientists.

By the time SANDIMMUNE was released, there was a better understanding of the so-called lymphomas which had been seen by Calne et al[53], Sweny et al[54], and us[56, 57]. Similar lymphoproliferative tumors, earlier called reticulum cell sarcomas, had been seen frequently under azathioprine-steroid therapy with or without ALG[61]. It was realized in the patients treated with SANDIMMUNE that these lesions probably were caused by Epstein-Barr virus infections[54, 56, 62, 63]. The conventional wisdom until 1983 was that once the resulting B cell lymphomas became monoclonal they had achieved malignant autonomy and were beyond cure[62, 63].

Curiously little thought had been given to the obvious expedient of stopping or lightening immunosuppressive therapy. When this was done, most of the lesions melted away quickly without regard for clonality[64]. The implications of these events for an improved understanding of host-tumor relationships is considerable, but at a practical level, the observations have removed the specter of a high SANDIMMUNE mortality caused by *de novo* lymphoid malignancies.

Transplantation of vital extrarenal organs

Because hepatic transplantation is the most difficult of all the grafting procedures, it is almost incongruous that the liver has always been the first extrarenal organ to which improvements in management have extended from the kidney experience, or from which advances have tracked back to the kidney. The reason was that those working with me or with Roy Calne in England on drug development or other aspects of transplantation had a lifetime passion to extend what was learned with the kidney to the even more difficult ultimate objective of liver replacement (Figure 3).

My own first efforts at liver transplantation were begun at Northwestern University in Chicago in the summer of 1958[65]. In Boston during the same summer, Francis D. Moore independently had begun a systematic exploration of the same possibility[66]. The young English surgeon, Roy Calne, came to Harvard in 1960 where in the course of his research with immunosuppressive drugs[35] he was exposed to Moore's work. Calne visited Chicago before he returned to England. I can remember his courteous manner, his determination to see everything that was going on, and his quick intelligence. Time has not dimmed these wonderful qualities.

Efforts to mitigate liver rejection in dogs with irradiation of either the donors or recipients failed completely[67]. Efforts with azathioprine were more successful[68, 69] and truly long survival was achieved by the mid-1960s using azathioprine[69], and ALG[42]. The first clinical efforts at liver transplantation were made at the University of Colorado in Denver in 1963[45], but the first unequivocal successes were not until 1967[11, 46]. Today, the longest survivor in the world is a young woman who is married to a United States marine stationed in Okinawa. She is in her eighteenth postoperative year.

In 1968, Calne began his pioneer English program of liver transplantation[70] and before long he established a fruitful collaboration with Roger Williams, the extraordinary hepatologist at King's College, London[71]. For many years, these single American and English programs shared the vicissitudes and sorrows of defeats more common than victories. In all that time, I never heard or saw Calne utter or write a bitter or complaining word. It was fitting that the first 2 liver recipients treated with SANDIMMUNE were his patients[53].

The advent of SANDIMMUNE changed liver transplantation from an exotic experimental procedure to a patient-service, tripled survival after that operation[41, 72, 73] (Figure 4), paved the way for more effective transplantation of the heart[74, 75, 76], and made possible the previously unattainable objectives of transplanting the heart and lungs[77], or single lungs[78]. The extraordinary change that had occurred was already reflected in the published collection of papers about extrarenal organ transplantation from the Cambridge symposium[60] in September 1981.

The crystal ball

The intellectual and pragmatic harvest made possible by SANDIMMUNE goes on. However, the search for improved immunosuppression merely has been intensified by what has been accomplished. New drugs are being evaluated even now of which some are even more potent than SANDIMMUNE. One example is the experimental drug, FK 506 which was developed by the Fujisawa Co. Ltd in Japan, first tested by Ochiai in transplant models[79], and made the topic of a recent international symposium in Sweden[80]. Whether these new agents will have acceptable toxicity, and the extent to which they can be used in combination with other drugs, must be determined. The techniques for rapid assessment of immunosuppressive drugs including examination of the most minute details of their mechanisms of action have been part of a revolution in the pharmaceutical industry which is sure to produce other promising drugs.

Organ procurement and preservation

It had not been perceived that practical immunosuppression was feasible until the synergism of azathioprine and steroids was demonstrated with startling clarity in 1962 and 1963. At that time, a similar void existed in organ procurement and preservation. Standard techniques did not exist for the removal of organs from either living or cadaver donors. There was almost no understanding by the medical and legal professions, much less the public at large, of the conditions which should govern such activities. Little thought or experimentation had been devoted to ways with which to treat the organ from the time of its removal to revascularization in the recipient.

The principle of core cooling

The potential benefit of lowering the temperature of an excised organ was grasped instinctively by early workers. In some of the most deliberate applications of this concept, intestinal[81] and cardiac grafts[25] were preserved almost 30 years ago by simple immersion in ice cold saline in Dr Owen Wangensteen's laboratory at the University of Minnesota. However, even such inefficient attempts at surface cooling were not made in any of the identical twin renal transplantations performed through 1962.

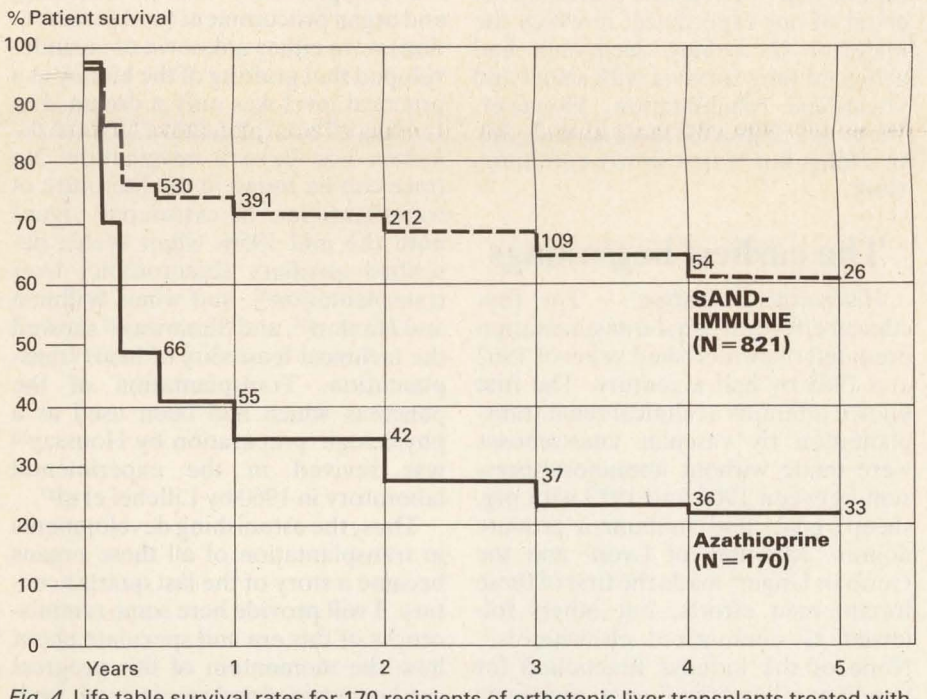


Fig. 4. Life table survival rates for 170 recipients of orthotopic liver transplants treated with azathioprine-steroids (March 1963 to February 1980) and 821 recipients treated with SANDIMMUNE and steroids (March 1980 to December 1986). Follow-up is complete through March 1987.

A far more effective way to cool an organ is to infuse a cold solution into its blood supply (core cooling). This simple concept was introduced into the laboratory almost 30 years ago to make possible liver transplantation in the dog[65]. Without core cooling, usually through the portal vein, liver transplantation in the dog was not possible. With core cooling, success became the rule. With such clear evidence, core cooling was promptly applied clinically for transplantation of the kidney[4] and eventually for all other organs.

Even today, the intraoperative infusion of cold fluids at the donor operation is the essential first step for effective organ removal and preservation. With all organs, the overriding objective is avoidance of warm ischemia. This is achieved by carefully timed *in situ* infusion of cold solutions into anatomical regions, the limits of which are defined by preliminary dissection of the abdominal and/or thoracic aorta and cross clamping at those levels[82].

Cooling of an organ graft by the intravascular infusion of chilled solutions at the time of circulatory arrest expands by many times the duration of organ viability and allows the unhurried application, if desired, of other more sophisticated preservation measures. Different solutions have been used.

Lactated Ringer's solution, the first infusate to be used[65], has a low potassium content and is nearly isotonic. Chilled special solutions with an electrolyte composition similar to that in cells were shown in 1969 by Collins, Bravo-Shugarman, and Terasaki[83] and by others to extend the permissible limit of cold renal ischemia beyond that achievable with isotonic solutions. The same effect has been shown with livers[84]. Cardiac surgeons have cooled the heart with various cardioplegic solutions having potassium concentrations of 20 to 30 mEq/L[75, 76].

Multiple organ removal procedures

Until 1981, transplantation of the extrarenal organs was a rare event, and one which was confined to a handful of institutions. Although renal transplant surgeons were concerned that removal of the liver and heart could damage kidneys from their cadaver renal donors, these anxieties were muted by the small number of cases involved. However, by late 1981, it had become obvious that liver and thoracic organ transplant procedures were going to be widespread, and that a method of multiple organ procurement would be required by which the kidneys, liver, heart, and lungs or various combinations of these organs could be removed without jeopardizing any of the individual organs.

Such a system was developed at the University of Pittsburgh hospitals, starting with the principle of *in situ* core cooling originally described for cadaver kidney procurement by Ackerman and Snell[85] and Merkel, Jonasson and Bergan[86]. At the request of the Surgeon General of the United States, Dr C. Everett Koop, what had become known as the Pittsburgh technique was described in detail[82]. Preliminary dissection of the great vessels of the abdomen and chest of the donor was carried out so that the organs to be removed could be core cooled *in situ* with cold intraaortic and intraportal infusates once the aorta had been crossclamped at preplanned levels (Figure 5).

The technique was adopted as a worldwide standard almost overnight. Since then, a simplified modification of this original procurement procedure has been used which entails virtually no preliminary dissection of any of the organs to be removed[87]. All organs are cooled *in situ,* and after their cooling, they are rapidly removed by dissection in a bloodless field. The incidence of well-functioning kidneys, livers and hearts has been better than with previous methods.

The collegiality between collaborating transplantation groups, often from different cities, has been greatly improved with the rapid procurement operation. Furthermore, the personnel at hospitals which are visited by the transplantation teams have been almost uniformly pleased with the new procedure which can usually be carried out in less than 60 minutes from beginning to end.

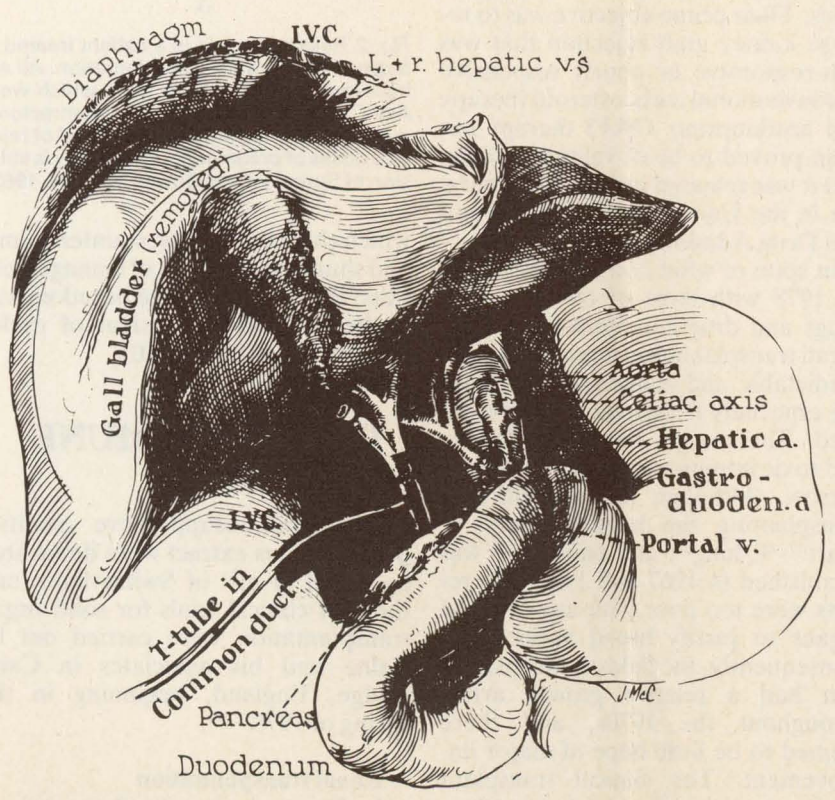
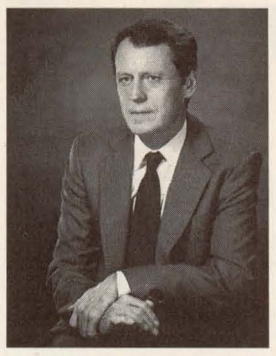


Fig. 3. Completed orthotopic liver transplantation. (By permission of W.B. Saunders Co., 1969. From Starzl T.E., *Experience in Hepatic Transplantation.)*



THOMAS E. STARZL, M.D., Ph. D., born in Le Mars, Iowa, USA, in 1926, is Professor of Surgery at the University of Pittsburgh Medical School, Pittsburgh, Pennsylvania, USA. 25 years ago he performed the first successful cadaveric kidney transplantation. Since he has continuously contributed to the science and art of transplantation and applied this knowledge in order to improve patient care. His innovative work with transplantation of the liver has been even more singularly outstanding. After 10 years of experimental work he performed the first successful liver transplantation in 1967. Since moving from University of Colorado Medical School, Denver, to Pittsburgh in 1981 he has led the development of one of the world's most successful multiple organ transplantation programs. More than anyone else, Dr. Starzl has contributed toward the concepts and practice of multiorgan transplantation.

Preservation by continuous perfusion

After their removal, the organs harvested with the foregoing techniques can be packed in ice chests and kept in the special cold solutions already mentioned near 0°C until their transplantation within time limits of 6, 8, and 48 hours for the heart, liver, and kidney, respectively.

Sophisticated techniques for continuous perfusion of all these organs have been developed, but have been widely used only for kidney grafts. Ackerman and Barnard[88] described perfusion with cold blood under hyperbaric oxygenation. A widely used perfusion technique for kidneys was described by Belzer, Ashby and Dunphy[89] using an asanguinous and oncotically controlled fluid. The method is a good one, but the quality of preservation in the first 2 days has not been markedly better than with the simpler and cheaper infusion and 'slush' methods.

Better continuous perfusion techniques should permit the extension of preservation times of all organs. However, efforts at continuous perfusion of hearts and livers in experimental laboratories usually have yielded results inferior to those with the simple infusion and refrigeration methods.

Preservation, the orphan of transplantation

It is a curious fact that preservation which once seemed the component of transplantation most susceptible to improvement, has been transformed so little. This vacuum in development was already perceived 17 years ago by professional liaison officers at the National Institutes of Health who sponsored a 'brainstorming' conference at which possible approaches to preservation and organ banking were considered[90]. The ideas that surfaced are still fresh, but practical improvements have not resulted. Aside from the presently unattainable objective of freezing organs solid, there appear to be two general approaches that could be probed.

One would be to improve the infusion approach by introducing novel ingredients into the solution which stays in the cold devascularized organ during storage, or by using agents to minimize the reperfusion injury after revascularization in the recipients. During the last decade, various mediators of the inflammatory response have been implicated in ischemic and postischemic injury. Furthermore, some of these mediators as well as their inhibitors have been synthesized in pharmaceutical research. An important mediator which is thought to be central to a wide range of pathologic processes is platelet activating factor (PAF)[91, 92]. A PAF-Inhibitor (PAF-I) has been developed by the Sandoz Pharmaceuticals Division [93, 94] and is being tested for its ability to reduce ischemic injury amongst other effects. Although numerous other specific possibilities could be cited, efforts to foresee history in detail would be inappropriate in what is a historical perspective.

The second broad possibility could be improved continuous perfusion, either at normal or cold temperatures. With the remarkable sophistication that has characterized research in artificial organ development, it is amazing that continuous perfusion techniques today offer so little more for organ preservation than they did two decades ago.

Tissue typing

Twenty-five years ago when the modern era of transplantation was in its infancy, it was predicted that tissue matching would have to be perfected if grafting procedures were to succeed. In 1964, the first efforts were made by our Colorado transplant group, working with Paul I. Terasaki of the University of California, Los Angeles (UCLA) to prospectively select ideal related or non-related donors for specific renal recipients, based on relatively primitive antigen matching[95, 96]. The results were disappointing. Since then, the validity of tissue matching, its genetic basis, and above all its complexity have become increasingly recognized. The value of tissue matching for transplantation between family members has been established beyond any doubt.

However, the very complexity of the human histocompatibility system has militated against easy matching between non-related people. Thus, at a practical level, close matching for transplantation of the cadaver kidney has become less and less of a consideration, especially since the availability of better immunosuppressive regimens made possible by SANDIMMUNE. With transplantation of the liver, heart and other extrarenal organs, tissue matching has not even been taken into consideration because the events leading to and connected with transplantation occur so quickly and often with such urgent recipient needs that a labored search for a well-matched organ is not possible. The somewhat surprising conclusion has been that good results can be obtained even with completely mismatched cadaver organs. This fact has reduced progressively the emphasis on antigen matching.

However, none of the immunosuppressive measures available today can prevent the immediate destruction of kidneys by preformed humoral antibodies in what has been called 'hyperacute rejection'. In 1965, Terasaki, Marchioro, and I[95] described the first example of this phenomenon. Kissmeyer-Nielsen et al[97] of Denmark, Williams et al[98], and numerous other observers have added to an understanding of hyperacute rejection. Kidney transplants are the most subject to hyperacute rejection, but the heart and liver in that order of susceptibility also can be similarly destroyed. The process of destruction is caused by thrombotic occlusion of the graft microvasculature and consequent devascularization[99, 100]. Hyperacute rejection can be avoided usually but not invariably by the so-called crossmatch test which detects antidonor antibodies in the recipient serum in advance of operation. The crossmatch has proved to be the single most important contribution of tissue typers to the practice of transplantation during the last quarter century[101].

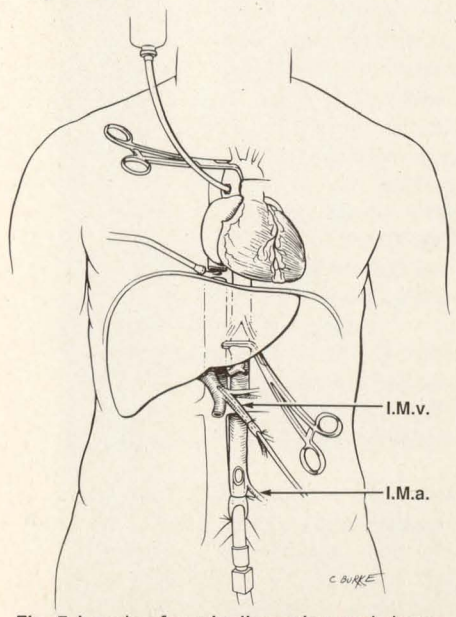


Fig. 5. Levels of aortic dissection and clamping for regional core cooling during multiple organ procurement. Notice double infusion of liver by portal cannula inserted through the inferior mesenteric vein (IMV) as well as through the aortic cannula. (By permission of W.B. Saunders Co., 1969. From Starzl T.E., *Experience in Hepatic Transplantation.)*

It is possible that the effector cascade set into motion by humoral antibodies can be aborted by pharmacologic intervention. One of the most interesting and promising possibilities was recently reported by Makowka et al[102] who used the PAF-I mentioned earlier in connection with organ preservation to delay the hyperacute rejection of pig kidneys which are normally destroyed by preformed heterospecific antibodies within a few minutes after transplantation to dogs. The same drug can prevent the hyperacute rejection of heterotopic heart grafts transplanted to rats presensitized with heart donor strain skin grafts[103], and if potent conventional immunosuppression was added, long survival followed[104].

The new options versus old values

Developments in transplantation and artificial organ technology have changed forever the philosophy by which organ-defined specialties such as nephrology, hepatology, and cardiology are practiced. Until recently, what could be offered victims of vital organ failure was a rear guard approach designed with diet, medicines, or surgical procedures to extract the last moment of life-supporting function from the failing organ. Now, and for the first time in human history, the breathtaking possibility has emerged when all else fails of starting over with an organ graft, or (in the not too distant future) with a manufactured organ. Much of the groundwork for this revolution was laid in the pharmaceutical industry. The consequences of changing human ecology are well known to those who have studied the amplifying effects of antibiotics on the population explosion that is said to threaten the earth or at least the quality of life of its inhabitants. It remains now to be seen how society will manage transplantation, the most recent product of its creativity and sponsorship.

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