

Organ Transplantation: Halfway through the First Century

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The ancient dream of successful organ transplantation was finally realized 50 yr ago, on December 23, 1954, at the Peter Bent Brigham Hospital in Boston. Over the subsequent half century, the separate disciplines of clinical transplantation and transplant immunology have made remarkable progress. The story of the convergent evolution of these two fields represents one of modern medicine's most important advances. This path of discovery has uncovered both the practical and the fantastic, and along the way, it has been marked by the awarding of more Nobel Prizes than any other field of medicine. The movement of functional organs from one individual to another and the clinical manipulation of the immune system necessary to make this movement successful have gone from being a tour de force to part of everyday clinical practice in just 50 yr. Perhaps most striking, however, is the enduring effect of these advances on the way we think and dream about medicine itself.

The purpose of this review is to enable the reader to share the hope and excitement present in the disciplines of immunology and transplantation, which together stand on the brink of what we believe will be a revolutionary second half century. We will focus in equal measure on the historical context in which the first successful kidney transplant operation occurred and the current milieu of transplantation, which itself is characterized by both rapid discovery and continued controversy. Finally, predictions about both the probable and the possible landmarks for the next 50 yr of transplantation will be proposed.

What Went Before

Humanity has long dreamed of hybrids between different creatures, as evidenced by their rich representation in the ancient mythology of many different cultures. The fantastic amalgams of human form and supernatural animal were often bestowed with qualities unavailable to the component organisms, suggesting a benefit from hybridization. An example is Ganesha, prominently featured in Hindu mythology, who was made when the god Shiva combined the head of an elephant with an anthropomorphic body. Another is the chimera, described by Homer in the *Iliad* as a flame-spewing mix of lion, goat, and serpent (Figure 1). It is from the chimera that the

modern term *chimerism*, representing the coexistence of both donor and host cells, arises.

The first actual attempts at transplant surgery came surprisingly early in recorded history. Sometime around 1000 B.C., the Indian surgeon Samhita wrote detailed instructions for transplanting a tissue flap from one area of the patient's body to another (autograft) to repair nose injuries. These techniques were revived and updated in Renaissance Italy in the 16th century by Gasparo Tagliacozzi (1). Because these autografts retained their original blood supply, the more complicated hurdles of immunologic barriers and of vascular anastomoses were avoided.

The first major transplant pioneer, and the first scientist to receive a Nobel Prize for work related to transplantation, was the French surgeon Alexis Carrel. Around the end of the 19th century, Dr. Carrel used newly refined sutures to anastomose blood vessels in animals. In 1902 he published his work on the anastomotic techniques, which were subsequently adopted by other surgeons and form the basis for the standard vascular anastomotic techniques used today (2). In 1904, he moved to Chicago to join a collaborator, Charles Guthrie, and together they launched a series of transplantation experiments involving animals (3). In one of these experiments, the kidney of a dog was placed in a different location in the same animal, which continued functioning, allowing this animal to live for a number of years and have offspring. After this animal died of unrelated causes, autopsy revealed normal renal histology of the transplanted organ. Other experiments transplanting kidneys into different animals of the same species (allografts) fared less well. Pictures published by Dr. Carrel of various animals with transplanted limbs and organs stirred interest within the U.S. public for the application of transplantation techniques to human disease. In a particularly prescient observation, Dr. Carrel noted that the allogeneic organs failed from what he termed *biologic incompatibility*, one of the first known articulations of the concept of an immunologic cause for graft failure.

In parallel to the advances in clinical medicine, biologists began to consider the immunologic mechanisms that underpin graft acceptance and failure. At the time when the initial attempts at human kidney transplantation were being made, the immune processes that mediated acceptance and rejection were not well understood. Indeed, the study of immunology was still in its infancy. Toward the end of the 19th century, separate investigators identified the basis for blood group antigens (Landsteiner), the presence of antibodies in the serum (Erlich), the existence of the complement system (Bordet), and the presence of phagocytic cells (Metchnikoff). Some of the most

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Figure 1. Etruscan bronze figure of a chimera.

revealing discoveries came from the study of tumor immunology. Of particular importance is the observation by Murphy and Rous, who, in their study of the behavior of virus-induced tumors in birds, noted that rejected tumors were accompanied by infiltrating lymphocytes. Other investigators studying tumor behavior identified the first components of the MHC in mice (George Snell and Peter Gorer). Concurrently, a cross-Atlantic collaboration between Jean Dausset and Felix Rappaport discovered the HLA system. Nevertheless, at this time the relevance of these and other separate observations to clinical transplantation was not fully appreciated.

A number of investigators, beginning in earnest in the 1940s, undertook to study the effect of the immune system on the fate of transplanted tissues. Prominent among these, Sir Peter Medawar, who many consider the father of transplant immunology, began to investigate why transplanted skin grafts so often failed. Dr. Medawar, working closely with colleagues Rupert Billingham and Leslie Brent, used various animal models to study the factors governing host tolerance (1). When they examined skin grafts in rabbits, they found that, as with humans, skin allografts were rejected. When the same animals were rechallenged with grafts from the same donor, the reaction would occur much more quickly, suggesting that the immune system of the recipient could learn from exposure, a process now known as an *amnestic response* (4,5). Ray Owen and colleagues also noted that nonidentical twin cattle that shared a placenta would not reject each other's skin grafts but could reject the grafts of other cattle, spawning the concept of donor-specific tolerance. They reasoned that exposure to shared cells while *in utero* was responsible for the long-lasting tolerance. On the basis of this key finding, Medawar's group conducted a series of experiments in different animal species, especially with newly available experimental congenic mice, and confirmed that if recipients were exposed to foreign cells early in development, they became tolerant, but that the same exposure later would sensitize them. The descriptions of rejection, immunological memory, and tolerance earned Dr. Medawar the Nobel Prize in medicine, shared with Macfarlane

Burnet, in 1960. Fifty years ago, this first description of acquired immunological tolerance (6) generated enormous excitement in a generation of young immunologists. Developing a reliable nontoxic method to achieve tolerance in adults became a holy grail for transplantation. Although tremendous progress has been made, 50 yr later, the "grandchildren" of the first generation of transplant immunologists continue to try and solve this elusive puzzle.

In the wake of animal studies such as these, experiments in human transplantation were also being conducted. The first recorded solid organ transplantation was performed by the Hungarian surgeon Emerich Ullmann who, in 1902, implanted a canine kidney into the neck of a goat (7). The kidney was noted to visibly produce urine for 5 d. In this case, the vessels were attached by metal tubes because no satisfactory means for joining vessels existed. Four years later, a French surgeon, Mathieu Jaboulay, performed the first xenotransplant into humans, placing a kidney of a pig into the elbow of a woman with renal failure. He later attempted a similar technique with a kidney from a goat (8). Both of these experiments were unsuccessful, with the patients dying shortly thereafter.

The first attempt at transplantation of kidneys between humans was performed by the Russian surgeon Yu Yu Voronoy in 1936. In this case, a cadaveric kidney was attached to the groin of a woman who had kidney failure from mercury poisoning. The report documents a brief period of urine output from the newly transplanted organ, followed by abrupt cessation. The woman died shortly thereafter, and autopsy of the allograft revealed necrosis. An explanation for the failure was not available at the time, but it almost certainly represents what would now be recognized as rejection.

In Boston during the 1940s, physicians at the Peter Bent Brigham Hospital began to acquire expertise in the treatment of kidney disease that would propel them to the forefront of organ transplantation. They had access to several of the early dialysis machines that had become available around 1950 but were not yet widely used. Early dialysis techniques, although fraught with difficulties, made it possible to bridge patients toward potential kidney transplantation. Also available was an active laboratory research program experimenting with animal models of kidney transplantation. In this setting of heightened interest in renal failure, the team of surgeons David Hume, John Merrill, and later John Murray pioneered many of the seminal advances in kidney transplantation. Building on the experience of some earlier attempts in Chicago and Paris, they used both cadaveric and living unrelated grafts for a series of nine patients. Although eight failed, one of the cadaveric grafts lasted for 5 mo, the most successful human transplant to that time (9).

The Beginning of the Modern Era of Transplantation

Finally, in 1954, the team of John Merrill, Hartwell Harrison, and David Hume, headed by Joseph Murray, ushered in the modern era of organ transplantation with the first successful organ transplant between humans. In that landmark opera-

tion, he transplanted kidneys between two identical twins, the Herrick brothers (1). Before the operation, the brothers were confirmed to be immunologically identical by demonstrating that they did not reject each other's skin grafts. The transplanted kidney was placed in a pelvic retroperitoneal position, similar to the technique pioneered earlier in France. Apart from some unexpected bleeding, the surgery went well, and the transplanted kidney worked immediately. The recipient later underwent a native nephrectomy to control hypertension, a first glimpse of a clinical reality only appreciated later—that restoring renal function generally does not correct the propensity toward hypertension. Both brothers went on to recover fully and live otherwise normal lives, suggesting both that a transplanted organ can be curative of organ failure and that donors might not be at undue risk if carefully selected. Dr. Murray reproduced these results in a series of identical twins, spurring others to do the same. The success of these seminal operations showed definitively that the technical challenges of patient care and surgical technique had been conquered. Nevertheless, the transfer of tissue between identical twins sidestepped the more intractable problems associated with immunological barriers recognized by Carrel and others earlier.

The Power and Threat of Immunosuppression

The next step was to expand the promise of organ transplantation to the much larger pool of patients who did not have identical twin donors. Drawing on the lessons from the immunologists and the early transplant pioneers, physicians realized that tools were needed to control the immune system to prevent rejection of allogeneic organs. Studies involving allografts between mice demonstrated that in rodents, at least, large doses of external beam irradiation suppressed immune responses and could prolong the survival of skin allografts. There was corroborating evidence in other animal models of allotransplantation, and in humans, it was noted that immediate survivors of the atomic bomb blasts had severely depressed immunity.

After a series of experiments that demonstrated the ability of lymphoid irradiation to prevent rejection of renal allografts in rabbits and later in dogs, some physicians began using this technique as a way to prevent rejection in human subjects (10,11). This was initially attempted in Boston in a series of 11 patients with renal failure (1). Ten of these original 11 patients died of overwhelming infection, an early demonstration of a well appreciated clinical fact today: too much immunosuppression can be as bad, or worse, as not enough. The remaining patient, however, did remarkably well (12). This individual received a kidney from a fraternal twin who was shown to be nonidentical by his ability to promptly reject skin grafts from his brother. In this case, lesser doses of irradiation were used. The renal allograft functioned immediately, dramatically improving the health of the afflicted recipient. As an early harbinger of what would ensue, this patient subsequently had two episodes of rejection that were successfully treated with the combination of low-dose irradiation plus the use of the newly available antiinflammatory corticosteroid medication, cortisone. One of Dr. Murray's collaborators, Dr. George Thorn, who pioneered the use of cortisone, remarked in 1959 that "It

will be easier to put a man into space than to do what we did here" (13). This fortunate early patient demonstrated that immunosuppression had to be carefully titrated and that rejection, if successfully treated, did not inevitably lead to graft failure.

Since the earliest uses of immunosuppression to cross allogeneic barriers, developments in pharmacology have continued to drive major advances in clinical transplantation. Out of early attempts to treat cancer with various compounds came the development of agents such as nitrogen mustard and 6-mercaptopurine, but they were too toxic for regular clinical use. The first breakthrough occurred when George Hutchings and Gertrude Elion identified a less toxic cogener of 6-mercaptopurine, azathioprine, which could be combined with corticosteroids to prevent rejection. This combination became the basis of clinical immunosuppression until the late 1970s and together with their other drug discoveries (including acyclovir, trimethoprim, and allopurinol) earned these scientists the Nobel Prize in 1988. The next sea change in immunosuppression came when Sir Roy Calne, drawing on laboratory work of Jean Borel and clinical studies of David White, introduced cyclosporine A to clinical practice (9). This compound, isolated from a soil fungus from Norway, probably represents the single most dramatic advance in immunosuppression to date (14). It offered a degree of potency and immune specificity heretofore unimagined, allowing for dramatic decreases in rates of acute rejection. The development of cyclosporine A was later followed by a series of advancements including monoclonal antibodies, tacrolimus, mycophenolate mofetil, sirolimus (rapamycin), and polyclonal antilymphocyte preparations. With the tremendous success of these new agents at preventing and treating rejection, drugs are no longer judged simply by this criterion. Success for immunosuppressive agents is now judged by a combination of tolerability (*i.e.*, lack of side effects), ease of use, and, most importantly, the ability to improve long-term graft survival.

The Enduring Challenge of Progressive Transplant Dysfunction

As these new agents have had tremendous success in overcoming the primary barrier of acute rejection, attention has become refocused on the factors that limit long-term graft survival. Chronic allograft dysfunction, the slow destruction of transplanted grafts by various mechanisms both immune and nonimmune, is the next great challenge for the transplant community. Despite the enormous improvements in early transplant survival rates, the half-life of transplanted cadaveric organs has continued to be a difficult challenge for the field.

In each of the principal solid organs transplanted, there is a defined pathologic syndrome of chronic scarring that eventually leads to graft loss in affected patients. In kidneys, this syndrome is known as *chronic allograft nephropathy*, defined pathologically by fibrous intimal hyperplasia, interstitial fibrosis, and tubular dropout (15). Although it is clear that acute rejection is a major risk factor for its development there are other nonimmune factors involved such as the quality/age of the donor, BP control in the recipient, and, especially, exposure

to calcineurin inhibitors. This has led to the current examination of the relative contribution of ongoing immunologic injury and whether, in established cases, immunosuppression should be intensified or reduced. Analogous entities and similar debates exist for heart (transplant vasculopathy) (16) and lung transplants (bronchiolitis obliterans) (17).

There is considerable interest in refining the techniques of immunosuppression to limit toxicity and prolong long-term graft and patient survival (18). According to the Scientific Registry of Transplant Recipients (SRTR) report, the trends in immunosuppression over the 10-yr period from 1993 to 2003 include greater use of induction therapy, a substitution of mycophenolate mofetil for azathioprine, and for a gradual switch from cyclosporine to tacrolimus (19). Induction therapy, especially common in situations with higher rates of rejection such as pancreas transplantation, has undergone a transition from agents such as OKT3 to polyclonal agents with multiple immune targets, alemtuzumab (directed at B and T cells), or antibodies directed at the IL-2 receptor. There is also an increased use of the new class of agents, TOR inhibitors (of which rapamycin is the prototype), although their exact role in maintenance immunosuppression is still evolving.

Globally, there is a trend toward minimization of long-term immunosuppression. This is driven in part by our recognition that in patients who are able to navigate the early pitfalls (perioperative complications and acute rejection), the real limits to long-term survival are chronic graft dysfunction and cardiovascular mortality, both of which are related to drug toxicity. Some centers have begun to use corticosteroid-sparing regimens, in which therapy is ceased early after transplantation, a maneuver that appears to be safer, for reasons that remain unclear, than withdrawing steroids later. Others have tried to limit exposure to the calcineurin inhibitors cyclosporine and tacrolimus, either withdrawing them in the initial months after the transplantation, or by avoiding their use altogether with alternative drugs such as rapamycin. The availability of rituximab, a monoclonal antibody directed at the CD20 receptor on mature B cells, has begun to spark interest in directing therapies at the humoral arm of the immune system. This may prove particularly useful in the treatment of antibody mediated acute rejection, or perhaps as part of a comprehensive strategy to approach highly sensitized renal allograft recipients, in whom preformed anti-HLA antibodies make it difficult to identify a suitable donor.

Social, Legal, and Ethical Challenges

The new technologies associated with the clinical practice of transplantation, coupled with the exponential increase in the number of organs transplanted, have prompted the need for far-reaching legal, ethical, and social changes. One of the challenges ushered into the forefront of both the public and the medical communities was how to know when someone was dead. From time immemorial, the definition of death had seemed obvious: the cessation of circulation and respiration. With the advent of life-support technology, this traditional concept of death became inadequate. In addition, with the newly recognized need to harvest adequately perfused organs,

the precise time of death became important to recognize. It was on this basis that some observers began to propose the idea of *brain death*, a state of irreversible cessation in brain function even if the heart was still made to beat or the lungs were able to provide gas exchange, as the overriding standard to define death.

In 1964, the concept of *coma depasse*, a condition of prolonged irreversible cessation of all brain activity, was introduced in France, providing the framework for acceptance of the idea that brain function had a critical role in what was considered to be the state of being alive (20). This was a concrete step toward the more formalized definition of brain death put forward in Boston in 1968 (21). Slowly, these ideas were discussed in clinical circles, generating more thought and controversy. In 1976 in the United Kingdom, the Conference of Royal Colleges and Faculties published a clinical guideline for brain death called the *UK Code*. Responding to a growing need for a standardized characterization of death in the U.S., in 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research published its *Guidelines for the Determination of Death*, which declared that death was defined by the cessation of brain function and that this determination could be made on purely clinical grounds (22). This report laid the groundwork for the establishment of formal rules in all 50 states.

In an attempt to codify, and thereby to define the legality of the process of procuring cadaveric or living tissues for transplantation from donors, a series of acts were debated and ultimately passed by the U.S. Congress. The first major step was the Uniform Anatomical Gift Act in 1968, which formally stated that organs could be donated postmortem (23). In 1984, this was followed by the National Transplantation Act, which formally prohibited the sale of organs. In 1986, an effort to increase the rates of donation in the face of growing organ shortages resulted in the establishment of the *Required Request* rules, which obligated suitable families be notified about the possibility of organ donation from their infirm family members. This idea has recently been taken one step further in some countries in Europe, where a system of presumed consent, a model that presumes that those who die would want to donate unless they have specifically documented otherwise before death, is being considered (24).

The Disparity between Organ Supply and Demand

The largest and most pernicious problem affecting transplant programs today is the shortage of suitable organs to transplant. Despite a sizable public awareness campaign, the number of cadaveric donors has remained fairly steady over the last decade. The numbers of patients on the waiting list, however, has skyrocketed, leading to burgeoning waiting times and increased death rates for those on the waiting list. Some of this shortfall, at least in kidney transplantation, has been met with the use of living donor transplantation. Living donation also has been utilized with patients who need liver allografts, because a part of the donor liver can be taken, which will

subsequently grow in to an entire organ. High rates of morbidity and some mortality has limited the widespread acceptance of living donation of livers, and for obvious reasons, this approach is not generally possible for the intrathoracic organs.

The number of patients on the waiting list increased from 13,943 to 52,766 in the 4 yr between 1998 and 2002 (25). Efforts have focused on raising public awareness about transplant-related issues and encouraging the signing of organ donor documents such as driver's licenses. Much of this effort has centered on increasing the efficiency of the consent process through a variety of methods, including legislation to reaffirm donor gift laws, strengthening the organizational structure for the individual Organ Procurement Organizations (OPOs), and improving the way that the members of the hospital and OPO staff interface with the families of potential donors. The data available for 2003 reveal that consent was obtained for 41,273 organs, of which 22,460 were recovered (25). Debate has also focused on moving toward a system of presumed consent, in an approach similar to the one adopted in parts of Europe, where consent for donation is presumed unless specific waivers have been sought out and signed. This approach was recently endorsed by the AMA during their 2004 annual meeting.

Because the rates of cadaveric donation have grown only modestly (1.6% in 2002) despite an ongoing public awareness campaign, efforts are beginning to be directed toward maximizing the utility of the willing living donor pool. These approaches include the use of heightened immunosuppression including plasmapheresis, intravenous Ig, and often splenectomy to transplant across ABO barriers. Another approach is to use two sets of donors and recipients that are incompatible in a paired donor exchange (26). A third approach, extending the use of altruistic donors to those they do not know (nondirected kidney donation) has met with some success where it has been piloted (27). Finally, some activists have argued going one step further and have argued for direct payments to suitable kidney donors ("vendors"). When this approach was specifically studied, it was found that from a purely economic standpoint to the U.S. society, the break-even figure would be around \$90,000 per donor (28).

The Next 50 Years: Hope and Promise

The next 50 yr are sure to deliver advances that will again revolutionize the way we think about transplantation and, more globally, about the health-disease continuum. Already the experience with autoimmune disease, immunosuppressive states such as HIV and AIDS, and transplantation has influenced the way we conceptualize the immune system and circumstances in which it malfunctions. The immune system is now understood to be a complicated overlap of multiple systems that can both fight and promote states of disease depending on the circumstances. The simple notion of a binary process of on and off, for example, were necessarily abandoned upon the discovery that "immunosuppressed" AIDS patients often demonstrated augmented types of allergic immune reactions and that "immune activated" autoimmune patients had suppressed reactions to normal pathogens. These patients did not have suppression so much as a *dysregulation* of their immune sys-

tems. Accordingly, we have now moved toward specific modulation of the immune system to achieve more precisely what is desired and are thus able to avoid many of the deleterious consequences of having simply too little or too much immune activation.

As the gulf between the science of immunology and the practice of medicine narrows, specifically targeted modulation of the immune system should become increasingly possible. In the world of clinical transplantation, three principal areas of active research promise to become part of the canon of medical practice in the near future: the development of donor tolerance, xenotransplantation, and the growth of adult organs from stem cells.

The holy grail of transplantation, as predicted by Peter Medawar in the 1950s, remains the development of donor-specific tolerance. This will set the stage for lifelong organ function and avoid, wholesale, all of the expenses, risks, and toxicities of current immunosuppression regimens. There have been a number of confirmed accounts of patients developing long-term tolerance to their allografts. One early example was a early patient of Dr. Thomas Starzl, who stopped all of her immunosuppression and yet retained excellent liver function for years. This reality, however, has remained elusive for most transplant recipients who generally face rejection and graft loss in the absence of immunosuppression.

Two strategies that are currently either in clinical trials or prime candidates for study are mixed hematopoietic chimerism and costimulatory blockade. The former approach uses bone marrow transplantation with nonmyeloablative approaches to induce engraftment of donor bone-marrow stem cells (29). The patient is then a mixed chimera (*i.e.*, has both circulating donor and recipient bone marrow-derived cells). The preparative regimen used for the bone-marrow transplant is sufficient to eliminate mature donor-reactive T cells. Furthermore, engrafted donor cells circulate throughout the body, and those that traffic to the thymus mediate the deletion of newly developing donor-reactive T cells, thus inducing central tolerance. This approach has been used successfully in nonhuman primates and in small numbers of patients to induce tolerance (30). At present, the requirement for bone-marrow transplantation, with the inherent morbidity of the preparative regimen plus the potential for graft *versus* host disease, has limited its application to renal transplantation in patients with an underlying hematologic malignancy (for whom bone marrow transplantation is part of their therapy).

Approaches that use costimulatory blockade take advantage of the fact that T cells require a second costimulatory signal, in addition to antigen, for optimal activation. Two of the most important costimulatory interactions are mediated by the CD28 receptor and the CD154 receptors on T cells (31). Blockade of either of these has been used to induce long-term graft survival in primates, although true tolerance has not been reliably achieved (32). Agents that block T cell costimulation are currently in clinical trials, as part of adjunctive immunosuppressive therapy. True tolerance trials are expected to follow.

Many believe that xenotransplantation could become a reality within the foreseeable future. Already, baboon bone mar-

row has been transplanted into an AIDS patient, and fetal pig cells have been injected in to the brains of patients with Parkinson's disease. Dr. Thomas Starzl, who experimented with xenotransplantation into humans, noted that in a patient in whom he had transplanted a baboon heart had baboon cells throughout his body, a type of xenochimerism that he called *baboonization* (33). Many researchers have felt the best source of potential organs would come from pigs, who have physiology remarkably similar to humans. The primary barrier for successful transplantation between pigs and humans was hyperacute rejection, which has been attributed to naturally occurring and ubiquitous preformed antibodies directed against carbohydrate antigens present in pig tissues but absent in humans and Old World primates. However, recent advances that use pigs transgenic for human complement regulatory proteins have been able to knock out by homologous recombination the enzyme that produces the "offending" carbohydrate antigen. This strategy has been utilized with some success with human decay-accelerating factor, allowing transgenic pig organs to be transplanted into primates (34). Other efforts are underway. In 1995, for example, the U.S. Food and Drug Administration granted Duke University permission to transplant pig livers that had three such genetically altered proteins in to humans and the use of porcine hepatocytes for a type of extracorporeal hepatic filtration for patients in acute liver failure.

Another barrier to xenotransplantation is the risk of introducing infectious agents into the human population. Traditional infectious agents can be limited by delivering the donor animals by sterile fashion into germ-free *gnotobiotic* colonies. The animals are essentially sterile, but this procedure still does not eliminate the more worrisome problem of porcine endogenous retroviruses, which are examples of species-specific retroviruses that are present in all species of mammals. The potential of this virus, which is harmless to its animal host, to become a human pathogen is not known, but is greatly feared in the aftermath of the public health experience with xenobiotic viruses such as HIV, Ebola, and monkeypox. For this reason, there remains an active debate within the transplant community about the risks that a society is willing to accept for the welfare of an individual. Although the risk to the xenograft recipient can be estimated to a degree, and the consequences of transplantation carefully monitored, the risk of horizontal transmission of porcine pathogens to contacts of the xenograft recipient are more difficult to calculate.

Ex vivo growth of organs from dedifferentiated stem cells is the final dream that would change the medical world as we know it. In this scenario, stem cells would be reprogrammed to develop into mature organs. It might involve a technique such as placing DNA into nucleated oocytes, then turning on genes that promote and regulate growth of cells toward an organ, such as a kidney or liver. This is something akin to the approach used to clone the now-famous sheep, Dolly. If successful, this procedure would circumvent each of the remaining obstacles that face the transplant community today: organs that fail over time, the inability to tolerize the recipient to the grafted tissues, and the undersupply of available tissues.

Conclusions

What is old is new again. Man began with a dream of fantastic human hybridization and a concept of health that centered on the balance of humors in the body. This dream coupled with the evolving understanding of the nature of disease prompted developments, both incremental and revolutionary, that led toward the placement of organs from one person into another. And now, 50 yr after the first successful transplant and more than two millennia after the first dreams of transplantation, the technologic and immunological challenges have been met, allowing transplantation to have become part of our everyday clinical practice.

The coming decades are likely to witness continuing advances. The challenges that dominate this field are adequate organ supply, improved graft longevity, and the development of immunologic tolerance between host and graft. The convergence of the fields of transplant immunology and transplant medicine will provide the crucible that drives the leading edge of medicine. If history is our guide, the next major developments may well affect more than our ability to successfully perform organ transplants. These developments could provoke a more fundamental change in the way we conceive the relationship between health and disease, bringing us back around to the ancient dreams again.

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