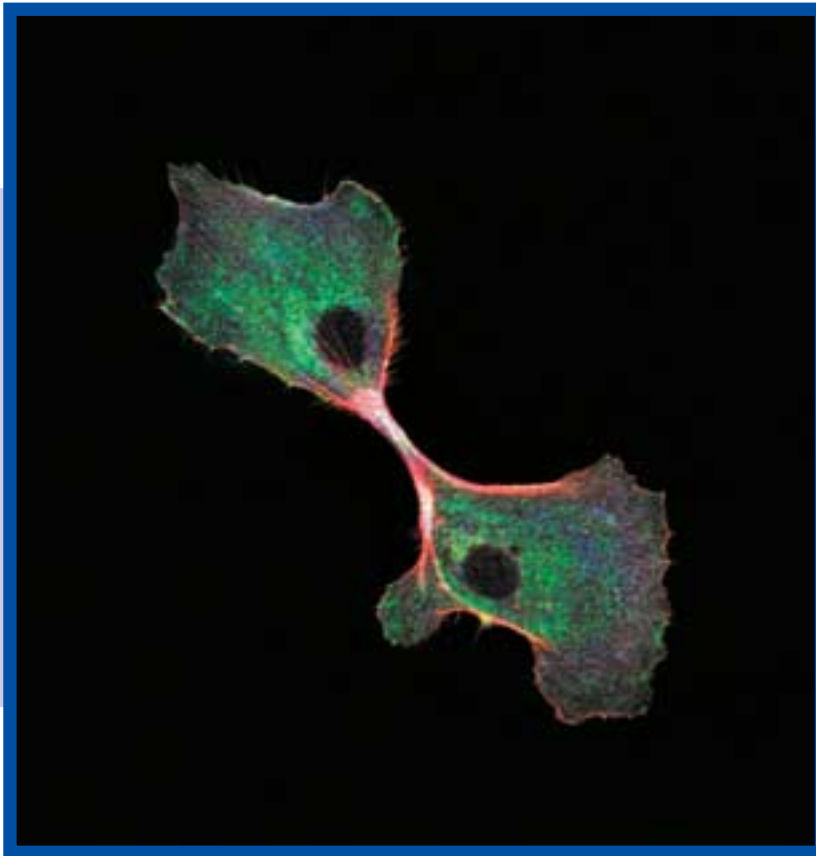


Breakthroughs in Bioscience

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Transplantation: The Challenging Road Ahead



By Daniel R. Salomon

Acknowledgments

TRANSPLANTATION: THE CHALLENGING ROAD AHEAD

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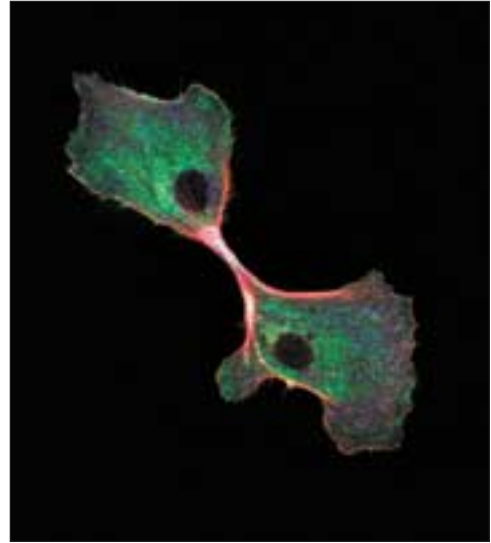
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COVER IMAGE: A false-color microscope image of two islet cells grown under special conditions in the laboratory as a possible source of insulin-producing cells to cure diabetes. Millions of diabetics depend on daily insulin injections because their islet cells no longer work. They could be cured if we understood how to transplant islet cells (and had enough of them). Photo courtesy Dr. Vincenzo Cirruli, Laboratory of Developmental Biology, The Whittier Institute for Diabetes, University of California, San Diego.

TRANSPLANTATION

Transplantation: the Challenging Road Ahead

Before his transplant surgery, Jack's failing heart left him so weakened and emaciated that he was virtually bed-ridden. But six months after that procedure to replace his damaged heart, he had rebuilt his strength and was once again brimming with energy and enthusiasm for the world around him. That chapter in his life was 15 years ago, and his transplanted heart continues to serve him well. But that post-surgical decade and a half puts him among the lucky minority of organ recipients—fortunate that his transplanted organ has thrived for so many years, fortunate that a heart was available when he needed it, and also fortunate in having adequate immunosuppressive drug regimens available to quell rejection and thereby making surgical transplant procedures possible at all.

No one yet knows how long any particular transplanted heart, lung, pancreas, kidney, or other organ will last. Some recipients survive with their transplanted organs continuing to fulfill vital functions for several decades or more. But others do not. The reasons behind this mixed success are complicated, depending on continuing refinements in surgical techniques and, to a great extent, how well the enor-



Figure 1. This is a picture of a patient before and after a heart transplant. In the “before” picture it is evident that the patient is stressed and has lost healthy weight and muscle mass (From *Geschenktes Leben* by Fernand Rausser, Stampfli Verlag AG Bern, Provided by Paul Mohacsi, University of Bern).

mous complexities of the body's immune system can be controlled. In any case, whole organs continue to be in abysmally short supply for transplant procedures, with the number of people waiting for them growing much faster than the number donating those organs.

One imaginative but still futuristic approach for overcoming this shortage calls for transplanting animal organs into humans (xenotransplantation). But for this strategy to work at all, researchers will need to develop a far deeper understanding of how to control the response of our immune system, which leads to rejection of such organs. They also will need to ensure recipients, as well as the general public, that xenotransplants will

not become a source of as yet unknown infectious agents.

Meanwhile, skilled surgical teams have made human donor-to-recipient organ transplant procedures seem almost routine. In some cases, those skills are being honed to ever more spectacular levels. For instance, in 1998 a team of surgeons in France successfully transplanted a hand, enabling the recipient to regain at least partial control over the wide range of functions that are associated with this intricately designed appendage. Another amazing procedure being done in several U.S. centers is living-related liver transplantation where a piece of the living donor's liver is removed and given to the patient. One can only marvel at the level of dedication

to life represented by the decision of a living donor to undergo such a complex surgery to save another person. Still other kinds of life-saving transplant procedures have gained ever wider use. For example, in treating certain kinds of cancer, bone-marrow or other cell types are infused into a patient's blood stream to restore functions that are damaged, suppressed, or lost following treatments designed to rid the body of cancer. Yet other transplant procedures being developed entail introducing specialized cells into patients with diabetes to replace damaged cells of the pancreas that no longer produce insulin, or nerve cells into the brain to treat diseases such as Parkinson's and Alzheimer's.

Organ Shortages, Immune System Complications Are Key Challenges to Progress

Research during the 1990s and earlier laid the groundwork for these and other remarkable biomedical innovations now under development. But there are important challenges to be faced before many of these innovative procedures come into wide use. One critical factor casts a broad shadow over the transplantation field—namely, the shortage of suitable organs from human donors. Demand for such organs perpetually exceeds supply, meaning that every year thousands of would-be recipients die before suitable organs become available to them (see Figure 2).

According to U.S. figures, more

Figure 2. The Organ Shortage

Transplants performed in 2000*

Kidney	13,372
Liver	4,954
Heart	2,198
Kidney-Pancreas	911
Lung	956
Pancreas	435
Intestine	79
Heart-Lung	48
Total	22,953

*Based on data from the Organ Procurement and Transplantation Network as of Aug. 3, 2001. Double kidney, double lung, and heart-lung transplants are counted as one transplant.

Patients waiting (January 4, 2002)

Kidney	50,790
Liver	18,710
Heart	4,119
Kidney-Pancreas	2,452
Lung	3,817
Pancreas	1,205
Pancreas islet cell	271
Intestine	179
Heart-Lung	211
Total	79,446*

*Some patients are waiting for more than one organ, therefore the total number of patients is less than the sum of patients waiting for each organ.

Number of donors recovered, 2000

Living	5,700
Cadaveric	5,984
Total	11,684

Source: United Network for Organ Sharing

than 70,000 individuals are waiting at any one time to receive organs from donors, but this total simplifies and greatly underestimates those needs.

Approximately 15 of these patients die every day because an organ that they need does not come available in time. However, this statistic does not capture the real tragedy of thousands of ill

patients waiting years for a transplant as they steadily deteriorate, stop work and cannot enjoy their lives or support their families. For instance, what if insulin-dependent diabetics were added to that official list? More than one million insulin-dependent diabetic children—who now endure regimented diets, restricted activities, and daily injections—might be spared those relentless life-long routines along with the risk of diabetes-related complications later in life, if they were instead to receive a new pancreas or transplanted pancreas cells to cure this disease. Unfortunately, less than 2000 whole organ pancreas transplants will be done this year, in large part due to the organ shortage, but also because this is a very complicated surgical procedure with significant risks. A much better approach would be the simple injection of insulin-producing pancreas cells called islets but this is presently just an experimental procedure.

The challenge of meeting organ shortages might be met if other critical complications can be better dealt with—those that arise because of how the body's immune system responds to “foreign” organs and cells. Serving to protect our bodies against intruders such as viruses, bacteria, and other pathogens that cause disease, the immune system instigates similar “protective” measures against transplanted cells and organs—leading, without appropriate drug interventions, to their rapid rejection.

This response to transplants between two humans typically arises in two phases, called acute and chronic (see Figure 3). During the past several decades, basic and clinical researchers made great strides in reducing the likelihood of failure of a transplanted organ in the acute phase during the first months following surgery. Much of that progress is due to the development of improved immunosuppressive drugs, which temper a recipient's immune system and thereby prevent it from immediately reject-

ing the transplanted organ. Thus, 80-90% of solid organ transplants work well not only for those first few months but at least for four or more years following surgery.

Over the longer term, however, survival rates decline steadily as many organ recipients slowly develop a progressive loss of transplant function. After ten years, about 50% of most transplanted organs are lost because of chronic rejection. For kidney transplant recipients, this loss means that they must undergo dialysis treatments several times

per week. For those with heart, liver, or lung transplants, the failure of the transplant often means death because medical science cannot offer appropriate procedures or mechanical devices to replace the vital functions that any of those organs play day in and day out. Chronic rejection thus is one of the most formidable challenges in transplantation today.

Figure 3: Acute Versus Chronic Rejection

Acute Rejection	Chronic Rejection
<p>Step #1: Recognizing the Transplant is Foreign Antigen-presenting cells (APCs) arrive and leave, taking with them a sample of the transplant's foreign HLA antigens. Transplant antigens are presented by the APCs, activating T lymphocytes and other immune cells.</p> <p>Step #2: Invasion of Immune Cells Activated immune cells circulating in the blood travel to the transplant.</p> <p>Step #3: Damage and Destruction Killer cells attack the organ. Killer cells attack the blood vessels, particularly small and medium-sized vessels. Activated immune cells secrete inflammatory substances called cytokines that increase the killing and damage.</p> <p>Step #4: Organ Function Deteriorates Heart failure Kidney failure Liver failure Lung failure Pancreas and islet failure</p> <p>Step #5: Repair and Resolution Organ repair is initiated if the rejection is stopped. Tissue is remodeled and new cells are produced. New blood vessels are created. Structure of the organ is restored.</p>	<p>Step #1: A gap in the immunosuppression Immune cells find a chance to activate again. APCs are activated and present transplant antigens to new immune cells. Antibodies directed against the transplant increase.</p> <p>Step #2: A low grade attack begins Activated immune cells and antibodies create small pockets of rejection. Large and medium-sized blood vessels are attacked.</p> <p>Step #3: Chronic Damage Blood vessels narrow as they react to the injury. As blood vessels narrow, blood flow decreases. Decreased blood flow starves tissue as vital nutrients and oxygen fail to arrive. Focal pockets of tissue injury end in cell death and loss of healthy structure progresses.</p> <p>Step #4: Unsuccessful Attempts to Repair The organ tries to repair the damage but can only do part of the job. Blood vessels also try to repair their damage but it ends up narrowing the channels only more and eventually the damaged vessels are completely lost.</p> <p>Step #5: Tissue Structure and Function Fails As damage and incomplete repairs progress, the structure of the organ is increasingly destroyed until it is beyond repair and the organ fails, slowly but without hope.</p>

Subtlety Required in Coping with the Chronic Transplant Rejection Challenge

Although immunosuppressive drugs provide a powerful means for controlling and preventing the acute phase rejection of transplanted organs, these drugs are difficult to use and their continued use can be a source of serious complications. For example, by their very nature, immunosuppressive drugs undermine the capacity of the body to ward off infections, leaving transplant recipients vulnerable to ordinary, even typically mild, infectious diseases as they run their course through the population.

Moreover, these immunosuppressive drugs tend to cause a medley of unpleasant, sometimes life-threatening effects among transplant recipients who are

required to take the drugs on a continuing basis. Hence, many researchers who study the role that the immune system plays in transplant recipients no longer believe that elevating the dose of immunosuppressive drugs or developing ever-more-powerful immunosuppressive drugs represent the best strategy for controlling chronic phase rejection of transplants. Instead, the key to meeting this challenge appears to lie in understanding the inner-workings of the immune system so that it can be harnessed to act in behalf of, rather than against, the transplanted organ.

Ironically, some of this improved understanding of the chronic, or long-term, immune response to a transplant comes from carefully reexamining what happens during the initial surgical procedures needed to introduce such an organ or cells into a

recipient. These procedures, especially those involving complicated organ transplant surgery, inevitably create both major and minor wounds that trigger an assortment of orchestrated healing and immune defense responses on the part of the recipient. For instance, perhaps during but certainly right after surgery, activated host system cells invade the organ transplant site where they help to lay down a complicated mix of new molecules—some serving as a scaffolding, others stimulating cell growth, and still others attracting vessels to reestablish blood flow at the site.

Amid this healing activity, activated immune system cells also trigger acute rejection of the transplanted organ in about one-fourth of all recipients. Although administering immunosuppressive drugs usually halts rejection at this stage, the drugs cannot

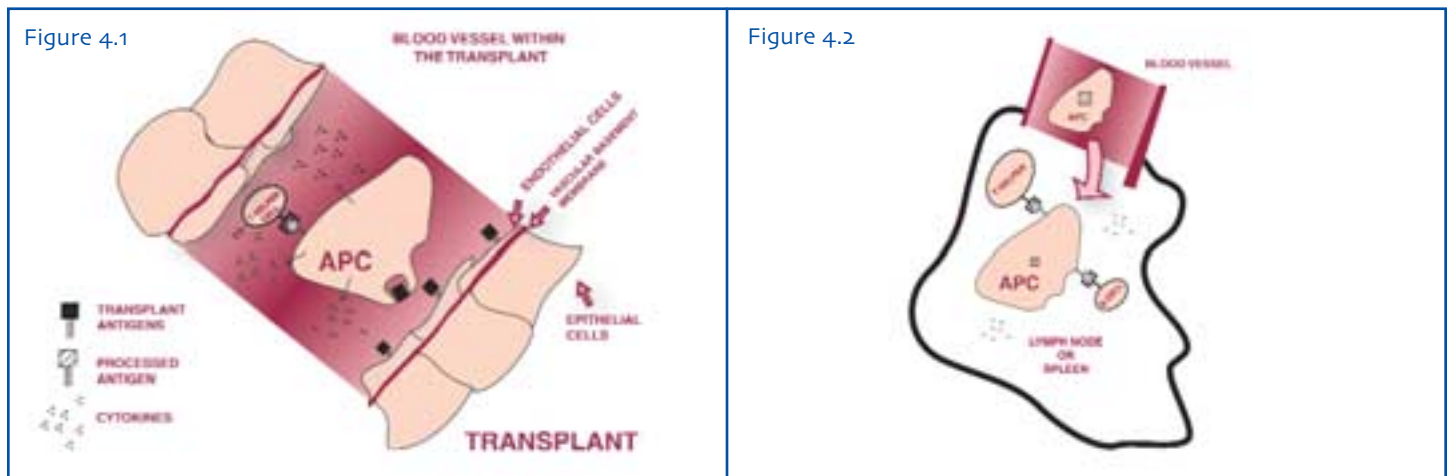


Figure 4. Immune Events in Transplant Rejection.

Figure 4.1: Antigen presentation and processing. The first event in the immune response is recognizing the transplant as foreign (in other words “not self”). Special cells called antigen presenting cells (APCs) constantly circulate in the blood and look everywhere for foreign invaders like viruses, bacteria, cancer cells or the transplant’s antigens. This is how our immune system protects us.

In this picture, an APC has just “swallowed” a foreign transplant antigen it has found in the transplant. The APC presents a special piece of this antigen to immune cells called “T helper cells”. The APC is also activated in this process and secretes substances called cytokines that recruit other APCs and helper cells to the area.

Figure 4.2: Instruction and expansion of the immune response. The APCs that “swallowed” and presented transplant antigens in Figure 4.1 return to the main organs of the immune system - the lymph nodes and spleen. There the APCs can efficiently present the antigens to many more immune cells including other T helper cells, and antibody producing cells called B cells.

entirely prevent a cycle of injury and repair that eventually—sometimes within months, more often after many years—leads to organ failure and rejection during the chronic phase. Telltale signs of these repeated injury-and-repair cycles include prominent scarring and narrowing of blood vessels that feed the transplanted organ.

In recognizing the serious impact of such damage on transplant organ longevity, researchers also identified the primary source for these damaging cycles—lymphocytes, more commonly known as white blood cells, which are an important component of the immune system. Lymphocytes and other specialized immune system cells are responsible for monitoring the body for evidence of foreign intrusion or cancerous

tumor cells. Usually, they prowl the gamut of organs and tissues by means of the blood stream looking for microbial pathogens or malignant cells. Unfortunately in the case of transplants, these circulating monitors can end up recognizing signature molecules on such otherwise healthy organs as “foreign.” Moreover, these vigilant immune system cells can stick to transplanted organs and remove samples of such signature molecules, carrying them to other immune system components where they generate ever-more-potent transplant rejection responses. Researchers call those signature molecules and their characteristic components “antigens,” and the specialized immune system cells that convey those antigens to other reaches of

the immune system are known as antigen-presenting cells (APCs) (See Figure 4).

“Blinding” the Immune System to Transplants May Prolong Their Usefulness

Researchers now realize that biochemically “blinding” these constantly prowling immune system cells may provide a new way of prolonging the functional lifetimes of transplanted organs. Of course, such cells do not literally “see” their way through the body. Instead, they roll along through the bloodstream, nudging against vessel surfaces while also entering and departing specialized tissues and organs where they again poke into surfaces that happen to

Figure 4.3

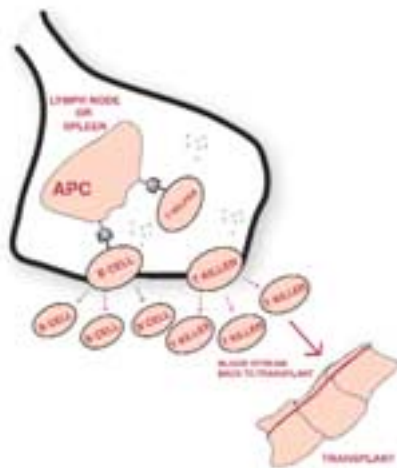


Figure 4.4

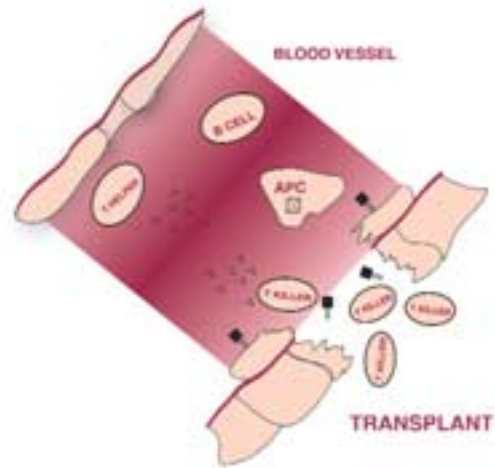


Figure 4.3: Proliferation and targeting of the response. Once APCs have activated enough helper immune cells (see Figure 4.2), they begin to work together as a team to activate the next wave of immune cells. The next wave are killer immune cells. The antibody-producing B cells are also activated and expanded. These waves of cell activation and proliferation that follow involve cytokines and other growth factors produced by the helper cells and APCs. In the final step, these activated cells return to the transplant via the blood stream. It is important to note that the processes described in Figures 4.1, 4.2 and 4.3 are circular. Initial events in the transplant drive subsequent events that in turn recruit more cells and expand the process further.

Figure 4.4: Acute Rejection and tissue destruction. In the last stages of rejection the killer cells, antibodies and activated APCs that have returned to the transplant initiate the death and destruction of the underlying tissue. Blood vessels are broken, blood factors are activated that clot the vessels, the killer cells spill into the organ itself and the organ’s cells are killed directly or by the loss of vital nutrients like sugar and oxygen. If the rejection is bad enough the function of the transplant will suffer or the transplant itself can be completely destroyed.

be along their path. Thus, these immune system cells are very different from oxygen-carrying red blood cells, which ride at high speed with the blood stream among the same organs and tissues. Rather the slow-rolling immune system cells—acting as guardians of the body’s internal integrity—meander these same pathways in a more deliberate fashion, prodding and interrogating as they move from site to site.

How do our immune cells actually recognize foreign cells? The slow movement of the immune cells is due to the fact that they actually stick to tissue surfaces. This sticking action is mediated by several types of specialized molecules that protrude from different organs and tissues. Called selectins, these molecules effectively control the pace of immune cells by grabbing at them as they wend their way through the body. Although the grip of the selectins is relatively weak, immune cells are grabbed at so often that their overall travel rate is retarded as they conduct their tactile inspections, moving from one organ and tissue to the next.

However, this plodding movement can slow even further when immune system cells enter the vessels of a newly transplanted organ where they are apt to engage yet another set of specialized molecules, called integrins and integrin binding proteins. Integrins are expressed by the circulating immune cells and integrin binding proteins are produced on tissue surfaces following injuries. In the case of a

recently transplanted organ, the integrin binding proteins reflect the sort of damage that comes inevitably from the trauma of its surgical removal from the donor and transfer to a recipient. Importantly, compared to selectins, integrins are far stickier and thus grip passing immune cells with much greater tenacity. Integrins also have the unique power to direct these cells to travel or migrate across the blood vessel surface into the transplanted organ itself. Held in this way to the damaged vascular surface of the “foreign” organ or migrating into the transplant, immune system cells respond by beginning a cycle of specific reactions that leads to further damage and eventual rejection of the transplanted organ.

Researchers, in recognizing that the encounter between integrins and integrin binding proteins on transplanted organs is so critical to everything that follows, are now testing several drugs that interfere with or prevent it completely. To test this strategy for prolonging transplant survival times, clinical researchers recently began evaluating various drugs for their ability to prevent by one means or another immune system cells from sticking to the surfaces of vessels that supply newly transplanted organs with blood. Some of those experimental drugs are intended to keep white cells from being grabbed as they circulate through the transplant. Others, including two recently licensed drugs whose primary medical use is for treating

rheumatoid arthritis, interfere with this same process, but by a less-direct way—blocking other signal molecules whose appearance would lead to more integrin binding molecules being placed on those blood vessel surfaces that supply the transplant. In both cases, the aim is to render the transplanted organ less visible to the body’s immune system, thereby avoiding the repetitive damage-and-repair cycles that ultimately may lead to organ rejection.

Researchers Also Seek to Make the Immune System “Tolerant” of Transplants

Individuals who receive transplants face a life-long commitment to taking immunosuppressive drugs. Chronic exposure to such drugs means an increased risk of serious side effects, including infectious diseases, high blood pressure, various kinds of cancer, and a greater likelihood of developing kidney, heart, and bone disease. Ideally, if the immune system of a transplant recipient could be induced to accept that organ as “self” rather than continuing to recognize it as “foreign,” there would no longer be a need for recipients to receive immunosuppressive drugs. Researchers consider this condition, called immune tolerance, a critical goal and are now pursuing several strategies to try to reach it.

One promising approach resembles the drug-based, injury-signal-blocking strategy described

earlier. However, here the aim is to interfere with part of the biochemical information being conveyed by antigen presenting cells, or APCs, of the immune system to other components of that system that are instrumental in rejecting transplanted organs. Except in the case of identical twins, the organs and cells from one individual carry molecular markings that distinguish them from those of anyone else. Ordinarily, portions of these markings on a donor organ are presented to other components of the recipient's immune system, which then set forth a cascade of responses that lead to transplant rejection. In simple terms, the immune system "reads" these

unique markings on the transplant's cells and returns to vigorously destroy them if it decides that they are not "self."

However, if that APC-triggered cascade is blocked at an early stage, the recipient's immune system cells would become tolerant of the donor organ, accept it as "self" and never reject it. APCs release an assortment of biochemical signals to trigger the cascade, and researchers now have identified at least a dozen of these along with the specific receptor molecules which must be activated before transplant rejection responses can begin. Not surprisingly, there is an active search to identify drugs that can interfere with these sig-

nals and thus might also induce immune system tolerance to transplants. Such drugs would very likely also prove useful for treating autoimmune diseases like multiple sclerosis, rheumatoid arthritis and systemic lupus.

Another strategy for achieving immune tolerance, takes a somewhat different route—one that entails reprogramming the immune system's own definitions of "self" and "foreign." Ordinarily during the early stages of development, an individual's immune system effectively catalogues its own characteristic suite of molecular signatures in such a way that they will not be mistaken as foreign. In much the same way but later during infancy and

T I M E L I N E

Milestones in transplantation



Karl Landsteiner



Mathieu Jaboulay



Alexis Carrel

Ancient China

The idea of organ replacement dates to ancient times. The first successful heart transplants were claimed by China during the Qing Dynasty: Two patients had their hearts exchanged in order to rebalance their vital energies.

1901

Karl Landsteiner classifies blood types. His discovery of blood group antigens—unique sugars on the surfaces of many cells—opens the door to safe blood transfusion. Realization that molecules on cells can differ between individuals is the first clue to why organ transplants fail within hours.

1905–6

Mathieu Jaboulay uses the kidney of a pig to perform the first human kidney transplant; it is rapidly rejected. Alexis Carrel replaces an artery with a segment of vein, founding the field of vascular surgery. Blood vessel grafts are still the basis of modern procedures such as coronary artery bypasses, over 600,000 of which were done last year in the U.S. Edward Zirm restores the sight of a man blinded by lime with a corneal transplant. Today eye banks supply corneas for more than 15,000 transplants each year in the United States.

1940s

Peter Brian Medawar uses refrigerated skin as a temporary dressing for burns. Today the United States has 20 skin banks supplying skin for grafts.

childhood, the immune system along the digestive tract comes to tolerate the wide array of “foreign” molecules that are encountered in foods. The overall process of instilling tolerance thus programs the immune system to recognize its own components and some from outside the body that it will need to sustain life, while safeguarding the body against pathogens, malignant cells and other threatening intruders.

Researchers who are trying to reprogram the immune system to make it tolerate transplants report

some noteworthy successes in a variety of animal models. In general terms, this approach entails trying to trick parts of the mature immune system into behaving as it did during the very early stages of development before definitions of self and foreign solidified. One specific set of experiments involves transplanting bone marrow cells from the donor animal along with the specific organ being transplanted. Because these transplanted bone marrow cells contain some of the donor’s critical immune system cells, this procedure converts the recipient’s immune system into a

mixture, or chimera, containing components of both immune systems and, thus, effectively renders the recipient system tolerant of both types. Tolerance has been induced in this way in several baboons and now experiments are underway to test if this can also be done successfully in human patients.

Indeed, these approaches for inducing tolerance to transplants appear so promising that leading researchers convinced officials at the National Institutes of Health (NIH) to create the Immune Tolerance Network. This program

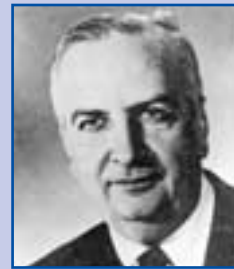
Milestones in transplantation



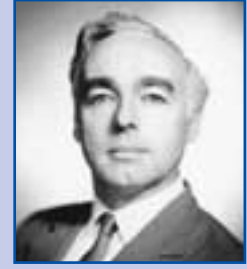
Jean Dausset



George D. Snell



Baruj Benacerraf



Rupert E. Billingham

1950s

Jean Dausset, George D. Snell and Baruj Benacerraf discover that transplant rejection is governed by differences between individuals of protein molecules called histocompatibility antigens (often called HLA or Human Leukocyte Antigens). HLA molecules create the equivalent of a unique personal signature on each cell. Antibodies and a subset of white blood cells known as T cells read and recognize HLA molecular self-signatures. Tissue typing matches HLA molecules between organ donor and patient as closely as possible in order to decrease the odds of a transplant being rejected.

1953

Experimenting with mice, Peter Brian Medawar, Leslie Brent and Rupert E. Billingham demonstrate that an immune system can be reeducated to tolerate transplanted tissue.

1954

If HLA and blood group differences are responsible for transplant rejections, then transplants between individuals who have no differences should be successful. Joseph E. Murray achieves the first successful kidney transplant, transferring a kidney between identical twins.

1956

Also using identical twins, E. Donnall Thomas performs the first successful bone marrow transplant. Today, more than half of all leukemia patients can survive, thanks to bone marrow transplants.

1960s

Corticosteroids and azathioprine, which was originally an anti-cancer agent, are the first immunosuppressive drugs. They prevent activation of the immune response, thwarting transplant rejection. Physicians suddenly are able to do kidney transplants between unrelated individuals, although less than 50 percent last five years. The drugs work too poorly to allow routine liver and heart transplantation.

operates through a network of clinical centers at major universities and medical schools throughout the United States and Europe where investigators will subject a variety of specific new ideas and experimental drugs to testing in clinical trials. Some of these efforts involve studying ways of inducing tolerance to transplants of organs such as kidneys or specialized cells, such as islet cells from the pancreas that produce insulin needed by diabetics, whereas other clinical trials will focus on treating allergies, asthma and various autoimmune diseases.

Engineering Might Ease Specialized Donor Tissue Shortages

More than 15 years ago, Marilyn had finished law school and her career hopes looked bright, except for the fact that her diabetes was becoming progressively more difficult to control. Even as she painstakingly tested her blood sugar levels and diligently injected herself several times daily with insulin, her health was declining. For instance, cataracts in both eyes along with diabetic retinopathy

made her vision so poor that she was considered legally blind, able to read legal tracts or the newspaper only by holding those texts flat against her face. Moreover, her kidneys were beginning to fail. But armed with a determination that seemed to come bundled with her new law degree, Marilyn began badgering her doctors to find a pancreas to replace her failing organ. Eventually, they did and, despite all the usual challenges of adapting to life with such a transplant, her health has been far better and, of course, her diabetes is cured. In fact, she recently had a baby, and the

Milestones in transplantation



James D. Hardy



Thomas Starzl



Norman Shumway

1962

Joseph E. Murray performs the first kidney transplant between unrelated persons; later, he transplants successfully a kidney from a cadaver.

1963

James D. Hardy performs the first lung transplant. Thomas Starzl carries out the first human liver transplant.

1967

Christian Barnard, building on surgical techniques pioneered by Norman Shumway, achieves the first successful heart transplant. Richard C. Lillehei does the first successful pancreas transplant.

1974

Jean Borel discovers cyclosporine, an immunosuppressive which increases one-year survival rates for kidney transplants to 80-90%, and five-year rates to better than 50%. Cyclosporine makes heart and liver transplants practical. The FDA approves the drug in 1983.

1984

The National Organ Transplant Act creates a national system for matching organ donors and recipients.

1998

Jean-Michel Dubernard performs the first successful hand transplant.

2000

Scientists learn how to clone pigs, enabling genetic engineering of humanized pig organs that will be tolerated by the human immune system.

complications she had to contend with during her pregnancy had more to do with her age—pushing forty—than with managing the transplant.

Although Marilyn's most pressing health needs were addressed when she received a new pancreas, obtaining such organs remains a constant challenge to physicians. Moreover, many diabetics do not need the whole pancreas and the major surgical risks this entails. In principle, their diabetes can be cured by transplantation of only the specialized islet cells, which produce the insulin that their own pancreases are unable to make. As an exciting proof of principle, purified pancreatic islets have recently been infused directly into the livers of a small group of diabetic patients and in several, their diabetes has been cured for up to one year. Unfortunately, this requires infusion of all the islets obtained from two to three whole pancreases, a situation that would really be a major setback to the existing donor organ shortage. It also makes it clear that the majority of the infused islets are destroyed or never function well since as little as half of a single pancreas can cure diabetes when transplanted as a whole organ.

One promising approach to overcoming difficulties associated with transplanting intact, insulin-producing islet cells is based on lessons learned about trauma and injury which occur during organ transplantation. The key point is that such islet cells are delicate, and are espe-

cially vulnerable to damages incurred during the transfer from a donor to a recipient. Tests in rodents indicate that introducing several preventive procedures can help in overcoming such damage. For instance, adding protective scaffolding molecules made from collagen, which is a structural protein found throughout the body, helps to hold the delicate islet cells in place at the implant site, protecting them from further damage. In addition, introducing signal molecules, called angiogenesis factors, helps to stimulate the development of vessels to supply blood and nutrients to the newly transplanted islet cells, further assuring that they will survive and function successfully in their new environment within a recipient's body. These new approaches to islet transplantation are a form of tissue engineering.

These exciting new ideas for how to protect and nurture specialized cells following their transfer from a donor to a recipient are not limited to the transplant of pancreatic islet cells for treating diabetics. For instance, within the next few decades, some 59 million aging Americans will suffer from degenerative arthritis, according to current estimates. Perhaps within this same time frame, it will become possible to transplant specialized cells into damaged joints to repair or replace cartilage and bone that become damaged as a result of osteoarthritis. And there are other degenerative diseases or other traumatic conditions for

which engineered tissue transplants could someday provide important benefits, such as better skin transplants for treating burn victims, improved corneal transplants for restoring normal vision for those with damaged corneas, or replacement nerve cells to help in mending or preventing diseases such as Parkinson's and Alzheimer's that affect the brain and the central nervous system.

One of the most exciting developments beginning in the late 1990s has been the prospect of producing transplant tissues from human stem cells. [Stem cells are "multipurpose" cells that can generate highly specialized mature cells for specific purposes.] Some stem cells, for instance, give rise to specialized red and white blood cells. Other stem cells develop into cells that carry out specialized tasks in particular organs and tissues, such as the kidney, liver, bone marrow, skin, or brain.

Theoretically, it should be possible to produce and implant stem cells to conduct specialized tasks in any organ or tissue that might otherwise require replacement by whole-organ transplantation. For example, new heart muscle after a heart attack or new spinal cords for accident victims. Thus, if stem cells harvested from an individual patient could be engineered into needed tissues, then transplantation would not require any kind of immunosuppression. Alternatively, if stem cells from another source such as a willing donor or even an animal could be transplanted with a

successful tolerance induction method and successfully replace damaged or missing tissues, we might find ourselves in an entirely new phase of transplantation medicine.

Xenotransplantation Eventually Might Ease Vital Organ Shortages

A new phase of transplantation medicine—one that some researchers welcome as very promising, while others dismiss as too controversial—focuses on animals as potential sources of badly needed whole organs and cells for human recipients. As stated earlier whole organs, such as hearts, livers, and pancreases, continue to be in abysmally short supply. One still experimental approach for overcoming this shortage calls for substituting xenotransplants—most likely organs from pigs, but possibly also from other animals—for those of scarce human organs. Why use organs and other tissues from pigs? For one thing, pig organs are close in size to human organs, and perform vital functions in similar fashion. For instance, pig valves are used to replace defective human heart valves, and pig skin has been used as part of dressings to provide temporary relief for severely burned patients.

Despite these and other outstanding advantages that suggest pigs would make a promising source of donor organs for human transplants, the biological gap between pigs and humans—indeed, between any two

species—looms as a formidable barrier for anyone attempting to transplant organs across that gap. The problem does not rest, for instance, with a pig heart failing to pump adequate volumes of blood. Instead, the problem centers on immune system differences, with the recipient's immune system very vigorously and very quickly rejecting a transplanted pig organ or other xenotransplant. In fact, the immune response of a species to xenotransplants is so nasty, brutish, and short that immunologists gave it a special name: hyperacute rejection, or HAR.

Nevertheless, researchers now studying xenotransplantation are optimistic about developing solutions not only to hyperacute rejection but to some of the other immune system and infectious disease-related challenges that are associated with this field of biological research. For instance, some of the current incompatibilities between donors and recipients undoubtedly can be addressed by genetically engineering pig organs to improve the chances of them being accepted by the human immune system. Already, some researchers are using such techniques to manipulate the molecular signatures ordinarily found on the surface of pig organs, making them appear more human-like and thus perhaps more suitable to a human recipient's immune system. In addition, human genes responsible for regulating blood vessel injury have been introduced into pigs to make their organs more

adaptable following a transplant, and the effects of making these changes are being evaluated in experiments in which another species of animal is serving as the recipient of such transplanted organs.

Under some limited circumstances, pig cells (or those from other species) can be transplanted into a second species without triggering acute rejection by the recipient's immune system. One way to avoid acute rejection is to place the transplant cells into an anatomic compartment that is not fully accessible to the recipient's immune system. For instance, when pig cells are transplanted into the central nervous system, the blood-brain barrier protects those inserted cells from antibodies that circulate in the blood and would otherwise trigger the HAR response. To take advantage of the brain being a partial sanctuary from this severe immune response and further test the validity of this approach to treatment, clinical researchers are inserting fetal pig nerve cells into the central nervous systems of patients with severe Parkinson's disease. Nerve cells controlling movement have so badly degenerated in these patients that parts of their bodies either shake uncontrollably or are subject to extreme muscular rigidity. These clinical tests will determine whether the pig cells can alleviate the symptoms of such patients by producing dopamine, a chemical that their movement-associated brain cells no longer produce. Patients who are participating in

these trials are also being carefully monitored for any infections that might arise from the transplanted pig nerve cells.

Concerns over such infections represent another critical challenge facing scientists who are studying xenotransplantation biology. Much of this concern focuses on viruses, which are typically more difficult to detect or treat than are other types of pathogens. Officials at the Food and Drug Administration (FDA) and researchers who specialize in such matters are currently evaluating strategies for detecting and characterizing even very rare or otherwise obscure viruses from pigs. Their study will look for any infections from such sources that might represent a risk to individual recipients of xenotransplants, their family members and healthcare providers, and the public at large.

For instance, investigators have learned that pancreatic islet cells transplanted from pigs into mice (with deficient immune systems enabling the pig cells to survive in these recipient animals) produce viruses that infect mouse cells. These results by no means prove that similar xenotransplant procedures involving human recipients would lead to a significant public health risk. Nevertheless, these animal models are providing the kinds of insights that FDA officials say are needed to build a better understanding of the infectious disease risks associated with eventually conducting xenotransplant procedures in humans.

Still other efforts are under way to make pigs more suitable for medical use as organ donors for transplant procedures. Early in 2000, for example, researchers successfully cloned pigs, a procedure that is essential if the full range of genetically engineered changes being introduced into pigs is to be put to full use.

Cloning enables researchers to produce genetically uniform animals, meaning that every pig within a litter carries the exact range of genes as any of its littermates, making all of them equally suited to serve as organ donors. Moreover, cloning also enables scientists reliably to delete those pig genes that provoke human immune responses that could lead to rejection of the transplanted organs (See the Breakthroughs in Bioscience article, “Cloning: Past, Present, and the Exciting Future” at [www.faseb.org/opar/break/.](http://www.faseb.org/opar/break/))

Conclusion— Transplantation’s next century

Attempting the transfer of an organ from one human to another was an exceptionally bold and complicated experiment. Since early in the 20th century, transplantation research and the clinical practice of transplantation have been in continual motion, challenging our basic understanding of immunity and genetics. The advances that have been made in regards to our understanding of the organization and function of organs and tissues benefit all mankind. Research in the 1990s has set the stage for the

next century of transplantation medicine. There is much to look forward to including the prospect of solving the severe shortage of donor material, producing tolerant transplants without fear of chronic rejection and advancing cell transplantation and tissue engineering into the routine practice of medicine.

New advances in transplantation therapies have the potential to benefit millions of patients—not only those waiting for whole organ transplants but also those who are candidates for cell or tissue transplantation. For example, it has been estimated that nearly 2 million diabetics in the U.S., both adults and children, could be helped by transplantation of insulin-producing cells. As the incidence of adult-onset diabetes increases, this number will only grow. Approximately 600,000 Americans per year who suffer from cardiovascular disease, hepatitis and chronic liver failure, and cancer could be helped by transplantation of various cell types. In the future, the successful use of cell transplantation using stem cell technology would expand these numbers significantly. Thinking globally, the number of patients who could be helped by various new transplant procedures is staggering. These technologies have the potential to reduce health care costs significantly and to dramatically improve the lives of millions of recipients.

To learn more...

To learn how you can become an organ donor, visit the website of the Coalition for Donation, a non-profit organization that promotes organ donation.

www.shareyourlife.org

Learn more about the organ shortage at the website of the United Network for Organ Sharing (UNOS). A non-profit corporation, UNOS is commissioned by Congress to match organ donors to waiting recipients without regard to financial or social status, sex, race, religion, or lifestyle. www.unos.org

For a detailed description of the immune response in transplantation, see D. R. Salomon (1998) Chapter 1 - The Molecular Basis of Transplantation Immunity, in *Kidney Transplant Rejection* (3rd edition), eds. L. C. Racusen et al., Marcel Dekker, Inc., pp. 1-31.

For a recent discussion of immunosuppression and its role in transplantation, see D. R. Salomon (1997) Rationale and mechanisms of immunosuppression. *Kidney International Supplement*, 58: S48-50.

For a recent review of progress in tissue engineering, see S. S. Kim and J. P. Vacanti (1999) The current status of tissue engineering as potential therapy. *Seminars in Pediatric Surgery*, 8: 119-123.

For a discussion of the future of islet transplantation in treating insulin-dependent diabetes, see N. S. Kenyon et al. (1998) Islet transplantation: present and future perspectives.

Diabetes/Metabolism Research and Reviews, 14: 303-13.

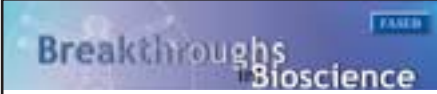
A new book explains the possibilities and problems of xenotransplantation: *Xeno—the Promise of Transplanting Animal Organs into Humans* by David K. C. Cooper and Robert P. Lanza. Oxford University Press (2000).

For more about the NIH Initiative on Tolerance, see <http://paramount.bsd.uchicago.edu/site-frameset.html>

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