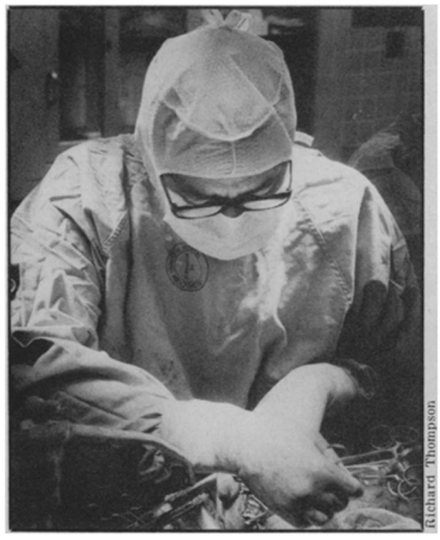
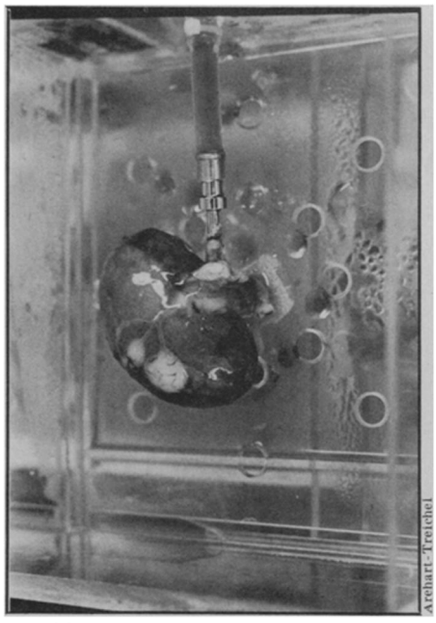
ORGAN TRANSPLANTS: WHAT HOPE FOR PATIENTS?

Three decades after the first transplant, rejection is still a major hurdle

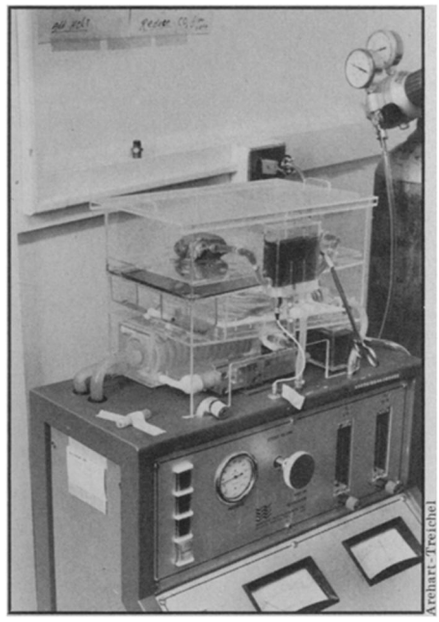
by Joan Arehart-Treichel



Hufnagel performs kidney transplant.



Bubbling antibodies through kidney.



Apparatus for perfusing the kidneys.

At midnight, in Peter Bent Brigham Hospital in Boston, an expectant mother lay dying from kidney failure. Three of Brigham's surgeons—Charles Hufnagel, Ernest Landsteiner and David Hume—attempted to save her life. They attached the vessels of a cadaver kidney to veins in the woman's arm, partially burying the kidney under her skin. The kidney started to drain poisonous wastes from her body. Several days later, her own kidneys started secreting urine again. The cadaver kidney was removed. She lived. . . .

This successful temporary organ transplant was undertaken in 1945. The first successful permanent organ transplant took place in 1954, also at Peter Bent Brigham. Since then 18,325 kidneys, 245 hearts, 217 livers, 35 pancreases and 34 lungs have been transplanted into patients throughout the world. These statistics, from the American College of Surgeons/National Institutes of Health Organ Transplant Registry, suggest that organ transplants have come of age.

The statistics, unfortunately, are misleading. Although one kidney transplant patient has survived 18 years, one heart transplant patient 6 years, one liver transplant patient 5.1 years, one pancreas transplant patient 2 years and one lung transplant patient 10 months, the bulk of transplant patients survive for lesser periods. And the burst of heart transplants during the late 1960's resulted in so many deaths that only two surgical teams in the world are now doing heart transplants regularly. One of them is at Stanford University Medical School, headed by Norman A. Shumway. The other is at the CMC Foch Hospital in Suresnes, France, headed by Daniel Guilmet.

"Overall," declares transplant pioneer Hufnagel (now at Georgetown Medical School), "the long-term fate of transplants is still very shaky."

Problems abound in transplant surgery. Transplants are costly (a heart transplant at Stanford runs $42,000). Donor organs are scarce; preserving and storing them is difficult. Patients are often critically ill when they receive an organ, a factor that compounds their difficulties in surviving. While the surgical techniques for kidney and heart transplants have been pretty well worked out, there are still thorny problms in liver, pancreas and lung transplants. And then there is the major hurdle in all kinds of transplants —immunologic rejection. The recipient's body tends to view the transplanted organ as foreign and vigorously tries to reject it, especially during the first several months after transplantation.

One way surgeons are trying to surmount immunologic rejection is by giving patients powerful drugs that blunt their immunologic defenses. But such drugs, while helping patients retain their transplanted organs, also open them to serious and often life-threatening infections. The experience of Shumway and his team has shown that patients who have had moderate-to-marked cardiac disability for more than five years are unable to tolerate the rigors of postoperative immunosuppresive therapy.

Bacterial infections are easier to handle than virus or fungus infections, reports Anthony Monaco, a kidney transplant surgeon with the New England Deaconess Hospital in Boston and Harvard Medical School. But unfortunately, he says, transplant patients usually succumb to the latter. The skin complications of immunosuppression are frequent and often emotionally traumatic. It is not uncommon for patients to stop taking their drugs because of adverse cosmetic effects, and hence to experience organ rejection and death. Transplant patients also suffer from a greater risk of cancer than do other people because of immunosuppression.

Still another way surgeons are trying to overcome the rejection problem is by matching organs and recipients according to HL-A antigens. The white cells of every person carry four of these chemical molecules—two inherited from the mother, two from

the father.

Immunologists started discovering these histocompatibility antigens in people about 10 years ago. Since then, 32 HL-A antigens have been identified. So there are hundreds of thousands of possible HL-A antigen combinations in the human population. It is this stupendous number of combinations that tissue-typing labs are contending with as they try to match available organs with needy recipients. Paul I. Terasaki, a pioneer in tissue typing at the University of California at Los Angeles, estimates that whereas there is a one-in-four chance of making a perfect match between siblings, the chance of making a good match between unrelated individuals is only one in a thousand.

HL-A matching does make a difference in living related-donor transplantation. This is the conviction of Terry Strom, a nephrologist with one of the nation's largest tissue typing labs, at Peter Bent Brigham Hospital. Strom reports that a four-antigen match, the ideal match that is hard to come by, gives a 95 percent survival the first year and an 85 percent survival the next, whereas a zero-antigen match does not give such a good survival rate. Terasaki also believes in the value of HL-A matching. He admits, however, that matching is far more critical for certain transplant patients than it is for others.

However, HL-A matching does not seem to be that valuable in cadaver organ transplantation. Shumway and his team have found no firm correlation between HL-A matching and rejection history. "We match by tissue typing, but I'm not sure it's that important," admits Marvin L. Gliedman, of Montefiore Hospital in New York City, and a pioneer in pancreas transplants. "There is no good correlation between HL-A matches and liver transplant success," declares Thomas Starzl of the Colorado General Hospital in Denver. Starzl was the first surgeon to do a liver transplant.

HL-A matching, in other words, has not proven to be a panacea for organ transplantation. One reason may be that other antigens besides the HL-A's are crucial for organ acceptance. "This is a central point in human genetics at the moment," declares Bernard Amos, an immunogeneticist with Duke University Medical School.

There is evidence, for instance, that so-called mixed lymphocyte culture (MLC) antigens may be important. These antigens are coded by genes that are closely linked to those that code for the HL-A's. Some European investigators have reported greater success from HL-A matching in cadaver transplants than have American investigators. The reason, Strom suggests, may be that HL-A antigens and MLC antigens are usually inherited as a package in homogenous European populations, but the package has become rearranged in the more heterogenous American population unless individuals are closely related. In other words, if an unrelated donor and recipient are well matched for HL-A's in Europe, they're probably also well matched for MLC antigens. But if an unrelated donor and recipient are well matched for HL-A's in the United States, they may very well not be matched for MLC antigens.

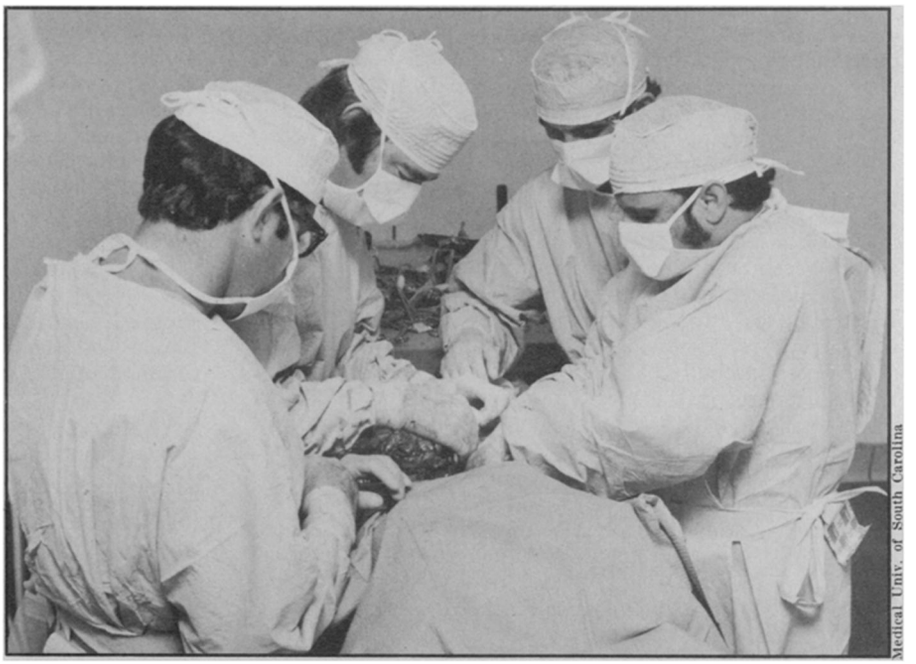
Still another set of antigens, the HDR, may play a role in transplant rejection, Amos and E. J. Yunis, an immunogeneticist with the University of Minnesota Hospitals, believe. These antigens are probably inherited in homogenous populations as a package along with the HL-A's and MLC's; they are coded by genes that are closely linked with the HL-A and MLC genes. And the HDR antigens, like the MLC antigens, may be redistributed in heterogenous populations.

So with immunosuppressant drugs and HL-A matching bringing less than satisfactory results, transplant surgeons and their co-workers are trying to come up with a better means of countering organ transplant rejection. One of their major thrusts is trying to come to grips with the rejection phenomenon.

"We don't know exactly how the destructive action takes place," Monaco admits. Hufnagel concurs: "We don't understand rejection entirely." However, microscopic sections of rejected tissues and other studies suggest that rejection works in the following way:

Antigens from cells in a transplanted organ—say the HL-A's or MLC's—are brought by the bloodstream to the lymph nodes of the transplanted patient. There, the patient's T lymphocytes, the major component of cellular immunity, become sensitized by any of the antigens that are foreign to the patient's body. The T cells are then swept by the bloodstream to the transplanted organ, where they attack cells in the organ that contain the foreign antigens. Once the T lymphocytes launch their attack, blood platelets and inflammatory cells rush to the site of invasion, clogging the blood vessels of the transplanted organ and leading to its death.

Antibodies also participate in organ rejection. Intriguingly, however, some antibodies, or at least parts of antibodies, try to protect the transplanted organ rather than reject it. Hufnagel and immunologist Anthony Chung are attempting to exploit this blocking role of antibodies in order to prevent organ rejection.



Sharbaugh and his colleagues try to resolve the rejection problem in sheep.

The concept, which they are now testing on dogs, is this: The individual to receive an organ is immunized with lymphocytes from the organ donor. Antibodies that the individual makes against the lymphocytes are then broken down into the parts of antibodies that are required for complement fixation, and the parts that are not. The parts required for complement fixation are presumably those parts that assist in organ rejection. The other parts are presumably those that enhance organ acceptance. These latter parts are bubbled through the organ to be transplanted. A coat of this enhancing antibody material should help protect the

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organ from being rejected once it is transplanted. The organ recipient will also be injected with the enhancing antibody material to further increase the chances of organ acceptance.

Hufnagel and Chung are also working on ways to solve cross-species rejection between organ and recipient in hopes that animal organs might eventually be used for human transplants. "Of the various approaches we are taking to the rejection problem," Hufnagel says, "this one has the greatest potential. But it is also the most difficult."

Monaco is taking a different tack in trying to solve the rejection problem —injecting bone marrow from the organ donor into the patient to receive the organ. His rationale is that bone marrow, which is rich in HL-A antigens, should stimulate blocking antibody action in the prospective organ receipient. Thus, when the patient receives the organ, his enhancing antibodies will already be primed to help protect the foreign organ. Monaco has obtained encouraging results with this approach in mice and dogs. He is now ready to try it with patients.

Monaco also looks forward to the day where enough HL-A antigens have been purified that they can be taken from an organ donor and injected into the prospective organ recipient. The would-be recipient would then make blocking antibodies against the antigens. The blocking antibodies would help protect the foreign organ upon implantation.

Robert J. Sharbaugh and his immunology colleagues at the Medical University of South Carolina in Charleston are trying to solve the rejection problem by working with large animals. They are looking for the transplantation antigens in sheep that correspond to the HL-A's in people. They will then coat a column with these antigens, insert a tube into the sheep's thoracic duct and circulate the sheep's lymph through the column in hopes that any lymphocytes in the lymph that have a predilection for transplantation antigens will stick to the antigens on the column. Once the sheep's body is cleared of lymphocytes that attack transplantation antigens, the sheep should be ready for an organ transplant, presumably with no rejection problem.

"Our approach is promising," Sharbaugh asserts, "but it's tough because few investigators are using this approach. In other words, we have little or no past experience to call on."

Still other investigators, such as Stanley G. Nathenson of the Albert Einstein College of Medicine in New York City, believe that a better understanding of the chemistry of transplant antigens should lead to ways of preventing organ rejection. Certainly progress is being made toward this end. But so far evidence is more provocative than gratifying. For instance, HL-A antigens are now known to share certain chemical sequences with antibodies and to be coded by genes that lie near genes that code for various immunological activities. Such evidence suggests that transplantation antigens may have some yet unidentified immunological function. This would be bizarre since they themselves provoke immunological reactions.

Certainly the problems of organ transplantation are many, and finding solutions to these problems is time-consuming and costly. But the clinicians and investigators who are dedicating their lives to furthering transplantation are convinced that the answers will come. "We haven't scratched the potential of transplants yet," declares Amos.

Meanwhile, they have the satisfaction of knowing that they are extending the lives of thousands of patients for a few precious months, or even years. A prime example of a patient who is profiting from transplant teams' efforts is Richard Cope of Patchogue, N.Y. Four years ago Cope received a new heart from Shumway and his team. Cope is alive today, working as an engineer for the Grumann Aerospace Corp., swimming in a pool he built himself and enjoying a full sex life. The latter he attributes "to having a 17-year-old heart with 49 years of experience." □

. . . Gravity

the electromagnetic and gravitational forces it comes down to a very important dilemma: Either you make Newton's universal gravitational constant a variable and admit that the strength of gravity may vary with time or you make the amount of electric charge carried by the electron (and every other charged elementary particle) be a variable.

In spite of—or maybe because of—the havoc that it would wreak in electrodynamic theory, the late George Gamow suggested that we should make the electron charge vary. He was promptly shot down by observers, who pointed out that if the electron charge had been different in past aeons, the spectrum of the light we receive from distant bodies (which was emitted millions and billions of years ago) should be different from the spectrum we receive from nearby bodies. It isn't.

Dirac's choice is to make gravity vary. This is something that the usual big-bang theory will not admit, nor will it admit some of Dirac's other conclusions such as continual creation of new matter. And this makes Alpher want to answer.

The answer depends on the critical time you choose. Is there a critical time that is important enough to merit trial in the context and that will make constants constant again? Alpher suggests what big-bang cosmologists call the crossover time. In the beginning, they say, the universe was dominated by radiation, that is, photons and neutrinos. In this the Biblical intuition was exactly correct: Light came first; all else followed. Gradually radiation begat matter, and eventually matter came to dominate. The time when the universe switched from a majority of radiation to a majority of matter is the crossover time. It happened once and for all. Its value—about 1 million years after the big bang—is constant so it will render the constants constant again.

Does it merit inclusion in the august company of the big numbers? Alpher thinks yes. It is a moment very significant in the history of the universe. A lot of interesting thermodynamics and fluid dynamics went on then, and those are both fundamental parts of physics. It may also be the time the galaxies started to form.

Another suggestion, not original with Alpher, depends on a belief in an oscillating universe. Granting that, there will be a time when the universe reaches its maximum extension and starts to collapse back. That number is also a constant and might also fix things up. At this point Alpher does not present a detailed cosmology or field theory based on either of these suggestions, but that too may come.

Meanwhile the question of changing gravity is becoming an observational one. Changing, specifically weakening, gravity is not unique with Dirac, but is contained in other recent cosmological theories. It was, however, rejected by Einstein, and the debate is decades old. Now a number of observers and experimenters are trying to settle it.

One of them, Thomas C. Van Flandern of the Naval Observatory, brings evidence he says shows a weakening, and his latest figures tend to favor Dirac more than the other current theories (SN: 8/24-31/74, p. 116). I. I. Shapiro of the Massachusetts Institute of Technology has been using radar astronomy to try to get a precise knowledge of the gravitational constant and its possible changes. His latest results would indicate a minute strengthening of gravity over time, but the error margin is bigger than the figure itself so the result is still very inconclusive. It may be some time before precise and generally accepted observational figures are available. Meanwhile the cosmic game of the big numbers continues. □