

IMMUNOGENETICS

By RAY OWEN

Through the immune system each individual knows its own molecules from alien forms: thus tolerance and thus rejection. What is the origin of this defense and how does it function?

Senator Walter Mondale of Minnesota, testifying before a Senate committee on a joint resolution for the establishment of a National Commission on Health, Science and Society on March 7, 1968, observed that "the scientific breakthroughs of the last few months, including the creation of an artificial viral core and the heart transplant operations, were current highlights in the dazzling half-century of truly unprecedented advance in the medical and biological sciences."

It is interesting that Senator Mondale's selection should have included two items from nearly opposite ends of the science-technology spectrum of modern biology—from the basic biochemistry of viral nucleic acids to the forefront of applied technology in human heart transplants—and that, in its way, Caltech has been importantly concerned with both of them. The reference to the "viral core" is, of course, the work in which R. L. Sinsheimer participated. We have been concerned with heart transplantation, in a much more indirect way, in immunogenetics. We have not transplanted any human hearts; in fact, about the closest we have come to that kind of surgery has been to exchange a great many skin grafts among mice. But we have worked for years in those fields of immunology and genetics related most closely to the advances that have made human organ transplantation a clinical reality (*E&S* — June 1959).

Transplantation research has been a very active and productive field during the past couple of decades, and a large number of workers, in many laboratories all over the world, have made important contributions to it. Rather than singling out our own contributions for parochial review, however, I will take this opportunity to outline, in a relatively non-

technical way, the current status of the organ transplantation field and some of its background.

As almost everyone knows nowadays (the knowledge is so common that it is difficult to recall how rare and inadequate it was just a few years ago), tissue or organ transplants between genetically different individuals are, under ordinary circumstances, unsuccessful. A graft from one brother to another, for example, at first "heals in" and appears to be doing all right. After only a few days there are signs of rejection; soon the graft dies.

The basis for rejection lies in the immunologic machinery of the recipient of the transplant—machinery that has been designed, through the long course of evolution, to recognize substances that are foreign to the organism and to respond by eliminating them. This machinery is of very considerable importance to us, because it leads to recovery from infectious disease and specific immunity to later attacks by the same disease. In clinical medicine it provides the basis for effective vaccination and, therefore, for the control of epidemic disease. But in the case of transplant rejection, as in some other kinds of immunologic malfunction such as allergies and autoimmune disease, the machinery operates to our disadvantage. It recognizes that a transplanted organ is foreign and destroys it.

The central problem of successful organ transplantation, therefore, is to understand enough about the machinery of immunity to devise ways of evading or controlling the immune response. As a significant side benefit, such an advance might well pay off also in the control of other unfortunate effects of immune systems. And the evasion or control of undesired immune responses should leave intact the desired responses, such as immunity to disease.

**HISTOCOMPATIBILITY
MATCHING**

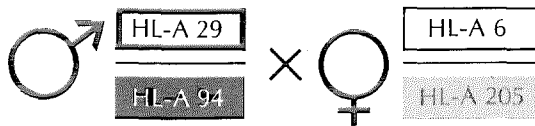
Given many different forms (alleles) of the main gene complex affecting graft compatibility (HL-A 1, 2, 3,N), and each allele individually rare, the two alleles present in a particular person (intended recipient) are likely to be different, e.g.:

$$\frac{\text{HL-A 17}}{\text{HL-A 126}}$$

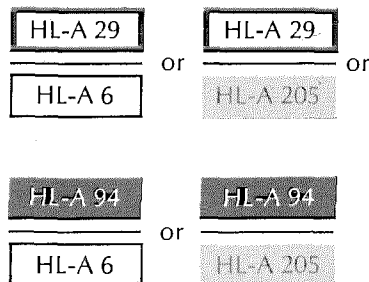
An unrelated prospective donor is very likely to be different from the intended recipient, e.g.:

$$\frac{\text{HL-A 3}}{\text{HL-A 241}}$$

But if two unrelated people marry, e.g.:



Each child receives one of the two alleles of the father, and one of the two alleles of the mother:



In contrast to the very low probability of a random match among unrelated people, therefore, pairs of children in the same family have about one chance in four of being perfect matches for this important characteristic, and three chances in four of being at least "half-matches," genetically.

In two very important ways the problems of evading or controlling immune responses to transplants lie as much in the field of genetics as they do in immunology. First, the basis of "foreignness" is genetic dissimilarity between graft and host. It is for this reason that grafts succeed between identical twins; being genetically alike, their relevant tissue and organ characteristics are identical. The inherited dissimilarities contributing to graft rejection, even among the members of a family, are in many respects very comparable to the blood-group differences that have been recognized for many years as important for blood transfusions or maternal-fetal compatibility. For the most part, however, they are not blood-group differences but a different set of individuality characteristics.

Until recently, practically all of our substantial information about the genetic similarities and differences involved in graft acceptance or rejection dealt with the mouse, because the mouse, in contrast to man, could be studied efficiently in the genetics laboratory. It became evident that many different genes are concerned with the kinds of individuality involved in graft rejection and that many different forms of some of these genes are present in laboratory mouse populations. Some of these genes could be identified with particular regions of particular mouse chromosomes. It also became evident that not all of these genes are of equal value for graft acceptance or rejection. In fact, only one complex of them, in the ninth linkage group of the mouse, provides for such strong tissue transplant barriers that differences between graft and recipient for them are very difficult to control.

We now know that the same facts hold for man; only one "major" tissue-compatibility gene complex has been found on one of the human chromosomes, though many "minor" genes are involved. Similarities or differences for the major complex of genes can be evaluated by tests of white blood cells in the laboratory. So great is human diversity for this complex of genes, however, that it is exceedingly rare to find two unrelated individuals who are alike for them. Within a family, the situation is different. Given an individual of any type, there is about one chance in four that his sister or brother will be just like him for this important gene complex (see chart left). This is undoubtedly the main reason why transplants of kidneys, for example, from living brothers or sisters have been more successful than have kidney transplants from

unrelated donors or cadavers. Of course, an important current hope in the field is that, through increased knowledge of the immunogenetics of the transplantation antigens, ways can be found of picking, from unrelated populations, relatively compatible donors so that cadaver sources of organs can be used more successfully. Adequate "matching" for transplantation, comparable to the system which has been so successful for blood transfusions, is currently the main hope of evading the destructive immune responses of graft rejection.

The other respect in which genetic approaches are basic to the transplant problem deals with the immune response itself. The main practical aim of these approaches is to control, rather than to evade, the response. Only within the past decade has it become generally recognized that the immune reactions are tailored by the genetic potentialities of the cell. The synthesis of a specific antibody, and the appearance of the immunocompetent cells that engage in graft destruction, are very probably dependent on the information available in the nuclei of the relevant cells, just as many other aspects of cellular differentiation and function depend ultimately on the cell's DNA. True understanding of the immunologic machinery, upon which reasoned efforts to control it must ultimately be based, is therefore in very large part a problem in developmental and molecular genetics.

Although a great many facts have been collected, we are still far short of the requisite understanding. Meanwhile, efforts to control graft rejection have proceeded in relatively arbitrary and empirical ways. They began, I suppose, with our 1945 observation of an experiment of nature—the fact that nonidentical twin calves, while they are embryos, accept and permanently tolerate blood-cell-forming grafts from each other. These efforts continued through the middle 1950's, with development of x-ray treatment to inactivate immune responses, particularly for the establishment of bone marrow transplants that saved the lives of heavily irradiated experimental animals. At the same time, rapid developments in experimental surgery paved the way for human organ transplants.

In the present decade, emphasis has been mainly on the chemical suppression of immune responses through the use of drugs that suppress particular steps in the series of reactions from DNA to protein synthesis. Chemosuppression, sometimes combined with irradiation, is now routinely used to promote

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The methods currently available for chemosuppression have great disadvantages. The drugs themselves are damaging, and they inactivate immune response nonspecifically, leaving the treated individual vulnerable to infection. In the human heart transplants that have been done to date there is as yet no compelling evidence that it is graft rejection that has led to the death of so many recipients. On the contrary, some of the patients have died of the directly poisonous effects of the drugs that have had to be used. These people were already in extremely poor condition, because a heart transplant, which involves removing the heart from the recipient, would only be undertaken when a patient is already near death. Others have died of infections, often established in their bodies before treatment began, because these patients have had many complications from prolonged and serious heart disease. The immunosuppressive drugs cripple the patient's immune system severely and nonspecifically.

What is needed is a way of interfering much more specifically with graft rejection, with the particular combination of donor and recipient involved in any given transplant—but, at the same time, leaving the recipient's immunologic system intact for other kinds of bodily defense. Agents with this desirable effect may now be on the horizon, but none of them is as yet established for human medical practice. Progress is imminent, too, in tissue matching.

There is much to be learned in the interdisciplinary field of immunogenetics. It is a field in which challenges to basic understanding are most provocative and currently productive; it deals with a system that is in some respects a model for development and specific differentiation; it has important population as well as individual aspects; and it extends readily into a technology of undoubtable human significance. □