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Guest Editor
ELI A. FRIEDMAN
State University of New York
Downstate Medical Center
Brooklyn, N. Y.

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INTRODUCTORY SYMPOSIUM

The Flaws of Immunosuppression in Organ Transplantation Today

T. E. Starzl

MY CHARGE in opening this session is to define some of the major problems in organ transplantation today, an order for which there is not enough time. For example, it would be possible to spend 20 min talking about developments in tissue typing and organ preservation, and the practical interrelationships of those two areas of endeavor. The complicating role of presensitization states is another topic of enormous pragmatic concern.

I want, instead, to look mainly at a different problem, but the one that gives transplantation uniqueness and that is central to a myriad of secondary difficulties. I am referring, of course, to immunosuppression.

In the context of my instructions, there is no point to speak glowingly of what has been achieved in the development of clinically useful immunosuppression. That is the well-known basis of our still-young specialty. Instead, my obligation is to emphasize what has *not* been achieved. Broadly speaking, there are two defective areas.

DEFICIENCIES OF TRANSPLANTATION

First, the predictability of treatment is imperfect. A reasonably accurate prognosis can be offered only to recipients of perfectly matched sibling kidneys. But even here there is an occasional unexpected graft loss from rejection that cannot easily be explained despite intensive retrospective study. Using other relatives than perfectly matched sibling donors, the predictability of rejection control is substantially less. When cadaveric organs are transplanted, the situation becomes too much like a lottery. Some patients have uncontrolled rejection, others have no difficulty at all, and about half are intermediate between these extremes.

In the cadaveric situation, kidney survival at 1 year using any of the presently employed regimens is seemingly more or less fixed at about 50% to 70% in all the world's great transplantation centers. The exact success rate is influenced to some extent by the inclusion or exclusion of candidates who have a high risk because of advanced age, coincident disease, or other factors.

The second general defect is related to the first. At the present time, even patients who eventually achieve a perfect transplant result often must first pass through a postoperative period of significant morbidity. The requirement for intensive immunosuppression is greatest early after transplantation. Because the steroids are the only highly dose-maneuverable component of the immunosuppressive regimens presently employed, the intensification of therapy translates inevitably into larger quantities of prednisone. If high-dose steroid therapy can be avoided or kept to a brief duration while at the same time maintaining good homograft function, the result is apt to be spectacularly successful. If steroids are needed chronically, their well-known side effects depreciate the value of post-transplantation life or may threaten survival itself.

From the Department of Surgery, University of Colorado Medical Center, and the Denver Veterans Administration Hospital, Denver, Colo.

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THE INGREDIENTS OF SUCCESS

In successful cases, a characteristic train of events is usually observed. To start with, if acute rejection occurs, it is readily and completely controlled with vigorous steroid treatment. Thereafter, prompt reduction of prednisone therapy is possible without graft deterioration. The fact that the required immunosuppression often eventually becomes lower than that which failed to control rejection at the outset has led many to conclude that a dynamic process of graft "acceptance" often transpires. The necessary combination of factors is apparently the continuously present antigen of the graft plus immunosuppression. The two main, although not mutually exclusive, mechanisms of graft acceptance have been envisioned as tolerance induction by depletion of specific lines of selectively susceptible lymphoid cells leading to tolerance or enhancement by antigraft antibodies.[1] The Seattle transplantation group headed by Marchioro, using the techniques developed by the Hellströms, has demonstrated changing host–graft relationships in kidney recipients that are consistent with the multifactorial graft-acceptance hypothesis.[2]

Let me restate the two clinically important propositions I have already mentioned. First, the present-day transplant recipient must face a kind of risk that is not precisely analyzable in advance. The transplantation itself is a ruthless test system that weeds out the biologically unsatisfactory recipient or at least the unsatisfactory donor–recipient combinations. Second, even in successful cases there is an interval of early postoperative peril, although this risk is not fixed since the donor–recipient immunologic relationship is subject to change during the first weeks or months of care.

Given these conditions, it is not surprising that all life-survival curves from 1962 to the present show the major patient and kidney losses in the first 3 to 12 postoperative months. In our own first 64 consecutive cases collected between the autumn of 1962 and March 1964, only 37 kidney recipients were left at the end of 1 year. After 3, 5, and 10 years, 32, 31, and 26 of these patients were still well and in almost all instances with good renal function. There are still 26 survivors, now after $10\frac{1}{2}$ to 12 years, who represent about half of the world's renal transplant recipients living after transplantation in the era before the spring of 1964.[3] The results in these early trials were incomparably better with related than with unrelated transplantations.

Through succeeding years patient survival has been significantly improved, especially in unrelated (now always cadaveric) cases. These improvements undoubtedly have derived in part from more clever manipulation of the original drug combination of azathioprine and prednisone, which together made possible what has been termed the modern era of transplantation. Nevertheless, the pattern of early losses is identifiable, though less extreme.

Increased survival has been seen in some centers such as ours, at about the same time as the introduction of heterologous antilymphocyte globulin as the third component of what has become known as triple-drug therapy. Although ALG is a potent immunosuppressive agent in man, its role in clinical transplantation, and even whether it adds significantly to kidney or patient survival after renal transplantation, is still unresolved. It has become clear as the years have passed that the only indispensable constituent of any drug combination used in the last dozen years is the steroid one. Even azathioprine, formerly considered the cornerstone of therapy, can be replaced with cyclophosphamide. But nothing has been found to replace steroids. Without steroids, the field of transplantation as it is presently practiced would disappear tomorrow.

THE PROSPECTS OF IMPROVEMENT

The drug combinations that include azathioprine, prednisone, cyclophosphamide, and ALG have evolved into the well-

known double- or triple-drug cocktails that have been used the world over. All are variations on the same theme of daily conservative therapy beginning with operation, with subsequent responses with steroids if there is rejection. Although much has been thereby accomplished, I do not believe further small adjustments in dosage and schedule are going to correct the deficiencies of transplantation that I mentioned at the outset. Some drastic changes in approach are going to be needed. I conceive the objective to be a very great foreshortening of the graft acceptance process, so that the transplant passes through this danger period in a few days instead of a few weeks or months.

How can this be accomplished? The first step is to acknowledge that our present methods of treatment represent only a halfway station toward acceptable clinical standards. In our field, there is a surprising resistance by clinicians to change. In turn, the proportion of clinical transplanters who retain a lively interest in laboratory experimentation has declined. Finally, the standard approaches to immunosuppression I outlined a few moments ago have become so well accepted that deviations from them are going to be submitted to close scrutiny in the increasingly rigid administrative matrix in which we practice.

Be that as it may, and admitting now to personal prejudice, I am looking forward to some practical clinical applications of the kind of work with tolerance induction that Monaco and his associates have reported in rodents, dogs, and at least 1 human. Under immunosuppression they have administered intravenous bone-marrow cells in close temporal relationship to the transplantation of kidneys.[4] In dogs, the renal grafts survived many times longer than with conventional therapy. Similar or related work has been carried out by Rapaport,[5] Lance and Medawar,[6] Brent,[7] and Iwasaki,[8] to give a very incomplete list. It is interesting that Kelly of the University of Minnesota attempted the contemporaneous transplantation of lymphoid cells plus kidney homografts more than a decade ago. Their clinical trial was abandoned when, in some cases, the magnitude of kidney rejection seemed to be made worse.[9]

The other approach is the use of passive or active enhancement. Many laboratory groups are working to exploit the immunosuppressive properties of antigraft antibodies.[10] Four years ago at The Hague, Batchelor told us of the first clinical use of enhancement. Of necessarily great concern here also is the possibility that therapy could injure the transplant by the direct action of the antibodies.

These efforts at tolerance induction and enhancement are obviously designed to mimic and accelerate the mechanisms by which it has been speculated that grafts are accepted under present-day therapy. The same drugs should make this possible (azathioprine, cyclophosphamide, ALG, and steroids), but I think these agents 10 years from now will be used in a very different way. I envision high-dose pulse therapy with long intervening treatment-free intervals and thus liberation of the patient from much of the chronic morbidity inherent in our present approach.

With renal transplantation, a high order of patient service can be provided today despite the limitations of immunosuppression so well known to all of us. The reason is that it is so easy to return patients to chronic dialysis if too much immunosuppression is required to retain homograft function. The same is not true for the liver, heart, and lung, for which artificial organ backup is not available. Using these organs, transplant and patient survival are nearly synonymous.

EXTRARENAL ORGANS

With the heart, the transplantation itself has no troublesome technical problems, and in Shumway's magnificent series the life-survival curve reflects very accurately the ability to control cardiac rejection. The 1-year survival has edged up to about 50%

in the Stanford series. Substantial further improvement will await the kind of advances in immunosuppression that I hope will be forthcoming.

It is probable that the liver is immunologically "easier" than either the kidney or heart, but the technical problems are far from solved. In our own experience we believe that the leading causes of death are technical misadventures. At the David Hume Memorial Symposium a few months ago, we showed that about a third of all the deaths after our liver transplantations were due in one way or another to troubles with bile duct reconstruction. Septic problems secondary to biliary duct complications proved particularly lethal. Early diagnosis of defective biliary drainage by transhepatic cholangiography with or without biopsy is the only way I know to make the necessary differential diagnosis in the patient who becomes jaundiced after liver transplantation. If intrahepatic ducts are dilated, prompt reoperation must be done.

With both the liver and lung, it is unlikely that a clear distinction between technical, infectious, and rejection problems will be possible until a much more reliable method is available for the promotion of graft acceptance. Then if something goes wrong it can be assumed that rejection is *not* the cause. Today the obverse assumption must always be made that rejection *is* responsible.

SUMMARY

In closing, no one denies that renal transplantation is a practical venture. Still, few would dare to assert that it is perfected. Using present regimens of immunosuppression, further exploitation of transplantation of extrarenal organs is not going to be possible without better treatment. With all organs there is a great need to look forward and not back, to emphasize to our basic science colleagues how dissatisfied we are, to not accept our present standards of care so rigidly that departures will be considered heretical by peer review groups, and to return to the laboratories ourselves if only to empirically test therapeutic regimens and modifications that are quite different than those now current.

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