EDITORIAL

Transplantation: The Realization of a Dream

Thomas E. Starzl

WHEN President John F. Kennedy was inaugurated on a frigid afternoon in January 1961, whole organ transplantation was a fantasy for the ignorant and an impossibility for the informed. In the New England Journal of Medicine (January 5, 1961), the Nobel Laureate, McFarland Burnet, had written: "Much thought has been given to ways by which tissues or organs not genetically and antigenically identical with the patient might be made to survive and function in the alien environment. On the whole, the present outlook is highly unfavorable to success. . . ."[1]

On the day Kennedy died, November 22, 1963, I was in an experimental laboratory at the Denver Veterans Administration Hospital carrying out an orthotopic liver transplantation in a dog. In the 34 months of Kennedy's tenure, the feasibility of transplanting kidneys from other than twin donors had been established, and the prospects of extending this new technology to extrarenal organs including the liver and heart was explored. What had happened to raise these expectations? The reasons were straightforward. Progress already had been made or was soon to be made in the three major areas upon which organ transplantation depends.

Most important was an explicit understanding of rejection and the possibility of controlling this process. The fact that rejection was an immunologic phenomenon was established by Medawar during the Second World War.[2] As a corollary, agents known to reduce immunologic responsiveness were predicted to mitigate rejection and this was proved to be the case with adrenal cortical steroids,[3] total body irradiation,[4,5] and 6-mercaptopurine[6-9] or its analogue, azathioprine.[10] However, the effects were relatively minor and of no practical consequence as yet for clinical application.[11]

In 1962 and 1963, combinations of these modalities were put together in therapeutic cocktails that allowed successful renal transplantation from other than twin relatives or even using nonrelated donors.[12-15] Furthermore, a state of host-graft nonreactivity was often achieved in such cases which allowed the eventual reduction of chronic immunosuppressive therapy.[12] When this occurred, rehabilitation and return to a full life was achieved in kidney recipients on more than rare occasions.[16] The gold standard for many years was azathioprine-steroid therapy,[12,16] to which heterologous antilymphocyte globulin (ALG) could be added.[17]

However, good results with renal transplantation could be obtained predictably only with transplantation between consanguineous donors and recipients. In 1979 and 1980, this picture which had remained unaltered for more than 15 years was changed drastically with descriptions by Borel et al[18] of cyclosporine and the first clinical trials of this drug, used alone[19] or in combination with corticosteroids[20] and eventually other agents. Even without cyclosporine, attempts had been made and sometimes successfully to transplant extrarenal organs including the liver,[21-23] heart,[24,25] lung,[26] and pancreas,[27] but these were highly experimental and dangerous undertakings. With pharmacologic cocktails that contained cyclosporine, the picture changed. The majority of all kinds of cadaver organs could be expected to function chronically.

At a somewhat slower pace, there were collateral developments in organ preservation that allowed an extension of graft viability for long enough to permit movement of organs from city to city and the establishment of organ sharing networks. The techniques used involved two principles. One was organ cooling with special infusates whose constituents were cytoprotective. Recent developments have allowed the reliable preservation of human livers for more than a day with simple refrigeration[28,29] and there is ample

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reason to think that the same or slightly modified techniques will allow improved "slush" preservation of all of the organs. The alternative was continuous perfusion with blood or with a fluid that did not contain a blood component.

Tissue matching is the third component of transplantation biology. Matching of antigens of the human histocompatibility complex located on chromosome 6 has proved to be impractical for cadaveric transplantation, largely because of the enormous complexity of the system. At a practical level, the most important application of tissue typing has been the "crossmatch" which attempts to identify with serologic techniques the presence of preformed antidonor antibodies in the recipient and to thereby avoid transplantation under such adverse circumstances. If present, such antibodies can cause an immediate or at least greatly accelerated rejection of kidney, liver, and heart grafts by a process known as hyperacute rejection.[30-32]

Developments in all three of the foregoing areas are not complete. The acquisition and application of further knowledge is certain to improve transplantation but by smaller increments. However, even now, what can be achieved is so substantial that transplantation has changed the basic philosophy of treatment of diseases of vital organ systems. Until recently, what could be done for diseases of specific vital organs was limited to dietary or drug management designed to extract the last moment of function from a failing kidney, liver, heart, or lung. Along the way, surgical procedures were sometimes used which ultimately were ineffective and worse, often illogically conceived and actually harmful.

When organ transplantation became a reality even in a limited sense, all of this was changed. Therapy including operations which jeopardized ultimate candidacy for organ replacement were reexamined. Surgical operations have been supplanted in many specific instances by the so-called interventional procedures carried out by radiologists and internists. In hepatology centers, patients with end stage liver disease and bleeding esophogeal varices now have sclerotherapy performed in preference to portal-systemic shunts, and those with intrahepatic bile duct strictures often undergo transhepatic procedures by radiologists instead of open operations which ruin the portal hilum for later dissection. About 20 years ago, the specialty of nephrology underwent a similar revolution, and the same readjustment is now occurring in cardiology within the limits imposed by the organ supply.

Fall-out dividends from transplantation have included a better understanding of the function and pathophysiology of different tissues and organs. Keener insight about the development of tumors and their potential regression under immune modulation has been made possible. However, the implications of transplantation have not been a matter solely for scientific and medical conferences. Adjustments have been made in the law to accommodate public need. Cottage industries concerned with transplantation have sprung up in ethics and in related philosophic fields. Discussions have covered such diverse subjects as new legislation, considerations of cost-effectiveness, and the appropriate allocation of both material and intellectual resources of these endeavors.

Radiologists have played a significant role at every step as the modern era of transplantation has developed. At the outset of this editorial, it was mentioned that one of the first forms of immunosuppression was with irradiation, and this therapeutic possibility has been kept alive by research with total lymphoid irradiation plus drug therapy and antigenic challenge for tolerance induction.[33,34]

Diagnostic radiology has played such an important role that transplantation has become the most "radiology-intense" of all specialties.[35-37] The function and anatomic integrity of transplanted organs has been studied with the rapidly evolving radiologic techniques of the last quarter century, including radionuclide scanning, the diagnostic and therapeutic procedures of interventional radiology, and particularly in the last 10 years with the mass utilization of the imaging techniques.

The suggestion that transplantation is the fulfillment of a dream imputes certain miraculous qualities to what has transpired. To see a patient who had been reduced by disease to a pitiful state, now restored to vibrant good health by transplantation of a kidney, liver, or heart does seem like a miracle. But, the way in which this happened can be explained easily by large and small developments in different disciplines, and

the deliberate application of these often unrelated advances into a coherent treatment plan. Radiologists have made their own contribution to this story and will continue to do so in the years ahead.

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