TRANSPLANTATION TODAY

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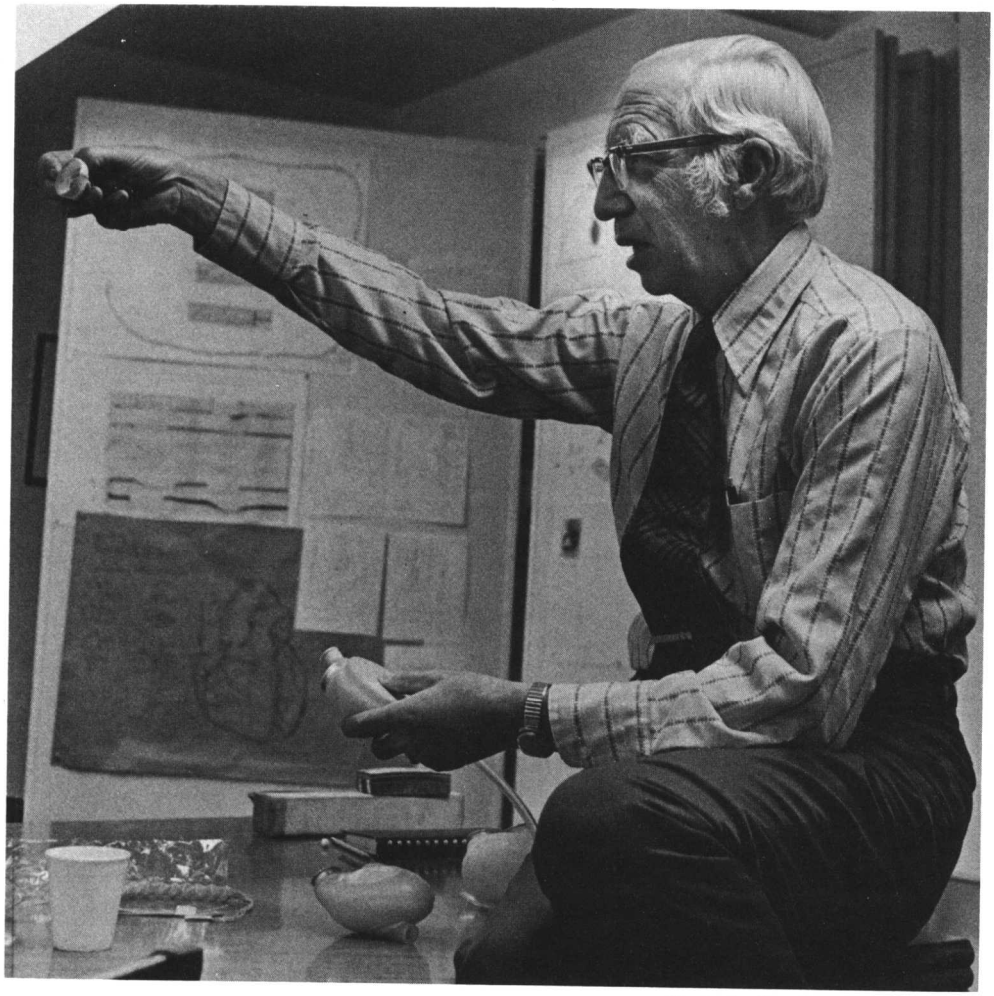

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WILLEM KOLFF

Dedication

Rupert E. Billingham

President of the Transplantation Society

IT gives me great pleasure to announce that the Council of the Society has resolved that the Proceedings of this Sixth Congress shall be dedicated to Dr. Willem Kolff in recognition of his outstanding contributions to transplantation. Forerunner of a number of distinguished Dutch "transplanters," Dr. Kolff was born in Leiden in 1911 and earned his M.D. degree from that University in 1938. He then moved to the University of Groningen to specialize in internal medicine. There, he established the first Blood Bank on the continent of Europe, and the experience gained in handling blood was destined to prove of enormous help in his future activities. As a consequence of having as one of his first patients a young man slowly dying of renal failure, Dr. Kolff became convinced that if means could be devised to remove 20 g of urea and other retention products per day from the plasma of such patients, their nausea and other symptoms would disappear and life might be prolonged. Familiar with the very limited literature on experimental hemodialysis, which dated back to 1914, aware of the dialysis membrane properties of thin cellulose tubing (as used to provide skins for sausages) and of the anticoagulant properties of heparin, he undertook experiments of his own on hemodialysis. In 1940, at an early stage of this work, came the German invasion of the Netherlands, and, closely in its wake, the imposition of a Nazi as Chief of Medicine at Groningen. Unable to accept this, Dr. Kolff left and became the head of the Department of Medicine at a hospital in the small city of Kampen on the Zuider Zee, an unlikely environment and unfavorable time for clinical investigation. Here, however, with various colleagues, he began to study the treatment of uremia and, with the clandestine help of the local Berk Enamel Works, made his first artificial kidney. Of the early patients treated, nearly all died, but fortunately not before some of them had manifested encouraging signs of clinical improvement. Ironically, the first patient whose recovery could definitely be attributed to the artificial kidney was a National Socialist.

Immediately after the war, which had virtually precluded scientific exchange, when he learned that no one else had developed an artificial kidney, Kolff, with enormous generosity, gave some of his early models to centers in Europe and North America. This enabled other investigators to study and perfect further the important device which he had developed from a biological concept to a clinically applicable engineering reality.

In 1949, Dr. Kolff and his associates, stimulated by their observation that blood changed color from blue to red and was automatically oxygenated through the dialysis membrane of the artificial kidney, began to focus their attention on heart–lung machines with which they subsequently succeeded in maintaining a dog's circulation. In 1950, he emigrated to the United States and continued his work on an expanded basis at the Cleveland Clinic. Here, Kolff converted the so-called coil artificial kidney into a membrane oxygenator which was used clinically. He also became very actively involved in the early phases of open heart surgery at Cleveland. Happily, he never lost his interest in the living (natural) kidney. In 1963, with others,

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he established the capacity of cadaver kidneys to resume function, even after relatively long latent intervals of shut-down due to tubular necrosis, in their new hosts when the latter had been maintained on artificial kidneys.

He also applied himself to the development of cardiac-assist devices, and in 1961, together with Moulopolos, a cardiologist, and Topaz, a mechanical engineer, he devised the so-called aortic balloon pump. His writings display justifiable impatience that 7 years had to pass before Kantrowitz pioneered the clinical application of this important and now widely used life-saving innovation.

Kolff's lab was the first to work on total replacement of the heart with a prosthesis, and this venture has now succeeded to the point where a few sheep and calves have been maintained by artificial hearts for up to 120 days. Dr. Kolff sees this as an indication that the total artificial heart, probably powered by an atomic device now under development, may be nearer at hand than many of us are willing to believe. Some of his views about the artificial heart are worth quoting: "We believe that the future of the artificial heart is bright" ... "Remarkable progress has been made in the past few years with the artificial heart. The last few problems are likely to be solved" and finally, "... it is quite conceivable to expect good rehabilitation for at least a year in a patient doomed to die."

Recently, he has voiced his concern about the threat of politicians interfering with the attainment of this meritorious goal in his characteristic candid manner. "The new device legislation under consideration by the Congress of the United States may make it necessary for investigators in the United States and for manufacturers to displace their activities to the European Continent."

Since 1967, Dr. Kolff has been working at the University of Utah at Salt Lake City where he is currently Professor of Surgery and Head of the Division of Artificial Organs, as well as Research Professor of Engineering and Director of the University's Institute for Bioengineering. In the latter position, he has displayed an outstanding capacity to inspire and motivate highly competent individuals from different disciplines to work together enthusiastically as a team towards the realization of the bold objectives generated by his fertile, far-seeing mind.

Time precludes my reviewing the broad and exciting spectrum of activities proceeding under his direction, which include an artificial eye program for which a microcircuitry lab was developed, and development of means of conveying signals from the brain to activate paralyzed limbs or induce motion in prosthetic limbs.

In his own words, "We will tackle any problem that can be solved with an artificial organ. The driving force has always been the desire to treat patients and usually to treat an otherwise hopeless patient, particularly if this can be done with some kind of mechanical or electrical device."

I wonder how an inventor of artificial organs really considers man. Would he feel any empathy with Isak Dineson's (1885–1962) comment, "What is man, when you come to think upon him, but a minutely set, ingenious machine for turning with infinite artfulness, the red wine of Shiraz into urine."

Very appropriately, this great pioneer of the artificial organ transplant, this *Divus vir et faber renum,* has won widespread recognition for his contributions. This includes honory doctorates, distinguished awards, prizes from Universities and learned Societies throughout the world, and appointment as Commander of the Order of Orange-Nassau from her Majesty Queen Juliana of the Netherlands.

INTRODUCTION

Contributions of Transplantation to Modern Biology and Medicine

Rupert E. Billingham

THE opening of this Sixth Congress marks the tenth anniversary of our Society, which was founded at the close of the seventh and last of an important series of biennial International Transplantation Conferences sponsored by the New York Academy of Sciences. The formidable collection of published proceedings of these past meetings, spanning a 22-year period, documents the tremendous growth, development, and differentiation of both the basic and the clinical aspects of transplantation. The purpose of this contribution is to identify some of its major accomplishments during this exciting period and also to indicate the variety of research done on grafts and the extent to which it has spread into other fields of research.

Only 22 papers were presented at the first conference in 1954. They were principally concerned with the relation of immunology to tissue homotransplantation and mobilized cogent evidence that rejection of various types of allografts, including kidneys in dogs and corneas in rabbits, is the outcome of acquired immunity. Peter Gorer[1] presented evidence of the antibody response—hemagglutinins and leukoagglutinins—of mice to skin allografts, which he felt was directed against the H-2 antigens. Prophetically, he remarked that, "... if homografts are to be used in clinical practice ... it will be desirable to type people in order to prolong the life of the graft, even if some clinically useful means of modifying the response is found." Medawar[2] spoke on acquired tolerance of skin homografts, a phenomenon which Simonsen felt "seemed to represent the future of transplantation biology." Nathan Kaliss[3] described the induction of an alteration of the normal tumor allograft/host relationship in mice that involved "conditioning" the host by prior treatment with donor material. In his opinion, the same biologic principle was involved as in tolerance. Evidence of the capacity of cortisone to overcome host resistance to tumor heterografts was also presented.[4]

Thus, at this time, coupled with establishment of the apparent universality of the rejection of living-tissue allografts and its immunologic basis, and despite ignorance of the effectors involved, there was compelling evidence of the feasibility of thwarting the host response in experimental animals—ample incentives and challenges to attract others to the field.

MATCHING AND TYPING PROCEDURES

Analyses of the early and quite remarkable results of clinical renal transplantation, obtained with the aid of the newly introduced immunosuppressive drugs in the early 1960s, indicated the urgent need for means of donor selection to obtain a greater degree of uniformity. In response, a number of ingenious in vivo matching procedures were devised which, though impracticable for large-scale clinical application, certainly established the feasibility of donor selection.[5] Some of these procedures, such as the normal lymphocyte transfer test and the

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irradiated hamster test, also fulfilled important experimental roles as means of studying allograft reactivity at the cellular level. In 1964, the addition of the mixed leukocyte culture reaction[6] to the histocompatibility tester's armamentarium played a role in enabling better results to be obtained with live related donor grafts. Subsequently, this procedure has played a major role in the recognition of one important system of antigens associated with the major histocompatibility complex (MHC) as well as furnishing an in vitro model of the initial recognitive phase of transplantation immunity closely paralleling the development of a local graft-versus-host (GVH) reaction.

Serologic studies on leukocyte antigens, based upon agglutination procedures, had been initiated by Dausset in the early 1950s. However, it was the application to man of variants of the more sensitive and reproducible lymphocytotoxic procedure, which Gorer and O'Gorman[7] had previously developed in mice, that enabled a full-scale study to be launched on leukocyte antigens for typing purposes. The recognition, in 1966, that compatibility with regard to ABO blood group antigens is important in the case of skin and renal allografts was another important step.[8] It also initiated a link between blood transfusers and transplanters. An invaluable contribution to the astounding progress made in tissue typing has been the cooperation between the various groups of investigators in exchanging reagents and the holding of Histocompatibility Workshops. Indeed, cooperation among individuals at all levels of organization has been an important contributory factor to progress in all facets of transplantation.

Tissue typers have established that in man, as in other species studied, the major transplantation antigens are coded for by a major histocompatibility complex (MHC), usually inherited as a single unit, though divisible genetically into a number of subunits that specify determinants on cell surfaces.[9] It is a genetic system of awesome complexity and such is the rate of progress that it is exceedingly difficult for the noncognoscente to keep up with the changing concepts of the organization of the HLA locus and the designations of its many antigen components. Each Workshop Report seems to go out of date as rapidly as a New York telephone directory.

Tissue typing has proved to be a tremendous success in living related donor situations, but far less useful when applied to cadaver donors. However, knowledge of the complexity of the HLA genetic region affords a satisfactory explanation for the great disparity in the effectiveness of typing in these two different categories of donor/host relationship.

The development of tissue typing is, of course, intimately related to the biologic and ultimately the chemical definition of alloimmunogenic specificities on cell surfaces. The study of transplantation antigens, genetically identified and labeled with great precision and actually visualizable on cell surfaces with the aid of the electron microscope, has probably been one of the most difficult facets of transplantation biology because it involves a combination of time-consuming assays and formidable difficulties of extraction and analysis. Progress has been slow, but has now taken us to the point where it appears that HLA molecules are glycoproteins organized in two-unit structures—the antigenic determinant-bearing heavy chain being linked non-convalently to a light chain identified as β_2 microglobulin.[10] Besides being integral components of cell membranes, HLA antigens are known to be present in serum and saliva.

The natural significance of the complex histocompatibility gene polymorphisms revealed by the unnatural act of grafting has long been one of the most fundamental and challenging questions in transplantation biology. In 1953, Medawar,[11] in his inimitable manner, expressed the situation very clearly:

> Although there are no factual grounds for supposing that antigenic diversity is anything but an unfortunate consequence of constitutional differences between individuals of a species, yet one is under some obligation to rack one's brains for evidence of any good it might conceivably do. Only thus can antigenic polymorphism be made genetically respectable.

Considerable progress has recently been made towards its resolution,[12] and its ramifications exceed the wildest imagination of the transplanters of 20 years ago who adopted a rather proprietary attitude to the genes that frustrated their therapeutic endeavors.

The MHC plays a central role in host responses to virtually all kinds of antigen, and alloantigens, in general, are concerned with a variety of cell-membrane functions, including surveillance, cell-to-cell recognition, etc. In 1971, Jerne[13] presented an ingenious theory of the somatic generation of immune recognition based upon histocompatibility antigens. Among other things, this afforded an explanation for the observed dominant genetic control of specific immune responsiveness by histocompatibility genes, and also for the apparent predominance of antigen-sensitive cells directed against allogeneic histocompatibility antigens. Jerne's theory was important in another sense: it helped focus the attention of immunologists in general upon histocompatibility genes. On the basis of evidence that, in certain viral diseases of mice, host T lymphocytes are apparently sensitized to altered "self" antigens (probably histocompatibility antigens), Doherty and Zinkernagel[14] have recently postulated that a central function of the MHC antigens may be to signal changes in "self" to recirculating T cells performing a surveillance role. These authors further argue that the extreme genetic polymorphism in the MHC of higher vertebrates may reflect evolutionary pressure exerted by this surveillance mechanism.

In the late 1960s, the demonstration of genetic linkage between the MHC in mice and their relative resistance to virus-induced leukemogenesis[15] stimulated a search for associations between antigens of the HLA complex and specific diseases in man. The subsequent discovery of immune response (Ir) genes and establishment of their linkage to the MHCs in several species provided further impetus for this search.[16] This has been exceedingly fruitful in terms of the number of striking associations that have been uncovered between HLA antigens and specific diseases.[17] In some instances, the associations established are so strong that HLA typing has become a diagnostic test and the intriguing possibility looms before us of being able to classify diseases on the basis of their having similar predisposing factors, such as the HLA-B27 disease group that includes ankylosing spondylitis, Reiter's disease, and psoriasis with arthritis. It is interesting to note that the First International Symposium on HLA and Disease was held last June.[18]

In mammalian reproduction, which of course entails natural transplantation and maintenance of the conceptus as a successful allograft, histocompatibility genes have also been shown to play a significant and unexpected role: incompatibility between conceptus and mother *favors* both its chances of implantation and, subsequently, its growth rate.[19] There is also suggestive evidence that in man the Y-linked antigen influences the sex ratio.[20] One thing is clear—if a world-wide moratorium were to be declared on clinical transplantation, studies on the MHC would probably continue at an unabated rate because of its implications for disease, immunology, population genetics, anthropology, reproduction, etc.

CONCERNING THE MODUS OPERANDI OF GRAFT REJECTION

Happily, an often heated argument that used to pervade our early meetings, whether

graft rejection is cell-mediated or mediated by humoral antibodies, is almost forgotten. The dramatic antibody-mediated hyperacute rejection of a renal allograft is familiar to all!

The discovery of graft-versus-host reactivity in 1956 introduced a highly versatile tool for studying allograft reactivity at the cellular level. With its aid came the demonstration that normal individuals have a widely disseminated, continuously peregrinating and recirculating population of immunocompetent cells.

The long-postulated capacity of lymphocytes to kill target cells was finally confirmed on the basis of the in vitro work of Govaerts and of Rosenau and Moon in 1960, which gave us the phenomenon of cell-mediated lympholysis (CML).[21] With the aid of CML and the mixed lymphocyte culture reaction (MLC) discovered later, great strides have been made in unraveling the entire sequence of events that leads to graft rejection, which had hitherto only been crudely defined by in vivo cell transfer systems. These in vitro techniques have also afforded sensitive assay systems with which to study means of interfering with both the development and the fulfillment of allograft reactivity. Indeed, many transplanters, including students of GVH reactivity, like many virologists, appear to have forsaken the animal in favor of the Falcon flask as the sustaining milieu for the cell systems in which they are interested.

Again, we find that progress in understanding graft rejection has entailed the revelation of complexity.[22,23] For example, *different* products of the MHC seem to be involved in the sensitization phase (as revealed by the MLC or GVH reaction) and in the effector phase (CML). In the former, at least two separate and identifiable subpopulations of T cells are involved, each of which is turned on by a particular type of determinant on the surface of the alien target cell. While direct cell–cell contact leading to cytotoxicity probably plays a subordinate part in allograft destruction in vivo, a significant component of the tissue destructive process appears to result from enlistment of pharmacologically active, but immunologically nonspecific, lymphokines and mediators. Another contender for a significant role in antiallograft cytotoxicity is the "armed" macrophage.[24]

The incisive distinction can no longer be drawn between antibody as one kind of effector of allograft reactivity on the one hand and of mononuclear cells on the other hand. This possibility was dismissed by the discovery of lymphocyte-dependent antibodies to MHC antigens.[24] These antibodies bind to target cells but, lacking the ability to fix complement, they are harmless. They can, however, activate a population of cytotoxic lymphocytes that bear a receptor for the Fc portion of IgG, and these cells can destroy the target cells.

TRANSPLANTATION AND IMMUNOREGULATION

The burgeoning interest in the artificial suppression or manipulation of immunologic responses and in the natural processes that control these responses owes much to transplanters's efforts to develop means of controlling host reactivity to allografts. The phenomena of immunologic tolerance and enhancement, shortly due for their 25th anniversaries, provided the encouraging beginnings and incentives. Despite the tremendous research efforts expended upon them, both phenomena are still in need of a complete explanation.[25,26] It has long been agreed that "tolerance" does not cover a single state of specific immunologic nonreactivity brought about by a single mechanism; rather, it designates a specific failure of the immune system to respond to antigen in one or more detectable ways, the emphasis being placed upon the lack of *functional* responses rather than upon lack of any response at all. Recent awareness that all immunologic responses result from complex interactions between definable subsets

of T and B lymphocytes and their products has helped us to understand how functional tolerance can be brought about in a variety of ways by selective actions of factors that include antigen/antibody complexes, anti-idiotypes, and suppressor or regulatory cells, now recognized as normal regulators of on-going immune responses.[27]

No survey of the contributions of transplantation to immunoregulation would be complete that failed to cite Kamrin's[28] demonstration in 1959 of a naturally occurring humoral factor in rat plasma, subsequently identified as alpha globulin, capable of prolonging the life of skin allografts in rats. Subsequently, the existence has been established of a number of natural immunosuppressive factors in serum and tissues (both normal and malignant) whose biologic significance is as yet unknown.[29]

In 1963 came the discovery, or more correctly the rediscovery, of ALG, the most powerful of all known biologic immunosuppressants so far as allograft and other cellular immunities are concerned in experimental animals.[30] Ability to erase immunologic memory and to halt ongoing GVH reactions are among its striking properties. Although first employed in human renal transplantation in 1966 and subject to some early euphoric reports, only now are the results of some large-scale, properly designed, clinical trials beginning to validate its effectiveness in man.

The ability of ALG to significantly prolong the survival of xenografts has done much to encourage interest in them. The striking reports by Reemtsma and others in the early 1960's that kidneys from chimpanzees and baboons sometimes survived and functioned in immunosuppressed patients for weeks and sometimes months were also important in this respect.[31]

SURGICAL ACHIEVEMENTS

Few discoveries in the lab have been applied therapeutically more rapidly than renal allotransplantation. The demonstration in 1960 of the capacity of 6-MP to prolong the survival of renal allografts in dogs was soon followed by the development of azothioprine (Imuran®) and its successful clinical application within 3 years.[32] This drug is now the "aspirin" of transplantation. An important early discovery of considerable theoretical significance was that rejection already in progress is controllable by steroids and other agents, i.e., the allograft reaction is reversible.[33] Although new immunosuppressive agents have been introduced, for the most part they have not been shown to have advantages over azothioprine and steroids. The success rate of renal transplants in man has been more or less constant over the past 7 years with a mortality rate in some centers no higher than that achievable by chronic dialysis.

The partnership between transplantation surgeons, tissue typers, and tissue bankers has grown closer year by year with the considerable progress being made in each field. Last year the pioneering U.S. Navy Tissue Bank celebrated its 25th anniversary.[34] Clearly, complete tissue and organ banks, rather than separate banking organizations dealing with specific tissues such as blood, cornea, and spermatozoa, are not far off.

We tend to neglect nonviable grafts in our Congresses, but an indication of their influence in surgery is afforded by the fact that about 200,000 bone grafts are used per year in the U.S.A. Prosthetic grafts are another category of transplants that gets short shrift on our programs. These include pump oxygenators, dialysis machines, plastic vessel segments, silica gel contour restorers, and endoprostheses, such as total joint implants and "endo-falsies" that have enabled truly amazing results to be obtained in orthopedic and plastic surgery.

One of the most dramatic events in transplantation surgery was the first successful transplantation of a heart in man in December 1967. Richard Lower[35] has expressed the situation very dramatically from the surgeon's viewpoint:

> . . . observing the empty pericardial cavity after most of the recipient's own heart has been removed illustrates quite convincingly that an individual's being dead or alive does not depend upon the presence or absence of his heart. The restarting of a vigorous heart beat after the transplant anastomoses have been completed is a moment of excitement seldom equaled in clinical surgery.

The success rates of cardiac transplantation obtained by several experienced teams have now become comparable to those reported for renal transplantation from unrelated donors.[36] Furthermore, the ability of cardiac transplants to extend life and improve its quality is beyond question. Currently, progress in this area, like that with unrelated donor renal transplantation, is restricted by inability to control the host response on a specific basis. Removal and transplantation of the human heart generated considerable controversy regarding the definition of death, and this has culminated in winning long-overdue legislative recognition of the concept of brain death.

Transplantation of the liver is an even greater surgical tour de force than that of the heart, and it is regrettable that only about 15% of all patients transplanted have survived for at least a year. An interesting and potentially important feature of hepatic transplantation is the rarity of graft failure from rejection and the remarkable degree of resistance of this organ to hyperacute rejection.[37] Most of the deaths of liver graft patients have been attributed to technical complications.

Bone marrow grafts have been used on an increasing scale over the past 8 years in the treatment of several diseases.[38] The feasibility of repopulating the marrow spaces of patients with aplastic anemia with normal allogeneic hematopoietic stem cells, leading to stable long-term chimerism has been established. Unfortunately, GVH disease remains a serious hazard of marrow transplantation, despite the expenditure of great effort and ingenuity to apply typing techniques and selectively to exclude offending cells from the graft and to control the GVH disease with drugs.

On the basis of clinical observations alone, we have learned that different tissues and organs are not equal with regard to their ability to survive allotransplantation. Anatomical differences with regard to their vascular supply may contribute. Experimental evidence has also been presented that different types of cells differ with regard to the density of alloantigenic determinants, and possibly the degree of exposure of these determinants, on their plasma membranes. Furthermore, studies on mice have shown that skin and at least some other tissues may express tissue-specific differentiation alloantigens.[39]

For some curious reason, the presence and possible significance of the population of donor leukocytes that is inevitably carried over in the vasculature and extravascular spaces of grafts was almost totally unheeded by transplanters until Steinmuller and Hart's[40] report on the significance of these "passenger" cells in skin graft rejection in 1971.

Over the past decade, evidence has gradually accumulated that, contrary to a widely held dogma, the apparent immunogenicity of allografts is susceptible to alteration by various treatments, which include maintenance in vitro for a short period prior to transplantation and exposure to various drugs, including steroids and other agents, in vitro.[41] Ridding them of their passenger cells may be a contributory factor, but their modification in some other manner such that they become more likely to evoke blocking antibodies instead of the usual destructive cellular immunity must also be borne in mind.

On the basis of both clinical and experimental evidence, the principle has been established that transplantation offers a means of controlling or reversing some inborn errors of metabolism. For example, it has been shown that a renal allograft from a normal donor can bring about a sustained clinical and biochemical reversal of Fabry's

disease, caused by an X-linked defect in glycosphingolipid metabolism, resulting from a galactosidase deficiency.[42] Various investigators have shown that transplantation of liver tissue or suspensions of hepatocytes from phenotypically normal rats to homozygous recessive Gunn rats lacking the enzyme uridine diphosphate glucuronlytransferase brings about a sustained decrease in plasma bilirubin concentration.[43]

The introduction of improved methods of microvascular surgery has exerted a considerable influence on organ transplantation research. To a significant extent, the dog has been liberated from its role as an experimental animal in favor of the rat, taking advantage of the availability of different inbred strains for studies on the transplantation of kidneys, hearts, livers, spleens, testes, and even lungs. Furthermore, it has relieved us of our dependency on the exceptionally exacting skin allograft for basic immunogenetic studies.

Although their goals lie in opposite directions, the relationship between cancer research and research in clinical transplantation has always been a close one because of their concern with immunology, dependency upon similar techniques, and employment of similar experimental subjects. The relationship between these disciplines became even closer with the discovery of tumor-specific transplantation antigens and fetal antigens. Recently, transplant surgeons have become regretfully aware that an unwanted side effect of immunosuppression-dependent organ allotransplantation is a relatively high incidence of neoplasms, predominantly lymphomas, in the patients.[44] The only consolation is that elucidation of the basis of the oncogenesis in these patients could well have a profound influence on the direction of cancer research.

CONTRIBUTIONS OF NATURE TO TRANSPLANTATION

Certain activities of nature, some sporadic and some very frequent or commonplace, have exerted a considerable influence upon the development of transplantation. The classic example, of course, is the key role played by dizygotic synchorial twin cattle in the discovery of the phenomenon of tolerance. But there are some other examples I'd like to mention.

It was awareness of a venereally transmissible tumor in dogs, which depends upon the survival of transmitted cells, that initiated speculation about the possible biologic significance of histocompatibility genes in the minds of some investigators. For example, in 1960, Gorer[45] wrote, "Were it not for the antigenic diversity of most species and the existence of a mechanism to react against the antigens, contagious tumors would be relatively common."

Analyses of various congenital immunologic deficiency diseases have provided information about the cellular requirements for allograft reactivity in man and attempts to reconstitute such patients has afforded important information about GVH disease in our own species.

The "nude," congenitally athymic mouse has been one of nature's greatest and most recent gifts to cellular immunologists.[46] In addition, it fulfills the long-felt need for a universal host for xenografts.

It is tempting to suggest that William Harvey had Syrian hamsters in mind when he wrote that, "Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path." These animals, by virtue of their peculiarities, have illuminated several facets of transplantation:[47] (1) studies on their cheek pouches have shed light on immunologically privileged sites in general; (2) their expression of immunity to tissue antigens in the form of a strong delayed cutaneous hypersensitivity reaction has made them useful tools for studying cellular aspects of transplantation immunity; (3) the particularly severe skin lesions associated with GVH disease in this species have afforded a model to study their pathophys-

iology;[48] and (4) despite the hamsters' ability to reject allografts quite promptly, there appears to be a lack of polymorphism at the SD regions of all hamsters studied, i.e., these animals reject allografts in the absence of any humoral responses.[49]

A fascinating example of a natural, intimate, long-term functional parabiotic union between adult individuals is provided by certain species of deep-sea angler fish.[50] The males are much smaller than the females, and their objective in life is to find a female in the sparsely populated depths and lock onto her body with their jaws. Subsequently, union of the skins and circulations of the two fish occurs, and the appendages and eyes of the male degenerate so that it becomes a reproductive parasite—in effect, the male and female become a single hermaphroditic organism. So far, the immunologic aspects of this union have not been studied.

Recognition that the fetoplacental unit is a highly successful allograft is of long standing, but only recently has it become the subject of intensive research. Although our understanding of the virtually consistent success of the fetus qua allograft is still far from complete, it appears that some kind of active immunoregulatory response, mediated by "blocking" antibodies, by antigen/antibody complexes, or by suppressor T cells, plays a role.[51] Indeed, fundamentally the success of fetoplacental allografts may turn upon the same principle as that of renal allografts in "enhanced" rats.

The availability of ready-made reagents in the serum of multiparous women has played an important role in tissue typing progress. Furthermore, placental tissue eluates and sera from pregnant individuals have become happy hunting grounds for biologic immunosuppressive agents.[52]

CONCLUSION

The early transplanters had one thing in common with that small group of embattled New England farmers who stood at Concord 200 years ago and "fired the shot heard around the world"—they couldn't possibly have envisioned what their seemingly parochial activities would eventually lead to.

The present status of clinical transplantation, with its essential backing of immunosuppression, tissue typing, and preservation procedures, in itself is a source of great satisfaction. However, I believe that in the eyes of the biomedical community at large, this accomplishment has been eclipsed by the totality of other developments resulting from unexpected discoveries in the transplant field. The discovery of various means of abrogating or manipulating immunologic responses, both nonspecifically as well as specifically, and the accumulation of information about the biology of lymphocytes have revitalized "classical" immunology besides giving it an entirely new territory for vigorous growth—cellular immunology. The MHC, discovered and partially defined by transplanters and, in one way or another, the subject of a large portion of their research activities, has been shown to have tremendous significance for virtually all kinds of immunologic responses and for susceptibility to a wide variety of diseases. Indeed, in clinical medicine, this superlocus is becoming just as important for the internist as for the surgeon. Other disciplines in which the MHC and other histocompatibility loci have proven to be important include oncology, developmental and reproductive biology, and physical anthropology.

The time is almost upon us when the majority of investigators interested in the MHC will not only be totally disinterested and uninformed about transplantation, but will feel that histocompatibility genes have been misnamed. Certainly, I, for one, feel surprised, delighted, and not a little awed by the tremendous breadth and depth of the knowledge that has emerged from some simple grafting experiments initiated a few decades ago.

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Historical Aspects of Hemodialysis

William B. Graham

IT is a pleasure to address this distinguished society on some of the historical aspects of hemodialysis. The inception of hemodialysis as a theoretical concept, and early clinical experimentation, have been well covered in earlier presentations to this body. I will touch on these aspects only in passing, and concentrate on the advent of hemodialysis as therapy available to the practicing physician for his patient.

The birth of hemodialysis as a practical therapy can probably be dated in 1955. In that year, Dr. Willem Kolff, then affiliated with the Cleveland Clinic, had developed a kidney model he felt was ready for volume production.

Dr. Kolff took his kidney model, which incorporated a variety of materials including beer cans and fruit juice cans, to several major pharmaceutical companies. In one, Dr. Kolff found immediate interest from the Medical Director and what Dr. Kolff describes as the Medical Projects Committee. After some 6 months of dialogue, Dr. Kolff said, the company's Medical Director informed him that the Medical Projects Committee had been overruled by a corporate committee and that company would not undertake production of the kidney.

Dr. Kolff remembers that on the very next day he telephoned Baxter Travenol's Medical Director, Dr. Robert Herwick, who showed immediate interest. I was then President of our company, and Dr. Herwick said he would get back to Dr. Kolff after talking with me. Dr. Herwick phoned him within 24 hours, Dr. Kolff recalls, with the definite answer that Baxter would undertake the project.

I later learned Dr. Kolff's interesting interpretation of why our company agreed so readily to work on the kidney. As some of you may know, my educational background includes chemistry as well as law. When Dr. Kolff found that I, a mere company president, not only could spell this strange word "dialysis," but moreover had acquired familiarity with dialyzable membranes in my graduate work, he knew immediately why Baxter Travenol's response was so prompt. And so our collaboration with Dr. Kolff and the Cleveland Clinic was begun.

The first encounters of Dr. Kolff and some of our technical people may be of interest, as remembered from their respective points of view. One of our medical engineers recalls that he looked with some dismay at Dr. Kolff's contraption, with its fruit juice can and other improvised materials, and said to Dr. Kolff: "We can surely do better than *that!*" As Dr. Kolff recalls, Baxter Travenol medical engineers promptly undertook to reinvent his invention. After having built several reinventions that did not work, Dr. Kolff says, they got around to recreating his model, which did.

Our technical people remember those early days of collaboration with Dr. Kolff as at various times stimulating and even inspiring, challenging, demanding, discouraging, frustrating, and ultimately fulfilling. Our people, experienced in volume production, were acutely aware of the need for standardization and quality in materials, parts, and construction that would stand up in widespread distribution and in a variety of settings. Dr. Kolff, although cognizant of these needs, also had a driving urge to build the best that could be created at the moment and was anxious to integrate potential improvements as new ideas occurred.

Although my assigned subject wasn't a tribute to Dr. Kolff, I want to comment here that he has unusual personal attributes,

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a number of which have been important to his contributions to dialysis. I think that the many of you who have worked with Dr. Kolff will recognize him in my description.

One most outstanding attribute is a genuine, deep concern for patients, out of which grew his unwavering goal of a practical dialysis system. One of Dr. Kolff's first patients died slowly of kidney failure, and Dr. Kolff deeply felt his inability to help.

Dr. Kolff is totally dedicated to his research objectives—one might almost say single-minded, if his research interests were not so many. He is both persistent in pursuing his own ideas, and generous in his willingness to share them and his work with others.

Some of Dr. Kolff's very human qualities have also contributed to his effectiveness. Although modest in his personal demands, he can be assiduous on behalf of his research. He can be as demanding of others as himself. And Dr. Kolff has always seemed to appreciate people who are as frank and outspoken as he is.

All of these attributes helped make our early collaboration with Dr. Kolff and the Cleveland Clinic a period on which we can look back with enjoyment, as well as the satisfaction of accomplishment. One of our people once said that for Dr. Kolff no obstacle was too great—even if it was someone else's obstacle. I have sometimes wondered in recent years whether other companies Dr. Kolff approached might not envy Baxter Travenol for taking on the artificial kidney—and if so, that's only fair, because there were times, when our early efforts ran into trouble, that we envied those companies that had *not* taken on the artificial kidney.

Nevertheless, we managed to produce 184 artificial kidney machines in 1956, all hand made. These machines were commercially available, and they worked. Even so, it could hardly be said that hemodialysis had arrived as a therapy widely available to patients. Before I turn to how this came about, however, I do want to touch, however briefly, on Dr. Kolff's early history and the work that preceded his first contact with us.

Dr. Kolff was born in Leiden, The Netherlands, in 1911. He gained his M.D. degree from the University of Leiden in 1938 and, shortly thereafter, joined the medical staff at the University of Gronigen. In 1940, Dr. Kolff set up the first blood bank on the continent of Europe, to treat casualties of the German invasion, and experience with this and other blood banks helped in his work with hemodialysis.

Dr. Kolff's work in dialysis was preceded by that of several others. In 1913, Abel, Rowntree, and Turner coined the term "artificial kidney" for the collodion tube apparatus they used to dialyze animals. In 1923, Necheles introduced an important principle, comprising a membrane between screens to keep blood volume small without sacrificing dialyzing surface. Van Gaarelts later obtained a favorable ratio between blood volume (in cellulose tubing) and dialyzing surface by winding tubing and wire mesh together in a stationary coil. Skeggs, Leonards, and Heisler designed an efficient conventional type of artificial kidney in which sheets of cellophane separate the blood from rinsing fluid that flows through shallow grooves of rubber plates.

In 1943, Kolff and Berk described the first practicable artificial kidney. A cellulose tube was wrapped around a horizontal drum that rotated in rinsing fluid. Later, however, Kolff returned to the stationary type of kidney. Inspired by Inouye and Engleberg's idea of fitting a stationary coil with a disposable plastic screen into a pressure cooker, Kolff and Watschinger further simplified the artificial kidney. The result was the kidney that Dr. Kolff brought to us.

And so, in 1956 we had 184 artificial kidney machines ready for patients, their hospitals, and physicians. Not many hospitals and physicians were yet ready for the artificial kidney, however.

As much later as 1958, we offered to give a kidney machine to one of our own city's leading research and teaching hospitals. After several talks, we received the response that they did not wish to undertake the task of developing and maintaining a team for the use of an artificial kidney. Accordingly, they did not wish to have us donate such a unit.

A number of roadblocks stood between appearance of the first volume-produced, practical artificial kidney and the widespread acceptance and availability of dialysis therapy. Although Baxter Travenol was able to provide support to a number of needed activities, many were beyond the province of a business organization and fell as primary responsibilities to other parties. Some of these needs were: (1) treatment institutions and physicians had to be convinced that this radical new therapy could be of practical benefit to their patients; (2) training for physicians, technicians, and nurses had to be provided, and treatment institutions had to be convinced that development and maintenance of dialysis t ams and ancillary treatment facilities warranted the necessary expense; (3) the expense of dialysis had to be brought down—this applied not only to the cost of equipment, but also to that of dialysis teams and facilities; (4) means had to be developed to support the cost of chronic treatment, which because of its continuing character, is beyond the reach of most patients.

For Baxter Travenol, which depends on earnings for its existence, an underlying problem was the considerable and mounting cost of a program which, however humane its goals, could most generously have been described as "visionary."

Credit for progress toward overcoming these roadblocks is broadly and diversely shared. Your Transplantation Society—and many of you individually—have played key roles. New frontiers have been opened, and new challenges are now being addressed. The renal and circulatory systems are much better understood today. Dialysis equipment is not only more reliable, but more varied and adaptable to varying clinical needs. An entire new industry has come into being. Not only hemodialysis, but organ transplantation has become a therapeutic reality.

For all of us, in observing the 20th anniversary of the birth of hemodialysis as a practical therapy, perhaps the most rewarding realization is that in this field especially, the past is truly prologue.