RES MEDICA
Journal of the Royal Medical Society

Tissue Transplantation

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Abstract
The transplantation of tissues from one site to another has been the subject of surgical endeavour for many centuries. Simple flap procedures for the repair of defects in the skin of the nose, mouth and cars were known to the Greeks and Romans of the first century A.D., and a form of rhinoplasty was carried out by Indian surgeons, using local flaps, more than two thousand years ago. A more sophisticated technique of rhinoplasty, involving the transfer of a pedicled skin flap from the arm, was used by Tagliacozzi in the fourteenth century. Powerful opposition to such interference in the works of the Almighty came from the Ecclesiastical authorities, and not only was Tagliacozzi discredited, but further progress in this field was firmly suppressed until the eighteenth century.

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ISSN: 2051-7580 (Online) ISSN: 0482-3206 (Print)
Res Medica is published by the Royal Medical Society, 5/5 Bristo Square, Edinburgh, EH8 9AL

Res Medica, Spring 1969, 6(3): 21-27
doi: 10.2218/resmedica.v6i3.852

TISSUE TRANSPLANTATION

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HISTORICAL BACKGROUND

The transplantation of tissues from one site to another has been the subject of surgical endeavour for many centuries. Simple flap procedures for the repair of defects in the skin of the nose, mouth and ears were known to the Greeks and Romans of the first century A.D., and a form of rhinoplasty was carried out by Indian surgeons, using local flaps, more than two thousand years ago. A more sophisticated technique of rhinoplasty, involving the transfer of a pedicled skin flap from the arm, was used by Tagliacozzi in the fourteenth century. Powerful opposition to such interference in the works of the Almighty came from the Ecclesiastical authorities, and not only was Tagliacozzi discredited, but further progress in this field was firmly suppressed until the eighteenth century.

In 1785, in Edinburgh, a series of experiments of some interest were carried out by a certain Mr. Fife and other members of the Royal Medical Society, and their work is recorded in the Society's Experimental Committee Records for that year.[1] They were interested in the possibility of blood transfusion, and used as their experimental subjects pairs of calves, one of each pair being bled via the carotid artery into a jugular vein of the other. In one instance they used as a conduit a pair of ivory cannulae connected by a piece of intestine which they had previously removed from a cat, and on other occasions they used simple metallic tubes.

The results of their work are carefully documented and, since they preceded Pasteur's discoveries by seventy-five years, and those of Landsteiner on blood groups by one hundred and fifteen years, the experimenters may be excused for marvelling that the recipient animals almost invariably took a violent rigor and expired shortly after the transfusion, and for concluding that blood transfusion was not a practical procedure.

In the ensuing years numerous advances were made which marked the development of transplantation surgery as we know it today. Throughout this period technical ability has usually been more advanced than understanding of the fundamental biological problems involved. Thus the nineteenth century saw developments in the field of bone transplantation, notably by Ollier of Lyons, who made observations on the fate of bone fragments transplanted both subcutaneously and into skeletal defects, and noted the importance of an intact periosteum to the fate of such grafts; and by McEwen of Glasgow who performed the first successful allograft (v. infra) of bone to reconstitute the humeral shaft of a child with osteomyelitis in 1878. Early attempts to transplant cornea, tendon, nerve, and cartilage were also made during the nineteenth century, but the transplantation of whole organs on a vascular pedicle had to await the development of satisfactory techniques of anastomosis of blood vessels, an exercise that was not accomplished with reliability until the early part of the twentieth century.

Although Humphrey Davey described the narcotic properties of nitrous oxide in 1798, and suggested its possible use in surgery, almost half a century was to elapse before

anaesthesia was applied, first in dentistry by Wells and Morton in the States, and later in surgery and midwifery by Liston and Simpson in Britain. These discoveries transformed surgery from the art of the lightning craftsman into a more leisurely exercise which would allow the more time-consuming and exacting work required for transplantation.

Any tissue that is severed from its blood supply in order to be placed in a new situation passes through a period of susceptibility to infection, a complication that was the fear of nineteenth century surgeons. The discovery of microbes in the 1860's led first to the eradication of infection by antiseptics and later to the notion that it was better to avoid it by the aseptic method that is a corner stone of modern surgical technique. The importance of these events to transplantation surgery cannot be over emphasised, but without the more recent discoveries of sulphonamides and antibiotic substances in the 1930's and later, the advances that were to follow the elucidation of the immunological rejection of transplants from one individual to another could not have taken place.

In the first two decades of the twentieth century there was much debate concerning the failure of allografts of tumour and normal tissues to survive. There is not space here to discuss all the theories that were advanced, but among them was the notion that the host developed an active immunity to the graft. Several clinical instances were reported of the behaviour of skin allografts used in burns and in extensive trauma during this period, but understanding that a failed allograft was fundamentally different from a failed autograft was slow to develop. In 1943 Gibson and Medewar[1] reported the accelerated rejection of a second set of allografts from the same donor to the same recipient in a case of burns, and this led on to Medewar's systematic study of allografts published in 1944 and 1945.[5,6] He established that in rabbits, such grafts were invariably rejected with a mean survival time of 10.4 days, and that if a second graft was made from the same donor to the same recipient twelve or more days after the first, rejection was accomplished more rapidly, with a mean survival time of 6.0 days. He also found that whereas first set grafts developed vascular connections and became infiltrated with mononuclear cells prior to rejection, second set grafts of skin failed to become vascularised at all; they rapidly became necrotic, and such mononuclear cells as were seen were heavily amassed in the recipient tissue which was the graft bed.

IMMUNOLOGICAL THEORY

These observations have been amply confirmed, and present day theory on transplant immunity may be summarised as follows: after the introduction of a graft into a recipient animal, material from the graft is carried into the host, either in the form of soluble antigens which pass into the bloodsteam, or else by way of host mononuclear cells which, on encountering the tissues of the graft, pick up antigenic material and carry it via the bloodstream, or via lymphatic channels, into the recipient's lymphoid tissues. Some of these mononuclear cells are members of the long-lived group of lymphocytes in the peripheral circulating pool, cells which are concerned in recognising foreign antigens. This may be referred to as the afferent mechanism.

Afferent antigenic material gains contact with the lymphatic tissues of the host via the bloodstream, but in particular with the regional lymph nodes which receive lymph directly from the graft. Lymphocytes in the paracortical areas of the lymph nodes respond to the antigenic stimulus brought to them by macrophages returning from the graft by transforming into a new, and now highly specialised group of cells, which are able to produce specific antibody to the antigens concerned. This change is in some way imprinted on the genetic mechanisms of the nucleus, so that the progeny of such transformed cells will possess this specific potentiality. These events may be called the central response.

These specialised cells may behave in two ways. Some, remaining in situ, produce specific antibody which passes into the circulation. Others, migrating from their lymph node origins, enter the blood stream and are able to penetrate the graft where, by mechanisms unknown, they exert a harmful effect on the graft. Such is the effector mechanism of transplantation immunity. It should be emphasised that a very great deal remains to be clarified about these immune responses, in particular with regard to the role and interrelationships of the cells involved; the foregoing is no more than a brief outline of prevalent theory. For more detailed information, the interested reader is referred to the series of articles by E. J. Holborow in The Lancet 1967 Nos. 7494-7503.

At this stage the current nomenclature of

transplantation surgery must be introduced. A graft transplanted from one site to another in the same individual is an autograft. If the recipient is a monozygous twin of the donor, or a member of the same highly inbred strain in the case of animal work, then the term isograft is used. A transplant to a different member of the same species, e.g. Jack to Jill, is an allograft, and when the donor belongs to a different species to the recipient, e.g. baboon to man, rat to mouse, the term xenograft is used. The last two of these terms were formerly referred to as homografts and heterografts respectively.

Clinical transplantation involves largely the use of autografts and allografts. In the case of paired organs, i.e. the kidney, transplants between monozygous twins are feasible, and some cases of transplantation across species barriers have been reported. The absence of an immunological problem in the case of autografts led to their widespread adoption many decades ago and the details of their application can be read in standard works on plastic and orthopaedic surgery.

METHODS OF IMMUNOSUPPRESSION

The fundamental problem to be overcome in the case of allografts is simply stated; the ability of the host's immunological mechanisms to destroy the graft must be suppressed without at the same time suppressing his immunity to other foreign material, e.g. bacteria, viruses and fungi. The reader will be quick to point out that these difficulties have not prevented the successful transplantation of corneas obtained from cadavers. The reason for this is that since cornea is an acellular and avascular structure, it is not subject to the cell mediated immune response mounted by the recipient. Any process leading to vascularisation of the graft results in its rapid rejection.

Even a cursory study of the complex nature of the immune mechanism will suggest that it may be possible to interrupt it at several points by agents which interfere with cellular multiplication or function. In fact numerous methods of immunosuppression have been developed, and some have found application in human transplantation.

Irradiation

Whole body irradiation using about 150 rads was used about a decade ago in the early days of renal transplantation. Irradiation interferes with the molecular structure of desoxyribonucleic acid, and thus with cell division, cells being most susceptible to this injury during early mitosis. The tissues most affected by this treatment, therefore, are those which divide most rapidly, namely, the cells of the bone marrow, lymphoreticular system, skin, and mucous membranes. In practice, the use of a non-specific agent of this nature may result in a dangerous and prolonged pancytopaenia. This, and the difficulties of choosing the correct dose to suit each case led to its early discontinuation as a clinical immunosuppressant. Nonetheless local irradiation of the graft, by destroying cells infiltrating the organ, and in the regional lymph nodes, is thought by some to be of value in the treatment of rejection crises.

Antimetabolites

It is possible to interfere with nucleic acid synthesis in other ways, however. The antimetabolite 6-mercaptopurine, by its similarity to certain naturally occurring purine compounds, can modify purine metabolism, thus interfering with the production of nucleoprotein and therefore with cell division. It also should be expected to affect all dividing cells, but in comparison with irradiation it has the advantage of manoeuvrability, the effect of a change in dose being more rapidly seen than in the case of irradiation. Despite this advantage, 6-mercaptopurine itself does not prove to be a very suitable agent for human use, because of the high incidence of toxic side effects. Investigation of a large number of related compounds led to the development in 1959 of azathioprine, a derivative of 6-mercaptopurine with broadly similar effects but with much better patient tolerance. This agent holds a position of great importance in human transplantation, and has been largely responsible for the improvement in renal transplant survival in the past decade.

Corticosteroids

The ability of corticosteroids to suppress inflammatory responses, including the immune response to transplants has long been known. Their mode of action is not clear, and although in some species, e.g. rabbits, guinea pigs and mice, cortisone prolongs the survival of skin grafts, in others, e.g. dogs, monkeys and

humans, it is ineffective when given alone. As an adjunctive treatment to azathioprine, prednisone has come to play an important part in clinical immunosuppression. Large doses of prednisone, e.g. 2-4 mg. per kilogram, are effective in reversing acute rejection phenomena, and in fact, in the case of renal transplants, many patients become dependent on a dose of 0.25 - 0.5 mg. per kilogram.

Actinomycin

Actinomycin C is a mixture of a group of antibiotic substances derived from Streptomyces chrysomallus which has a cytotoxic effect. This appears to take the form of an interference in the control which desoxyribonucleic acid exerts over messenger ribo-nucleic acid. It is most useful in the treatment of rejection crisis, when it is given as a short course of one or two intravenous injections in conjunction with increased doses of prednisone and maximal doses of azathioprine.

Antilymphocytic globulin

The above agents, by their nature, have an effect on all the cells and tissues of the body, and therefore produce various unwanted side effects. The antimetabolite and cytotoxic drugs may be responsible for agranulocytosis, thrombocytopaenia, ulceration of the alimentary mucosa, and loss of hair. Prolonged treatment with steroids produces the typical Cushingoid facies, with triae, moon face, osteoporosis, and increased incidence of hypertension and peptic ulceration. It has long been hoped that a more specific agent might be produced which would inhibit the mechanisms primarily responsible for transplant immunity without at the same time interfering with resistance to bacterial infection, or damaging other important groups of cells, e.g. the epithelial cells of the alimentary tract. To some extent, these hopes are fulfilled by antilymphocytic serum, which has recently been the subject of intense study in many laboratories throughout the world, and has been used in a number of cases of renal transplantation. The concept of an antilymphocytic serum is not new, and such a serum was prepared as early as 1937 by Chew and Lawrence, who demonstrated its ability to suppress the peripheral blood lymphocyte count *in vivo*. Similar suppression was obtained by Woodruff, Woodruff and Forman in 1950[8] when it was noted that the lymphopenia was relatively short-lived; because of this, it was at that time thought that antilymphocytic serum would be unlikely to have a significant influence on allograft survival.

Slight prolongation of skin graft survival was shown in 1961 by Waksman, Arbouys and Arnason,[7] but later observations in Edinburgh by Woodruff and Anderson, in 1963 and 1964,[9] demonstrated that skin graft survival in rats could be significantly prolonged by the administration of a serum raised in horses against rat lymphocytes. It was then shown that prolonged lymphopenia was not a necessary prerequisite for graft survival. In the past four years, extensive research into the production and properties of these sera has been carried out, and highly significant contributions have been made in our own medical school.

Antilymphocytic serum is made by injecting a preparation of the lymphocytes of the species in which grafting is to be carried out into another species. Usually the serum is raised in a large animal for transplant experiments in a smaller animal, for example, horse anti-dog serum, rabbit anti-mouse serum, and so on. It is possible to prepare cell suspensions rich in lymphocytes from spleen, thymus, lymph nodes, thoracic duct lymph, or peripheral blood. After a course of active immunisation by these cells, the animal is bled and the serum so obtained is heated to 56°C to destroy complement.

At this stage dangerous anti-erythrocyte activity is present, irrespective of the origin of the innoculated lymphocyte suspensions; the serum also contains large amounts of unwanted protein which must be removed. Purification may be carried out by several techniques, but our method has been to carry out sodium sulphate precipitation and batch chromatography on diethylaminoethyl cellulose, restoring the salt concentration to physiological levels by dialysis prior to storage at −20°C. The final preparation consists of immunoglobulin G, or IgG for short. It is absorbed against red cell stroma and platelets in order to reduce its activity against these elements in treated animals.

Animal experiments have shown that antilymphocytic globulin (ALG) possesses powerful immunological properties. For instance, it has been shown to suppress the production of humoral antibodies to primary immunisation by numerous antigens; it can inhibit cutaneous phenomena which are due to the cellular re-

sponse of delayed hypersensitivity, for example, the tuberculin reaction; it can prolong the survival of allografts of skin, kidney and other tissues, and it can modify the course of certain auto-immune diseases, for example allergic encephalomyelitis in mice.

Evidence is now available, notably from Starzl in Denver, [1 10] that ALG, used in conjunction with reduced doses of azathioprine and prednisone, gives results in human renal transplantation that are at least as good as, and probably better than, those obtained with these agents administered together in their usual dosage. Since both azathioprine and prednisone have potentially serious side effects, this observation is highly significant. However, this powerful new tool is not without its problems; its antiplatelet activity is sometimes troublesome, and the injection is often painful. Although it is able to suppress humoral and cellular immunity, it is itself a foreign protein, and in fact it has been shown to be if anything more antigenic than normal gamma globulin derived from the same source. The reason for this probably lies in the fact that it homes onto lymphocytes which, being altered in some way, are taken up by macrophages resulting in the absorbed ALG being concentrated in the very centre of the treated animal's immune defence mechanism.

The mode of action of antilymphocytic globulin is only partly understood. There is no doubt that the active molecules in an ALG preparation adhere to lymphocytes, but what they do in this situation is less certain. Three main theories have been advanced; that the lymphocytes are destroyed by ALG; that their cell membrane is so occupied by ALG molecules that it is unable to respond in the normal way to other antigens (blind-folding); and that lymphocytes are transformed into a type of cell which is immunologically inactive (sterile inactivation). Space will not allow a discussion of these and other theories, and the experimental evidence which supports or refutes them, for which the reader is referred to specific works on the subject.[1]

TISSUE TYPING

These then are the ways at present available to overcome the homograft reaction. At best they are imperfect tools, and therefore the problems involved in avoiding or minimising rejection achieve the greater importance. The laws governing the transfusion of blood which concern the ABO grouping system must not be transgressed. Rhesus antigens are of much less importance, as are the numerous antigens which have been identified on the red cell membrane. In recent years attention has been turned to antigenic determinants which are present in the leucocytes of peripheral blood. Pioneers in this field have been Terasaki in Los Angeles, Dausset, Van Rood and Cepellini in Europe, and Batchelor in London. They have collected sera from patients who have been sensitised to foreign leucocytes, for example from pregnant women, or from people who have received multiple blood transfusions. The antibody content of these sera has been characterised and it is possible by their use to define which antigens are present on a given patient's cells, and to correlate the degree of compatibility between recipient and donor with the clinical course of a transplant. Evaluation of leucocyte typing continues, but it would appear already that there is in many (but not all) cases a correlation between high donor-host compatibility and smooth clinical course, free from rejection episodes. That some cases of complete compatibility nevertheless develop a rejection crisis may be taken as evidence that there are other parameters of compatibility testing of which we are not as yet aware. Among them may be preformed humoral antibodies, particularly in the case of kidney recipients who may have been transfused with scores of bottles of blood during their period of rehabilitation on dialysis prior to transplantation. Although the importance of such antibodies has been doubted, it may be necessary to revise this view when sufficient information becomes available.

BACTERIOLOGICAL PROBLEMS

The management of patients on immunosuppressive treatment presents certain problems, especially in the case of renal transplants where general resistance to infection is diminished and the rate of excretion of drugs uncertain. The effects of a change in dosage of azathioprine are not seen for a few days, and it is sometimes very difficult, demanding considerable experience, to negotiate the narrow way between too little suppression, with the dangers of rejection, and too much, with the equally unwelcome dangers of infection. It is because of this problem that it is preferred to manage these patients in a sterile area such as has been constructed at the Nuffield Trans-

plantation Unit in Edinburgh, where all possible precautions such as the design of the unit, an elaborate ventilation system, bacterial surveys and decontamination of nursing and medical staff, have been taken to minimise the colonisation of the patient by organisms other than his own.

ARTIFICIAL AIDS TO VISCERAL FUNCTION

A patient who is in the terminal stages of disease of one of his visceral organs, be it kidney, liver, lung or heart, such that his only hope is transplantation of a new organ, is usually in a desperate clinical state. Looking back at the early days of renal transplantation, there is no doubt that a great deal of the peri-operative mortality, and the early failures, were due to the fact that the recipients were often moribund, having been saved from death itself by one or two hair-raising haemodialyses. The developments in dialysis technology in the early 1960's, leading to the introduction by Scribner of long term intermittent dialysis for chronic renal failure, transformed the situation in two ways. Firstly, an alternative to transplantation became available in what has become known as repeated dialysis treatment or, by that habit of abbreviation to which medical men are so addicted, as "R.D.T." Secondly, repeated dialysis treatment allows a patient with terminal renal failure to be rehabilitated so that his physical condition is no longer a bar to the relatively major operation of transplantation with its attendant hazards relating to immunosuppression. Such complications as hypertension, oedema, ascites, congestive heart failure and infections can usually be eliminated or controlled during this period, leading to a greatly improved chance of surviving the operation.

For some patients, notably those with lower urinary tract anomalies or disease, transplantation is not successful, and management by R.D.T. is preferable. Opinions may differ as to whether and when a patient successfully launched onto repeated dialysis should have his transplant, but since dialysis treatment and transplants fail for entirely unrelated reasons, a combination of the two methods of treatment can significantly prolong the life expectancy of patients with terminal renal failure.

When one surveys the transformation that repeated dialysis treatment has brought to the scene of renal transplantation, one is bound to ask how similar facilities, if available would affect hepatic and cardiac transplantation. Perhaps the greatest advances in these branches of transplantation surgery in the next decade will be the development of artificial aids capable of adequate patient rehabilitation.

THE WAY AHEAD

Looking to the future, there are several problems in transplantation surgery which require careful thought and well directed research. One of the most difficult of these is the procurement of organs. Of necessity, cardiac and liver transplants are obtained from cadaver donors, but so also are a large proportion of renal grafts. In the latter case sufficient time is available to ensure that by all necessary criteria, death has occurred. A more urgent time scale in the case of the liver, and, in the case of the heart, cessation of function in the organ to be transplanted being a previously essential criterion of demise, has led to serious suspicions of ambivalence on the part of the physicians responsible for the treatment of the donor, and of excessive zeal on the part of the would be transplanters. For our part we have gone to great lengths to avoid any influence whatever in the good treatment of any potential donor, and have preferred to allow an organ to pass by rather than become the object of such suspicions. It is quite clear that a period of several years will be necessary in which painstaking effort is applied to the forming of public opinion, and perhaps new legislation enacted to facilitate the procurement of organs while safeguarding the interests of the potential donor.

Having obtained an organ for transplantation, time is vital, and the complex logistic problems involved in mobilising the surgical team, the recipient, and such ancillary services as for example, blood transfusion, blood coagulation and clinical chemistry would be much simpler if the organ could be stored in a viable state for a number of hours or even days. Certain advances have been made along these lines in the case of the kidney, and, more recently, the liver, using hypothermic perfusion with electrolyte solutions, blood, low molecular weight dextran, mannitol, or combinations of these materials, in conjunction with hyperbaric oxygen and, when temperatures below freezing point have been employed, such antifreezing agents as dimethyl sulphoxide. These crude methods have allowed experimental preservation of the kidney for up to 24 hours in

a viable state, but much greater reliability would be required before they could justify so great a delay in a case of human transplantation.

The immunological battle is the central and most difficult problem to be solved. Improved methods of tissue matching, and more specific immunosuppression probably along the lines of antilymphocytic globulin, will no doubt be developed, but there remains the immunologist's dream that specific tolerance to an organ transplant may one day come within the bounds of clinical possibility.

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DIAGNOSTIC PROBLEM

SET BY A. STRONG, B.A.(Oxon), M.B., Ch.B.

SUBJECT

Miss A. B., aged 18. Right handed.

PRINCIPAL COMPLAINTS

Tremor, paraesthesiae, obesity, headache.

HISTORY

(1) Tremor, impairment of fine movements and paraesthesiae of the right side, principally of the arm. The tremor worst at rest and exacerbated by concentration. Three months' duration and steadily deteriorating.
(2) Increase in appetite and weight and excessive thirst for three weeks.
(3) Frontal headache on rising in the morning for the past three weeks.
(4) General medical and family histories negative.

GENERAL EXAMINATION

A tall, obese girl: otherwise negative: blood pressure normal.

NEUROLOGICAL EXAMINATION

1. Intellect not significantly impaired: no intracranial bruits: no papilloedema.
2. Slight slurring of speech.
3. Mild right facial weakness of central pattern.
4. Sensation depressed on right side of face and right arm.
5. Severe resting tremor of right arm and leg.
6. Increased tone of right limbs: equivocal right plantar response: drags the right foot on walking.
7. No inco-ordination or rombergism.

INVESTIGATIONS

Routine haematology and biochemistry normal; CSF pressure and protein normal.

Serum cortisols: (a) 11 p.m. — 8 μg/100 ml. (b) 9 a.m. — 11 μg/100 ml.

A. Where is the lesion and what is it likely to be?
B. What neurological investigations are required?

FURTHER PROGRESS

After investigation a diagnosis was made and in view of her rapid deterioration the patient underwent craniotomy in an attempt to arrest the expansion of her lesion. During surgery there was marked venous oozing. Postoperatively she was slow to recover consciousness and suddenly deteriorated 18 hours later. Re-exploration showed an accumulation of clot from recurrent venous oozing. She remained deeply unconscious and some 24 hours later developed an intense jaundice: urobilinogen and bilirubin appeared in the urine. Prothrombin activity was 29%, S.G.P.T. 570 I.U., serum indirect bilirubin 2.5 mg/100 ml, direct 5.7 mg/100 ml. Bleeding time was 9 minutes: no increase in fibrin degradation products: direct and indirect coombs' tests negative: slight depression of vitamin K — dependent coagulation factors (II, VII and X). In spite of treatment including triple strength plasma and vitamin K1 her condition deteriorated and she died 6 days after operation.

C. What was the cause of her jaundice?

(Answer on page 48)