Memoranda

BASIC REQUIREMENTS FOR THE INTERNATIONAL EXCHANGE OF TRANSPLANTABLE ORGANS*

Many thousands of people die each year in consequence of the failure of an organ or pair of organs, from conditions affecting the haemopoietic or lymphoid tissues, or following extensive skin loss due to severe burns. Many of these people cannot be adequately treated by conventional or conservative means, but could benefit from the transplantation of tissues or organs, and the resources of a single area or country will frequently be inadequate to provide the needed well-matched tissues. This memorandum which, it is hoped, will serve as a guide to those attempting collaborative efforts, is intended to cover the transplantation of any organ, but since experience with the kidney has been far more extensive than that with any other tissue reference will frequently be made to it.

In severe irreversible renal damage two forms of treatment are available: chronic intermittent dialysis and transplantation of a kidney. In most patients it is advantageous to use both methods of treatment. The number of new patients requiring one or both has been variously estimated to be between 2 and 5 per 100,000 population every year. Although anticipated developments may alter the position, haemodialysis, the principal method of treatment used at present, has several disadvantages:

1. It is not curative, nor is it indefinitely palliative, because an estimated 10% to 15% or more of patients die during the first year of dialysis and up to 10% of the survivors die each year thereafter.

2. It is expensive in terms of money (hospital dialysis is estimated to cost US$10,000 per year and home dialysis US$6,000) and in terms of the medical facilities employed.

3. The repeated transfusions usually necessary in long-term haemodialysis involve the continuing hazard of hepatitis or other infections.

4. The patient has to be connected for several hours, usually twice a week, to the machine. Problems of recurrent vascular obstruction often limit the use of dialysis.

No comparable form of treatment as an alternative to transplantation is available for the failure of other organs such as the liver, heart, lungs, and pancreas. Long-term transfusion as practised in the treatment of bone-marrow failure is only of limited value, and only comparatively small skin defects can be repaired by autotransplantation. Allograft transplantation would be of great value if prolonged survival could be achieved.

The value of allograft transplantation of tissues other than the major organs is indicated by the observed success over a long period of transplanted cornea, cartilage, bone, or heart valve. Here, for various reasons, the success rate is high. Additional measures such as immunosuppression or tissue matching have been tried only exceptionally. However, except in identical twins the usual course of an allograft is acceptance followed after an interval by rejection, and even the tissues mentioned above are not entirely exempted. Rejection is a much more severe problem with well-vascularized tissues or organs such as the kidney, liver, and heart.

Rejection may be delayed and rendered less intense by the use of immunosuppressive agents, so that organs such as the kidney may function well for many years.

Immunosuppression, however, involves the risk of infection, an increased incidence of certain types of tumour, and other serious complications. Moreover, the risk is a continuing one since, with the agents in current use, it is rarely possible to stop immunosuppressive treatment completely. It is therefore important to find ways by which the dose of immunosuppressive agents can be reduced to a minimum. Extensive experience in animals indicates that a state of unresponsiveness or immunological tolerance can be induced by appropriate treatment with donor tissue. Tolerance has generally been most easily induced when the genetic disparity between the donor and the recipient has been slight.

The central problem, then, is how such objectives as reduction in the severity of the rejection, reduction

* This memorandum was prepared by the signatories listed on pages 917-918, who took part in a consultation arranged by WHO. Requests for reprints should be addressed to the Chief Medical Officer, Immunology World Health Organization, 1211 Geneva, Switzerland.

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in the amount of the immunosuppressive agents, and provision of a basis for the induction of tolerance can be reached. Improvement could be expected to follow the widespread adoption of tissue typing for matching donors and recipients and to increase as knowledge of tissue antigens improves. At the same time, the use of typed donors and recipients should provide a more controlled environment for trials of new immunosuppressive agents and of new procedures, including studies on immunological unresponsiveness. Although a certain mortality is almost inevitable in any surgical intervention in patients at the end stages of intractable disease, the recent two-year survival figures of over 80% for patients receiving kidneys from living related donors and of over 40% for patients receiving them from cadavers emphasizes the practical relevance of transplantation.

There will always be a chronic shortage of human organs suitable for transplantation. If the supply of human kidneys was utilized to the full, it might meet the requirements. The supply of hearts would certainly fall far short of the need. The objective must therefore be to make use of more than one organ from every available donor. It is also essential, in order to take advantage of tissue typing, achieve good donor-recipient compatibility, and use the scarce and valuable tissues optimally, to have available a pool of pre-typed recipients sufficiently large to ensure that there is a compatible recipient waiting for each organ that becomes available for transplantation. This may necessitate the transport of organs over long distances and between different countries.

It must be stressed that one of the desiderata for the successful transplantation of organs is a close antigenic relationship between donor and recipient. This has not always been obtained in the past, partly because the size of the pool of recipients maintained at any single transplantation centre is relatively small and partly because of the slow realization of the importance of matching (not merely typing) in transplantation. Obviously, many other factors are associated with successful transplantation. They include: the experience of the clinicians; the type of immunosuppression used; the immunological reactivity of the patient; and the state of preservation and the capabilities of the transplanted organs. Some of these are subjects for further research and are outside the scope of this memorandum, which describes the different prerequisites that should be met by groups seeking to establish a transplant region. Ultimately they could be the basis for intercontinental exchanges.

The procedures suggested are as follows:

1. The HL-A types and ABO blood groups of the patients requiring a transplant should be determined. This should be done either by the reference laboratory for the region or by a local laboratory under the general supervision of the reference laboratory. Standardized techniques should be used throughout the region.

2. The data and other relevant information (such as the presence of anti-HL-A antibodies) should be stored in a sorting system or computer. This should be done by the reference laboratory.

3. When a donor becomes available, his HL-A types and ABO blood group should be determined by the local laboratory, which then can either communicate with the reference laboratory or consult a computer print-out.

4. As an essential component in donor selection, a cross-match should be performed. If it is negative, immediate arrangements should be made to transport the kidney to the recipient.

We are fully aware of the ethical and legal problems linked with the use of cadavers as sources of supply, but we do not feel competent to discuss them in this memorandum. We refer readers to the laws and/ or ethical codes that have been or are being elaborated in the different countries. We feel, however, that some uniformity in legislation and rules should be aimed at in the different countries participating in a common transplantation programme.

Tissue Typing

Definition

The rejection of the allograft (a graft between genetically different individuals of the same species) is an immune phenomenon brought about by antigenic cellular structures that are present in the graft but absent from the tissues of the recipient. When immunocompetent tissues such as bone marrow are transplanted, the reverse situation must also be taken into account in order to avoid a graft-versus-host reaction. Tissue typing may be defined as the ability to recognize these antigens (histocompatibility factors) by laboratory methods (usually serological) and thus of selecting a priori the donor-recipient combinations that will best enable the transplant to survive.
It must be stressed that in practice an acceptable match does not imply compatibility for all the possible factors, because the effect of some weak incompatibilities can easily be overcome by immunosuppressive treatment.

Among the many immunogenetic structures for which man is polymorphic, two systems play a special role in transplantation: the ABO blood groups and the HL-A antigens. Their great importance is probably due to the fact that they are expressed in most tissues and are the sources of incompatibilities that are not predictably controlled by present immunosuppressive treatments.

The importance of the ABO groups in organ transplantation has been clearly established from clinical experience with kidney transplants and experimental experience with skin transplants. Organ grafts should follow the same grouping and matching procedures as for blood transfusion. As with blood transfusion, group O constitutes a universal transplant donor (except for immunocompetent tissue) with respect to the blood group antigens, and grafting in the face of incompatibility for the A and B antigens should not be done.

With the possible exception of the P group, other red cell antigens such as Rh and MN do not seem to act as histocompatibility factors in the transplantation of most solid tissues and organs. It is likely, however, that they are relevant in the transplantation of bone marrow.

For HL-A typing, leucocytes and platelets are the elements of choice, although fibroblasts or other cells grown in tissue culture are occasionally used. The HL-A antigens are well expressed on these blood components and on most if not all tissue cells, but they are not found on mature red cells.

The HL-A system has been shown to be very complex because at least 20 different antigens have already been recognized. They are controlled by a chromosome region, probably corresponding to several closely linked genes. At least two such genetic units have been designated as the first sublocus or the “LA” series comprising specificities HL-A1, 2, 3, etc., and the second sublocus or the “FOUR” series comprising HL-A5, 7, 8, etc. Both are highly polymorphic, i.e., they can be represented by different alleles, all having a significant frequency in the population. Thus two large series of mutually exclusive specificities are already known, and each individual cannot be positive for more than two factors in each series.

The increasing number of factors being identified suggests the probability that blank alleles (amorphs, similar to blood group O) are infrequent, at least at these two loci.

Because of these many genetic alternatives, the number of different HL-A phenotypes in the population is very high (of the order of thousands).

It must be noted, however, that in any sibship no more than four different HL-A genotypes (and hence phenotypes) can be found (corresponding to the combinations of the four parental chromosomes). Thus the *a priori* chance of identity for HL-A is low between two unrelated individuals but higher than 25% between siblings.

The validity of HL-A typing for transplantation has been proved by clinical and experimental observation. In this regard, the most convincing evidence corresponds to the very significant difference in the rate of survival of kidney grafts exchanged between siblings classified as genetically identical or different on the basis of HL-A typing. In fact, according to the most recent data, the rate of kidney survival years after operation is as high as for grafts between monozygous twins when the two siblings are HL-A identical, but not significantly higher than between unrelated persons when the two siblings are HL-A different (for both chromosomes). Corresponding results have been obtained in experimental skin grafting, where the mean survival time is 11 days for grafts exchanged between HL-A different sibs but more than 20 days for HL-A identical sibs. This is overwhelming evidence that HL-A is the most important histocompatibility system in man.

Survival rates in kidney grafts exchanged between parent and child, as well as comparable skin graft experiments, have also shown a good correlation with the degree of HL-A matching. However, for tissue typing to be of broad practical use it should also be valid for selecting donors (cadavers) unrelated to the recipient. In this respect fully convincing evidence has not yet been obtained but, in addition to the theoretical considerations derived from understanding of the genetics of the HL-A system, all the clinical and experimental data indicate that a similarity of the HL-A phenotype in the donor and recipient gives a better prognosis for the graft. As in ABO blood-group incompatibility, clinical experience with kidney grafts and experimental evidence from skin grafts strongly indicate that grafting should not be performed in a patient sensitized against HL-A antigens present on the
tissues of the donor. Since the HL-A system is so complex, it is also essential to expand tissue typing for unrelated donors in order to accumulate the data necessary to give a final answer to the question which of the antigens or alleles are the most potent.

Because of the high genetic polymorphism, already mentioned, of the HL-A system in all the populations studied, the chance of finding two unrelated individuals who have the same HL-A phenotypes is on the average low (lower than 1 : 1000). While it is possible to grade incompatibility on the basis of the number of HL-A factors for which the donor and the recipient are different, the aim in correct tissue typing must be to find for each recipient an HL-A identical donor. This is the reason for expanding the pool of individuals to be matched to include the country and groups of countries. While the pool should be as large as possible, on the basis of what is known at present one of 500 recipients would permit a good allocation of most cadaver organs for transplantation.

Choice of antigens and interpretation of data

Because amorph alleles are probably rare, at least at the two HL-A genetic subunits at present identified, a negative reaction with all available sera detecting the known factors of a series may still correspond to at least one (if homozygous) and possibly two (if heterozygous) antigenic specificities that cannot yet be directly recognized but are nevertheless immunogenic. At present, it is not possible without family analysis to decide whether an individual who is positive for only one factor of an allelic series is a homozygote for this factor or a heterozygote for one of the as yet unknown specificities.

As a consequence, the definition of compatibility cannot follow exactly the criteria used for blood transfusion in relation to the ABO system. The phenotypic identity should therefore be regarded as a better match than mere compatibility (apparent absence in the donor of antigens that are also absent in the recipient). This has an important bearing on the interpretation of the data for the choice of the best donor-recipient pairs. A graded rank of combinations from complete identity to multiple incompatibility should be considered on the basis of the above criteria; in particular it must be realized that a compatibility in the usual sense (donor— at a given sublocus; recipient+ or even —) may mask a potential incompatibility. Computer programmes can be worked out giving the probabilities for such undesirable combinations on the basis of the available genetic data (allele frequencies in the population, etc.). Parenthetically, it may be noted that this lack of complete information is the major reason for the much higher efficiency of tissue typing for genetically related than for unrelated individuals (negative reactions in siblings are probably due to the same unknown antigens).

From these considerations are derived the following criteria for the choice of the antigens to be used for tissue typing:

(1) Priority should be given to sera that detect a narrow specificity, thus excluding as far as possible multispecific sera and even cross-reacting monospecific sera.

(2) As many “allelic” factors as possible at each sublocus should be typed for, in order to reduce to the minimum the ambiguity due to apparent blanks.

It is, however, realized that at present these aims can be partially achieved in only a few highly specialized laboratories. As a practical compromise, for each region the best combination of informative sera available should be decided upon and used by all the typing centres. It must be emphasized that the use of only a few randomly chosen sera is totally unjustified and cannot be regarded as adequate tissue typing.

At present, as well as ABO, the factors to be typed for as the acceptable minimum are the HL-A antigens that have received official recognition through the Committee for the Nomenclature of Leucocyte Antigens. Sera positively associated with certain specificities such as 4a and 4b as well as other anti-HL-A sera should also be added, to increase the chance of detecting relevant incompatibilities.

Choice of techniques

The techniques used for tissue typing (which at our present state of knowledge is HL-A typing) should be:

(a) reproducible;
(b) so quick in performance that they enable cadavers to be typed rapidly; and
(c) of the micro variety, so that the limited supply of good antisera is taken into consideration.

An increasing number of HL-A antigens are being recognized on leucocytes, lymphocytes, and

platelets, and the following techniques more or less fulfil those criteria:

(1) lymphocytotoxicity;

(2) complement fixation;

(3) leuco-agglutination.

Lymphocytotoxicity. This test can be done in two hours or less and only microlitre quantities of antiserum are required for one test. It can recognize a larger number of HL-A antigens than any other technique and is the preferred technique today. However, because of very restricted supplies of good antisera defining some of the HL-A antigens, other techniques are being used in some regions.

Complement fixation with platelets. This technique is less sensitive than lymphocytotoxicity and requires larger volumes of antiserum. Micro-modifications are under investigation and an increasing number of HL-A antigens can be recognized with this technique. The ease of storage of platelets at 4°C and the suitability of the test for quantitative work make it useful.

Leuco-agglutination. The number of HL-A antigens that can be defined with this technique is somewhat limited. Paradoxically, agglutinating sera active against some specificities are more frequently encountered than sera active in the other techniques. A few specificities, especially those of other genetic systems such as those of the F II or NA systems, can be defined only with agglutinating antisera.

The three techniques supplement one another, but it should be stressed that the sera and techniques used in any one exchange region should be uniform. It is recommended that cells (lymphocytes, platelets, or other tissue) from donors and recipients should be preserved for re-evaluation of the matching.

Other techniques such as mixed lymphocyte cultures and typing of fibroblasts and other cells might also be considered. However, they are all time-consuming and impracticable for the typing of cadavers, and although they might give valuable information they must, for the time being, be considered as experimental as far as the exchange of organs is concerned.

Production and standardization of typing reagents

Restrictions on the supply of typing reagents are today the limiting factor in reliable HL-A typing and the search for new reagents must be given a very high priority.

The main sources for typing reagents are the following:

(1) sera from women immunized by pregnancies;

(2) sera from patients immunized by blood transfusion (febrile transfusion reactions);

(3) sera from volunteers immunized by skin grafts and/or injections of blood cells; and

(4) sera from patients who have been grafted with organs or skin (burns).

Sera from pregnant women are one of the main sources of good reagents, but it should be realized that thousands of sera have to be screened in order to find a reasonable number of good monospecific reagents. HL-A typing of the whole family might help in defining the specificity of the antibody in question. Sera from all pregnant women should be screened, as 10%-20% of sera from primagravidae contain antibodies and the chance of finding monospecific reagents must be greater the lower the number of stimulations in the form of pregnancies.

Sera from patients suffering febrile transfusion reactions may contain very strong antibodies, but because of the often large number of transfusions given these antibodies are prone to be polyspecific in agglutination or cytotoxicity tests. However, they are a good source of reagents—often after dilution—for the complement-fixation technique.

Planned immunization, conducted in an ethical manner, of volunteers by skin grafts and blood cells is an extremely efficient procedure for the production of antisera under certain highly specific conditions. A number of excellent antibodies have been prepared in this way, but the ideal conditions are difficult to achieve.

Antibodies formed during the reaction against a graft may also be extremely valuable in certain instances.

It is quite easy to find antibodies by screening procedures in the material mentioned, but it should be emphasized that only a minority of the antisera found turn out to be good monospecific reagents and, even when they are found, considerably more effort is required for their proper characterization by absorption and testing on panels of donors of known and representative phenotypes.

A limited number of centres in the region will do HL-A typing, and they and other centres, such as blood banks, should also establish screening procedures for the detection of new antisera. When antisera are found the preliminary investigations
should be done locally and those that are promising should be shipped to the regional centre for further evaluation and standardization. Whenever possible, quantities should be collected by plasmapheresis under fasting conditions as soon as the antibody is recognized. The standardization procedures should follow the rules proposed by the Committee for the Nomenclature of Leucocyte Antigens.¹

DATA PROCESSING

The data-processing system shared by a group of medical centres co-operating in organ exchange should be used to assist the physicians responsible to achieve the best matching of an available donor with the waiting recipients in the shortest possible time.

Because the logistics of organ exchange within a large region are greatly complicated by the need to identify rapidly the most suitable histocompatible recipient, a data-processing system becomes essential. The larger the pool of recipients awaiting a transplant, the more complex the system will become.

Standardization of data

The co-operating centres within a region should agree on:

(a) a standard typing system;
(b) a standard data format;
(c) criteria for matching; and
(d) the priority to be assigned.

Three methods of data processing are currently employed.

A matching system based on visual scanning. An example of this type of system, using punched cards, is used in Scandiatransplant. The advantages of this system are that it is inexpensive and does not require a computer. The system becomes cumbersome for large numbers of recipients.

A system providing a computer listing of the recipients. The recipients are grouped according to their phenotype so that, upon referring to an index, those most suitable for a given donor can be easily found. A system of this type is currently used by Eurotransplant. The system makes efficient use of computing facilities and makes it possible to detect errors readily; and the print-out is clear and can be read by a relatively untrained person. The disadvantages of the system are that a computer is necessary and that revised copies of the listing must be distributed to the collaborating centres at frequent intervals.

A system of direct on-line computer access to a large file of recipients maintained on a computer disc. This system is being used in Los Angeles. A cathode-ray-tube terminal in the typing laboratory is used daily to enter new patients directly, remove patients, and detect phenotypically identical recipients. A print-out is made weekly on the kind of transplant, the ABO groups, and the tissue types to be used if the machine fails.

The advantage of this system is that it permits rapid updating and rapid retrieval of the data, but it requires highly sophisticated computer facilities.

Communication

Good communication, both between and within centres, is necessary for the proper functioning of any of the systems described. Eurotransplant has found that Telex communication between centres is useful. Telephonic communication via teletype terminals is being used in the US Eastcoast system.

Collection of clinical data

The evaluation of the efficacy of histocompatibility matching requires that a system be established for the uniform collection of data on the patient and donor. This should include information concerning:

(a) the identity, age, sex, race, and disease state (as given in the International Classification of Diseases) of the donor and recipient (and in the case of living donors the relationship to the recipient); and

(b) the date, name of surgeon, and hospital where the transplantation was performed.

Survival data should be updated at least yearly and include the date of death of the patient or the date he was last reported alive, the date of removal of the transplant, the cause of death (according to the International Classification of Diseases), and whether the diagnosis was based on autopsy. The evaluation of clinical data should carefully distinguish between graft failure from immunological causes and failure for other reasons.

SOURCES OF TISSUE AND ORGAN DONORS

For the reasons mentioned above, transplantation centres and/or countries are forming pools of reci-


² By transplantation centre is meant several specialized units in one locality that together are concerned with the transplantation of tissues or organs.
patients for organ transplantation. When the donor of an organ is a living person, the policy in general will be to send him to the centre where the organ is going to be transplanted. Therefore, it will be only when they are from cadavers that organs will have to be sent from one centre or country to another. Several matters thus have to be regulated between the participating transplantation centres and/or countries. Bone marrow, unlike organs, can easily be removed from living donors and preserved in the frozen state; it will therefore not be discussed.

(1) As many hospitals as possible in each participating centre or country should assist in obtaining donors. It is therefore anticipated that each transplantation centre will also obtain organs from peripheral hospitals. It will be necessary to designate someone in each contributing hospital to be responsible for organ collection. Such a person (or persons) must be approved by and receive instructions from the transplantation centre. In most cases he will be a surgeon who has been trained in the transplantation centre in organ removal and preservation techniques.

(2) The potential organ donor must be pronounced dead by a physician who neither belongs to the transplantation team nor is involved in the removal of the organ or organs.

(3) Criteria for the suitability of organ donors should be drawn up. It could, for example, be decided which age-groups are acceptable in the particular region and which diseases make a patient unacceptable as a donor. An autopsy should be performed immediately after the organ has been removed to exclude undiscovered disease and for legal purposes. Another point of importance is that the maximum acceptable period of cold and warm ischaemia should be determined and observed.

(4) The legal aspects of organ transplantation will primarily be a matter for each individual country. One point of great importance is the question of liability, i.e., who is responsible in the case of a mishap.

When organs are going to be exchanged between different countries, special bilateral or multilateral contracts will have to be drawn up between the countries. Supranational organizations could be most helpful in drafting these international contracts, as the Council of Europe was, for example, for the exchange of therapeutic substances of human origin.

(5) When large pools of patients are compared with a specific donor it could happen that several of them, as far as histocompatibility is concerned, will be equally acceptable. Some criteria that will help to decide which of the patients is or are going to receive the organ or organs could be envisaged, for example:

(i) One is that preference should be given to a patient from, or nearest to, the centre that procured the donor.

(ii) Another is the severity of the disease and the period the patient has been on dialysis.

(iii) A third, other conditions being equal, is the rarity of his phenotype, since one of the recipients may have a poor chance of finding another compatible donor.

(iv) A fourth, in the absence of any other consideration, is that the organ should be assigned to the centre that has procured the largest number of donors.

(v) A fifth is the absence of a positive cross-match with a recipient known to have preformed antibody.

PRESERVATION AND TRANSPORT OF ORGANS

Since most tissues and organs deteriorate rapidly in function after death or removal from the living body, it is essential to use the best possible methods of keeping the patient and, in special cases, the organ in condition before it is removed. Various special preservation procedures have been and are still being introduced. It would be desirable for centres to decide on the most practicable methods for short-term and long-term preservation and to adopt uniform procedures, modifying them as better methods become available.

It is clear that the conditions under which organs are transported are governed by preservation procedures. Transportation should generally be organized by the centre that procures the donor in order to save as much time as possible. The cost of such transportation should be paid at the receiving end. It would be advisable to establish or utilize the services of a special organization to regulate and organize the transportation of organs, and each participating centre and/or country should contribute to the costs of such an organization.

A supranational organization could facilitate the transport of organs across customs boundaries, as has been done for therapeutic substances of human origin.
## Organ Exchange Programmes

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<th>Euro-transplant</th>
<th>Eurotransplant: Italy (ETI)</th>
<th>Scandinavia: transplant</th>
<th>Eurotransplant West</th>
<th>US East Coast system</th>
<th>Los Angeles (local) system</th>
<th>Los Angeles (USA) system</th>
<th>Geneva system</th>
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<tbody>
<tr>
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<td>Benelux and Federal Republic of Germany</td>
<td>Italy</td>
<td>Denmark, Norway (Oslo), Sweden (part)</td>
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<td>Central Atlantic coastal area, Eastern USA</td>
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<td>Air</td>
<td>Car</td>
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* Eurotransplant, University Hospital, Leiden, Netherlands. Further information can be obtained from Professor J. J. van Rood.
* Eurotransplant: Italy (ETI), Institute for Organ Transplants, National Research Council, Rome, Italy. Further information can be obtained from Professor Ceppellini.
* Scandinavia transplant, Blood Bank, Municipal Hospital, Aarhus, Denmark. Further information can be obtained from Dr F. Kissmeyer-Nielsen.
* Eurotransplant West, Hôpital St. Louis, Paris, France. Further information can be obtained from Professor J. Dausset.
* System operated by Dr D. Hume, Medical College of Virginia, Richmond, Va., USA. Further information can be obtained from Dr Bernard Amos.
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The number of topics that could be studied in relation to organ transplantation is almost endless. The following are specially relevant to national and international collaboration.

(1) It is necessary, from the very nature of any project based on collaboration between different units, that procedures, techniques, and criteria for recording and evaluating results should be as uniform as possible. This should be achieved first among units engaged in the same programme, then among different programmes.

The need is particularly urgent to adopt standard techniques for tissue typing, for the collection of reference sera, and for the distribution of the same or equivalent typing reagents on a worldwide scale. Experience has already shown that tremendous progress has been made in this respect, through international workshops and close collaboration between experts. Such international collaboration, as in the case of the nomenclature of leucocyte antigens, should be encouraged.

The problem of establishing a worldwide pool of recipients (starting with very rare phenotypes) for a future world transplant exchange scheme deserves to be studied on the international level.

(2) The collection of clinical data and the follow-up of patients is another problem of paramount importance that has not yet found a satisfactory solution. Detailed information on the results of transplantation can best be obtained at a regional level, and it is a matter of urgency that an analysis be made so as to evaluate the "strength" of histocompatibility antigens or alleles. Objective information collected on a worldwide scale from donor-recipient pairs of known phenotypes on the function of the graft, the frequency and severity of rejection crises, and the nature and dosage of immunosuppressive drugs required would lead to a rapid solution of the problem.

(3) Circulating antibodies against tissue antigens from the donor will cause rapid rejection of the grafted tissue in most transplantations. Research aimed at refinement of cross-matching procedures is required in order to avoid this risk. Further research is also needed on the antibodies important in glomerulonephritis and on the consequences to the patient of the reaction against the graft.

Blood transfusions are the major cause of the production of these circulating antibodies. It is believed that the use of blood with few leucocytes and platelets reduces the risk of sensitization, but further research on this is required.

Individual cases of successful transplantation have been recorded in the presence of antibodies. Investigation into the possible enhancing effect of some circulating antibodies is therefore of great interest.

(4) Tolerance is readily induced in certain combinations of laboratory animals, but not in others. Low-dose tolerance can similarly be induced to certain soluble antigens, but apparently not to others. As human phenotypes become better characterized and purified antigen preparations more readily available, attempts at inducing tolerance will become practicable. It seems that the greatest probability of success will occur in exchanges between subjects who are highly compatible for HL-A factors.

(5) It is important to devise uniform procedures for the short-term preservation of different organs, so that tissue typing and organ exchange can be done within the time available. Identical containers should be used for the transport of organs. More experiments are needed to find out if long-term preservation is better achieved by perfusion, in vivo banking, or deep freeze. Tests should be devised to check the vitality of an organ after preservation.

Participating centres should exchange experience in this field and direct their experiments towards suitable and improved methods.

ANNEX

Although matching for transplantation antigens is not yet routine when cadaver organs are used, in a number of centres it is already being done. The most pertinent data are shown in the accompanying table.

It should be pointed out that experience with the kind of programme shown in the table has so far rarely exceeded one year. For that reason all the figures given represent first attempts only and should not be considered to represent the best attainable results.

The list of programmes is by no means complete but represents the experience of the signatories.

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RÉSUMÉ

CONDITIONS FONDAMENTALES REQUISES POUR LES ÉCHANGES INTERNATIONAUX D'ORGANES DESTINÉS À LA TRANSPLANTATION

Le rejet de l'hétérogreffe est une réaction immunitaire due à la présence dans les tissus transplantés de facteurs d'histocompatibilité qui ne se trouvent pas dans les tissus du receveur. Le typage tissulaire, basé sur l'emploi de méthodes sérologiques, en permettant d'identifier un certain nombre de ces antigènes, facilite le choix de la combinaison optimale donneur-receveur. Le rôle des facteurs des systèmes HL-A et ABO en tant que principaux antigènes d'histocompatibilité est maintenant clairement établi et c'est de leur compatibilité au moment de la mise en présence des tissus de donneur et de ceux du receveur que dépend en grande partie la survie du greffon. En raison du polymorphisme génétique très accentué du système HL-A, il n'existe cependant que peu de chances (moins de 1 sur 1000) de découvrir deux sujets non apparentés porteurs du même phénotype HL-A. L'objectif est donc de tirer profit des méthodes de typage tissulaire, de rechercher la compatibilité la meilleure possible entre donneur et receveur et d'utiliser au mieux le matériel tissulaire, rare, destiné à la transplantation. Ce but ne peut être atteint que si l'on dispose d'un groupe de receveurs (préalablement caractérisés par typage cellulaire) suffisamment important, de façon que chaque organe susceptible d'être greffé puisse être attribué à un receveur présentant le degré requis de compatibilité. Il peut devenir nécessaire d'assurer le transport d'organes à de longues distances et entre différents pays, ce qui implique une action concertée des centres de transplantation établis dans une région, un pays ou même plusieurs pays afin de permettre les échanges indispensables. Ce sont les modalités de ces échanges qui sont esquissées par les signataires du présent mémoire, consultés à l'initiative de l'OMS. Ce document traite de la question en termes généraux, mais l'exemple de la transplantation rénale, qui est en passe de devenir un procédé thérapeutique courant dans les cas d'insuffisance rénale irréversible, est fréquemment cité.

L'introduction du mémoire est consacrée à un examen d'ensemble des problèmes que pose la transplantation d'organes. On y expose des considérations sur les méthodes actuellement utilisées, les difficultés rencontrées et les résultats obtenus, et on y trace les grandes lignes d'un programme destiné à favoriser une éventuelle collaboration sur le plan national et international.

Le chapitre suivant traite longuement du typage cellulaire, décrivant en termes généraux les facteurs d'histocompatibilité, leur rôle dans la survie du greffon, leurs aspects génétiques, vus sous l'angle des connaissances actuelles et des nécessités de la recherche future. On définit les critères qui doivent présider au choix des antigènes servant aux types tissulaires, on discute de l'interprétation des données ainsi recueillies et on mentionne brièvement les techniques actuellement en application: éprouve de lymphocytotoxicité, de fixation du complément et de leuco-agglutination.

La question de l'approvisionnement en sérum de typage et de leur normalisation est ensuite évoquée. Le dépistage et la caractérisation de nouveaux sérum sont parmi les objectifs prioritaires. La complexité des problèmes que pose la mise sur pied d'un programme concerté d'échanges rend indispensable le recours aux méthodes modernes de traitement des données.

Les possibilités d'approvisionnement en organes et en tissus destinés à être greffés, le choix de donneurs appro-
priés, les modalités du prélèvement, de la conservation et du transport — sans parler des aspects administratifs et légaux de la transplantation — sont autant de questions qui doivent être résolues collectivement par les centres spécialisés. Le mémoire énumère un certain nombre de critères susceptibles de faciliter le choix du bénéficiaire prioritaire, lorsque les recherches d'histocompatibilité montrent la possibilité de greffer un ou plusieurs organes d'un donneur spécifique à plusieurs receveurs.

La dernière partie du document définit un certain nombre de secteurs de recherche, en relation avec la transplantation d'organes, qui sont d'un intérêt tout particulier pour le développement de la collaboration nationale et internationale. Enfin, un tableau annexe résume un ensemble de données sur les activités d'échanges d'organes déjà en cours dans différents pays: nombre de centres chirurgicaux et de laboratoires de typage tissulaire, nombre de receveurs potentiels, nombre d'organes (prélévés sur des cadavres) typés et utilisés, nombre d'antigènes HL-A disponibles, nature des techniques sérologiques mises en œuvre, procédés de traitement des données et moyens de communication et de transport.