

Animal-to-human organ transplants – a solution or a new problem?

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Xenotransplantation is seen by some mainly as an opportunity and by others mainly as a danger. It could help overcome the shortage of organs from human donors, but it raises a number of questions, particularly about safety, ethics and human nature. This article reviews the progress of research, debate and decision-making in this area.

Voir page 59 le résumé en français. En la página 59 figura un resumen en español.

The current definition of xenotransplantation includes the grafting of cells, tissues or organs from non-human animal species into humans (although technically it can be the other way round or between any two species). It is obviously a subject that has fascinated people for a long time because we find examples of this kind of organ grafting in the mythologies of many religions. Perhaps the one best known is the grafting of the head of an elephant onto the body of the boy who went on to become the very popular Hindu god, Ganesha. The fascination seems now to have reached fever pitch, with high stakes for those concerned, particularly patients, scientists, the biotechnology industry, and infectious disease specialists. We seem to be poised on the brink of clinical success, but with advocates on opposite sides of the argument about whether we are ready to embark on large-scale clinical trials of vascularized whole organs or not. In this presentation I will try to capture the main elements that have brought us to this pass, where we have a division between “those who want to get it right” and “those who want to get it right now” (1).

Short history

In modern biomedicine there have been efforts at xenotransplantation dating back to the early part of this century, well before we knew anything about the immunological principles underlying transplantation in general. Most of these efforts have failed, although in one of Keith Reemtsma's patients in the 1960s a chimpanzee kidney did survive and work for about nine months (2); we do not know why this success occurred, as there were no powerful immunosuppressive agents in the 1960s, and no so-

phisticated immunological or genetic manipulations of donor or recipient. Table 1 is a summary of these transplants.

In the very modern era, which I will define as anything after 1980, we have had a number of well-publicized whole-organ (vascularized) xenotransplant attempts, as well as several less-publicized cellular and tissue transplants. These provide us with an opportunity to examine and define the issues of current concern in xenotransplantation.

Sources of discomfort

There are many issues that make people uncomfortable about xenotransplantation. At a very fundamental level it seems to transgress those boundaries which define us as human, and so challenge and threaten our identity and sense of order; the sense of order and disorder, according to some anthropologists, is the very basis of our entire cognitive world.

In some Eastern mythologies we do have a certain amount of fluidity between the human and animal categories, with movement in both directions. It may be tempting to speculate on this basis that these cultures would easily assimilate xenotransplantation, but it can also be argued that this very fluidity might make people anxious to maintain clearly distinct categories in the physical world.

In the Islamic and Judaeo-Christian traditions the concerns are easy to identify, and fundamental amongst them is the question of morality: man is held accountable because he has choice and responsibility. Is this responsibility as a moral agent reduced if one's functioning depends on a foreign organ? Will the characteristics of the animal be incorporated into the consciousness of the human recipient? Of course, at present, there is no scientific evidence with which to answer such questions, but as we begin to transplant pig neural tissue into the human brain and demonstrate neuronal connection between the two

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(as has already actually been done), and as the purpose of the transplant is to restore biochemical activity and neural transmitters, surely it is time to raise them.

At the psychological level we have very little information about the possible effects of the xenotransplant on the recipient. Will someone who harbours the heart of a pig begin to worry about this? In allotransplantation, partly because of the neurotoxic effects of drugs such as the corticosteroids, ciclosporin, and FK506, we do see psychological problems (3) and there certainly are examples of recipients beginning to identify with imagined or real qualities of the donors. The drugs used in allotransplantation, some of which are very likely to be used in xenotransplantation as well, lead to bodily changes such as hirsutism, rounded facies, obesity and hypertrophied gums. In fact, in their extreme forms these dramatic changes can make the recipient look a little simian - and one can imagine the kind of comments from schoolchildren if they suddenly learn that their odd-looking classmate has recently received the liver of a baboon.

Xenotransplantation after 1980

In 1982, in Loma Linda, California, a team of surgeons led by Dr Leonard Bailey transplanted the heart of a baboon into Baby Fae, an infant born with hypoplastic left heart syndrome. Dr Bailey's team proceeded because it had some laboratory evidence that xenotransplants would work, but also because the powerful new immunosuppressive drug, ciclosporin A, became widely available to transplantologists in the United States at about this time. The operation was technically successful, and the child lived for about three weeks before the heart was rejected. In the early days after the transplant the media were full of praise for the operation and its success, but this soon turned sour when the child died. Questions were asked about the adequacy of the information given to the parents. The surgeons were faulted for not looking hard enough for a human heart to transplant, and for being too optimistic. The scientific evidence, in retrospect, was inadequate and many have come to view the Baby Fae episode as having had an overall negative effect in the field of xenotransplantation.

In 1992, the team that was most advanced in the quest for success in xenotransplantation was the one led by Dr Thomas Starzl in Pittsburgh. In the 1960s Starzl had performed about half a dozen baboon-to-human kidney transplants, all of which subsequently failed. This time his team had permission to perform four baboon-to-human liver transplants. The experimental nature of these attempts naturally leads to the selection of very sick persons; thus the first recipient was a patient with advanced AIDS and near-terminal hepatitis. This time, too, there was an extremely powerful new immunosuppressive drug called FK506, which is 100 times more

powerful than ciclosporin A on a weight-for-weight basis. Powerful immunosuppression means greater predisposition to lethal and generalized infections, and so both of the first two patients succumbed.

Interestingly enough, after the death of the second patient, Dr Starzl's team decided not to go ahead with any more transplants; in 1995, in an interview with a reporter from the *Scientist*, Dr Starzl indicated that he thought there was not enough scientific knowledge to do any more xenotransplants, and that, although they had permission to perform two more, they would have been "nuts" to have done them (4).

At about this time, the field was progressing very rapidly in terms of accumulation of relevant scientific knowledge. The Pittsburgh team documented microchimaerism in transplant recipients, especially those who had had a (human) liver transplant, and there was speculation about whether this phenomenon, by setting up a subclinical level of graft-versus-host disease, somehow blinded the recipient's immune systems to the graft (5); in some instances this active biological accommodation was so effective that chemical immunosuppression could be stopped without graft rejection.

From the same scientific milieu in Pittsburgh came the discovery by Dr Suzanne Ildstad of putative "facilitator" cells - a distinct subpopulation of cells that facilitates the engraftment of bone marrow transplants (6). Subsequent evidence seems to

Table 1. Animal organs transplanted into humans, 1906-1995

Donors	Organ	Transplants	Survival time	Author	Year
Pig	Kidney	1	3 days	Jaboulay	1906
Goat	Kidney	1	3 days	Jaboulay	1906
Macaque	Kidney	1	32 hours	Unger	1910
Sheep	Kidney	1	9 days	Neuhof	1923
Baboon	Kidney	1	4 days	Hitchcock	1963
Macaque	Kidney	1	12 days	Reemtsma	1963
Chimpanzee	Kidney	3	9 months	Reemtsma	1963
Baboon	Kidney	6	60 days	Starzl	1963
Chimpanzee	Kidney	1	-	Hardy	1964
Chimpanzee	Kidney	1	1 day	Hume	1964
Chimpanzee	Kidney	6	one 9 mths	Reemtsma	1964
Baboon	Kidney	6	max 60 days	Starzl	1964
Chimpanzee	Kidney	31	49 days	Traeger	1964
Chimpanzee	Kidney	2	4 months	Goldsmith	1965
Chimpanzee	Kidney	1	31 days	Cortesini	1966
Pig	Heart	1	0 days	.	1968
Baboon	Heart	1	-	Barnard	1977
Baboon	Heart	1	20 days	Bailey	1985
Pig	Heart	1	< 1 day	-	1992
Baboon	Liver	1	70 days	Starzl	1993
Baboon	Liver	1	26 days	Starzl	1993
Baboon	Bone marrow	1	-	Gorman	1995

Source: Mohacsi, Thompson and Quine (27)

Other sources indicate that in fact there have been eight xenogeneic heart transplants and 11 xenogeneic liver transplants, of which one was with a pig liver (C.G. Groth, personal communication, August 1998).

have borne out its existence in animal models. Dr Ildstad suggested in 1995 that a baboon-to-human bone marrow transplant could be used to cure a patient with advanced HIV infection. She did not perform this experiment in Pittsburgh, but was able to collaborate with clinicians and scientists at the University of California, San Francisco. The recipient was a 38 year-old AIDS activist from Oakland, California, called Jeff Getty, who was himself suffering from AIDS and was not expected to live long; the theory was that if his marrow was partly reconstituted by that of a baboon (to develop chimaerism), he would be much improved because baboon lymphocytes are not infectable with HIV.

This is a very instructive episode in the annals of xenotransplantation from a number of different perspectives which illustrate the current issues of concern in the field. From the regulatory point of view in the United States, the freewheeling days when any surgeon could transplant an organ from an animal with the permission only of the local Institutional Review Board were over. All such experiments now required a specific Initial Notification of Drug application to the US Food and Drugs Administration (FDA). The field was new, and so the FDA set up a panel to review the application. Arguments in favour of proceeding were that this was a valid experiment, that the scientific justification was adequate, and that if the experiment was not done in the United States it would be done elsewhere, and the United States would lose out. The opposing arguments were that the risk of infection from known and unknown viruses in the baboon bone marrow was just too high to ignore, and that contacts and the public might be exposed to a risk whose extent was unquantifiable.

Two things influenced the decision to proceed: one was the powerful lobbying from Getty's family, and of course from the scientists and clinicians who were advocating the transplant. The other was the persuasive argument that the patient was likely to die anyway, and so the risk of spread of infection would be minimal. The transplant went ahead, and although it did not succeed in terms of engraftment of the bone marrow, it did succeed in terms of making the patient better (higher T-cell count, general well-being in the months after the transplant). Three years later he is alive, apparently in fairly good health, and writing and speaking on behalf of experiments using animals, especially in HIV infection (7).

Increased awareness of risk of infection

The emphasis in discussion of xenotransplantation has changed from concern about the rights and welfare of potential non-human source animals to concern about the risk of zoonoses. One of several things that brought this change about was a letter published by Dr Jonathan Allan and about 40 other scientists, including a number of virologists, who

pointed out the real dangers of infection from non-human primates (8). The authors of the letter and others again reminded us that, almost certainly, HIV came from simian sources, and that the incubation period of retroviruses can be many years before any clinical symptoms are manifest. We were also reminded that if these infections were transmitted to the recipient, they could be rapidly lethal because of the heavy immunosuppression, and could also be transmitted, theoretically, to immediate contacts and even to the public.

This widely publicized letter was written in response to the draft guidelines for reduction of the risk of zoonoses published by the Public Health Services (9), a federal umbrella body which encompasses both the FDA and the Centers for Disease Control and Prevention (CDC) in the United States. The main point of the Allan letter was that these guidelines were not strict enough, that the risk of infection from non-human primates was real enough, and that we should therefore embargo the use of primates completely.

The Public Health Service draft guidelines were also criticized by other organizations, including the American Society of Transplant Physicians. The criticisms included the vagueness of the document regarding the funding of the regulatory instruments and, again, its failure to exclude the use of primates.

Guidelines

In 1994 and 1995 something stirred those concerned with ethics and public policy in both Europe and the United States. In January 1995 in the United Kingdom the Nuffield Council on Bioethics set up a Working Party to look at many xenotransplant issues and it produced a report, which came out in 1996 (10). Subsequently the United Kingdom Government's Advisory Group on the Ethics of Xenotransplantation examined a similar range of issues and came up in 1997 with the definitive Kennedy Report (11), named after its admirably capable chairman, Professor Ian Kennedy.

The essence of the Kennedy Report was that it was worth pursuing xenotransplantation research, and that using pigs, but not non-human primates, as source animals would be ethically acceptable. Furthermore, it was ethically acceptable to alter the pig's genome to the extent foreseen so as to facilitate the transplant, provided the pig remained recognizably a pig. Primates could ethically be used only as recipients, in small numbers, in animal-to-animal experiments.

Non-human primates were not ethically acceptable as source animals partly because of the emotional attachment that human beings have to them, and partly because their being phylogenetically closer to man increases the risk of infection. In comparison to the pig, there were other disadvantages such as their depletability, slow breeding, small lit-

ters, and the fact that there are no specified-pathogen-free (SPF) colonies of primates, while there are such SPF colonies of pigs. These factors also mean that the cost of breeding non-human primates for xenotransplantation would be prohibitive. Furthermore, the organs of primates are often too small for humans.

The pig, on the other hand, has lived close to man for many generations without spreading any serious infections (leaving aside the swine-flu epidemic); its physiology is quite similar to man's; its organs are roughly the same size; it breeds very quickly, has large litters, and in any case is eaten by millions of people throughout the world. The matter of physiology, however, is not yet really resolved – particularly for major synthesizing organs such as the liver, which would be pouring out pig molecules into the human recipient's circulation. Also, not much is known about the response of these organs to normal homeostatic signals. This is a subject that has not received the attention that it really deserves (12).

The most significant conclusion of the Kennedy Report was that the base of scientific knowledge was inadequate in 1997 to proceed to clinical trials, and that there should be an effective embargo until a formal regulatory authority was established, with an opportunity to review the evidence at the time of submission of any applications to it. The Government of the United Kingdom rapidly responded by setting up the Xenotransplant Interim Regulatory Authority under the Chairmanship of Lord Habgood.

In the United States the consultation process was initiated by the Institute of Medicine, which held a workshop in June 1995, and its report was published in 1996 (13). Its conclusions differed from the Kennedy Report's in that non-human primates were not excluded as source animals, and the scientific base was considered to be adequate to "proceed with caution" to clinical trials. The American approach was emphatically to have an *advisory*, not a regulatory, body to deal with xenotransplantation.

International consultation

By 1997 it was obvious that there was a risk to the public's health, that the magnitude of this risk was not really known and was perceived differently by different countries, and that there were a number of ethical, social and cultural ramifications to xenotransplantation. There was a distinct need for an international and interdisciplinary dialogue. The World Health Organization responded to this global challenge by convening a consultation in Geneva in October 1997. Participants included experts from several countries in Europe, as well as from Canada, Cameroon, Japan, Oman, the Philippines, Sri Lanka and the United States. The main tasks given to the consultation were to work out technical and ethical guidelines to minimize the risk of

infection, safeguard human dignity and human rights, and ensure animal welfare.

Despite the apparent differences of approach and perceptions amongst the participants, the consultation was very successful, and formulated a unified set of recommendations. One of the points that became clear was that if xenotransplantation did succeed, developing countries might well be among the main beneficiaries. This is because in most of the developing world organ replacement therapies such as haemodialysis are beyond the means of governments or individuals, and organ transplantation, especially through cadaveric donation of organs, has not really taken off. For many of these countries, at the current level of expenditure, allotransplantation necessarily has lower priority than basic public health needs. Here, xenotransplantation holds out the hope that one day, when the ethical, technical, infectious disease and cost problems have been resolved, developing countries will be able to embark on this type of transplantation without having to divert too much of their scarce resources to it. The fundamental need for international cooperation in research, communication and standardization was recognized. The report of the WHO Consultation was issued in February 1998 (14).

Cellular and tissue xenotransplants

In 1993 a Swedish team transplanted 10 diabetic patients with pig islets of Langerhans. None of them succeeded in producing pig insulin in the long term, but the experiment is nevertheless important because the future of xenotransplantation may well lie in such cellular transplants for very common conditions such as diabetes mellitus. The other significant outcome of this experiment was important data on the presence or absence of risk of viral infection. All 10 of the patients have developed antibodies to pig viruses, some to the influenza virus and some to picornavirus. According to the Swedish team, none of the patients has actually become sick with any pig viruses, and they believe that there is a possibility that the antibodies may simply be cross-reactive (Anne Tibell, personal communication, 1998).

Neural tissue transplants have been performed from pig to man to alleviate Parkinson disease and more recently for intractable epilepsy. One of the patients treated for Parkinson disease died of other causes; a post mortem examination showed connections had developed between the pig neural tissue and his brain — answering a critically important biological question, but at the same time raising philosophical and theological questions about the brain, identity and responsibility.

Summary of current status

The field is moving very rapidly. There are a number of important stakeholders, and the stakes are high for some of them. Major research is now being

funded and carried out by venture-capitalized biotechnology companies, and one of the considerations in the current discussions is the part played by these companies in determining the timing, the technology and the development of xenotransplantation as a whole.

There is a distinct difference in the approaches to xenotransplantation in Europe and the United States. In Europe the feeling is that the scientific base is inadequate to proceed to clinical trials and so there is at present an effective embargo. In the United States the consensus seems to be that further laboratory and animal-to-animal experiments will not answer the key questions, and that the only way to advance the scientific base is to "proceed with caution" (15) to clinical trials. In the United States, therefore, while the Public Health Services draft guidelines are becoming more strict in response to comments, criticisms and consultations, the Food and Drug Administration has been receiving applications. It has already authorized a number of clinical trials, most of which at present involve cells and tissues rather than whole vascularized organs, although a number of researchers are preparing for the latter. Furthermore, rather than completely excluding the use of non-human primates, the approach in the United States is to set the requirements for their use at levels that are virtually impossible to achieve. This effectively embargoes their use without actually using the dreaded term.

The question of consent to the clinical trials, especially in the early patients, is likely to be a vexed one. We have argued (16) that some of the fundamental traditional principles of consent would need to be violated, and that because of the continuing need to monitor the patient and perform invasive investigations even if the graft failed, the agreement may need to be more of a contract, with specifically binding requirements, than the traditional consent whereby the patient has the right to withdraw at any time from the experiment. Since the community is in a sense being put at risk, there is a real argument for considering some form of community consent as well – but at present, with our inability to quantify the xenozoonotic risk (to calculate the risk–benefit ratio), it is not clear how far we should push this point. In any case, there is little experience in obtaining such community consent.

On the purely scientific side, the evidence has accumulated rapidly on both sides of the divide. On the one hand, our understanding of the hyperacute rejection phenomenon is increasing, and scientific enquiry is already being directed to the subsequent "delayed xenotransplant reaction". More and more animal models are being developed; and immunological manipulations are becoming more sophisticated. Animal models have been developed which

no longer express on their endothelium the alpha-gal molecule, which is the main target of the antibodies mediating the hyperacute rejection response. Also, transgenic animals have been developed which express on their endothelium human molecules such as the decay-accelerating factor, which helps to inactivate complement components in a species-specific manner.

At the same time, however, we have growing evidence of viruses, in pigs and in primates, which can theoretically cause xenozoonotic infection. New pig endogenous retroviruses, which would be very difficult to eradicate and which have been shown to infect human cell lines *in vitro* have been described (17). While it is fair to say that there is little evidence that such viruses will be pathogenic in man, it cannot be assumed that they will not become so, especially if introduced into an immunocompromised host. Evidence has also accumulated of trans-species transmission of viruses from pig to man, causing infection, for example, with paramyxovirus in Australia (18), and in the case of primates we now know that the simian foamy virus (and other viruses) can be transmitted via scratches and bites to animal handlers (19).

The effect of xenotransplantation on the donation of cadaveric and living-donor human organs needs to be taken into account. Xenotransplantation itself can be seen as serving one of several purposes: to be a complete substitute for human organs; to supplement human organs, thus alleviating shortage; or to be "bridging" rather than "destination" organs. Whatever the purpose, it would be a setback if the effect was to reduce the supply of human organs because the public now perceives a lack of need since pigs are plentiful, or for whatever other speculative reasons (20). We think that xenotransplants will be very expensive in the first decade of their application, and so, for at least this reason, they will not be an adequate substitute for allotransplantation for at least a decade after xenotransplantation is truly established.

One major issue for developing countries is the phenomenon of "expatriate" experiments: it is possible that, because of restrictions imposed in industrialized countries, researchers may bring these experiments to be done in developing countries, with potentially disastrous results in terms both of safety and of human rights. This is only one of the reasons for which developing countries need to be represented in formulating guidelines for this exciting, challenging and potentially useful new technology. Attempts are now being made to predict factors that would affect the response of the public to xenotransplantation (20), but surveys of public attitudes are beset by deficiencies and are cumulatively contradictory at present (21). ■

Résumé

Les xénogreffes : solution ou problème ?

Ces dernières années ont été marquées par un regain d'intérêt pour les xénogreffes. Cliniciens, scientifiques, spécialistes de l'éthique, analystes politiques et chercheurs ont aujourd'hui des opinions divergentes sur le risque de transmission des xénozooses. Certains veulent dès à présent passer à l'acte et procéder à des essais cliniques alors que d'autres, partisans d'une approche prudente, souhaitent d'abord évaluer les risques. Mais presque tous sont d'accord pour que la science progresse dans ce domaine.

Le battage médiatique suscité en 1982 par la transplantation d'un cœur de babouin chez une petite fille «Baby Fae» en Californie, favorable dans un premier temps, s'est rapidement mué en critiques lorsque l'enfant est décédée. Le Dr Thomas Starzl, qui a effectué deux transplantations de foie de babouin chez l'homme à Pittsburgh au début des années 90, a décidé après le décès du deuxième patient que des recherches supplémentaires s'imposaient avant que d'autres essais cliniques puissent être réalisés. La transplantation de la moelle osseuse d'un babouin sur Jeff Getty, un patient atteint du SIDA, a échoué du point de vue de la greffe mais a été un succès en ce que l'état du malade s'est amélioré.

L'inquiétude suscitée par le risque de transmission des xénozooses a conduit à exiger que les xénogreffes fassent l'objet de contrôles d'autant plus rigoureux que le VIH, par exemple, est probablement d'origine simienne et que plusieurs années peuvent s'écouler avant que la maladie ne se déclare chez l'homme : un argument venant renforcer le sentiment largement répandu que les organes de primates non humains ne devraient pas être transplantés chez l'homme. Au Royaume-Uni, le rapport Kennedy indiquait en 1996 que les xénogreffes pourraient être éthiquement acceptables si le donneur animal était le porc. Mais le rapport appelait à un moratoire jusqu'à ce que soit créé un organe national de réglementation des xénogreffes qui serait chargé de fixer des normes, d'examiner les demandes d'autorisation d'essais cliniques et d'étudier au fur et à mesure les données scientifiques. Actuellement, tout essai clinique doit faire l'objet d'une demande d'autorisation adressée à l'Organe intérimaire de Réglementation des Xénogreffes (Royaume-Uni) qui indiquera au Secrétaire d'Etat à la Santé s'il convient ou non d'accorder cette autorisation. A l'inverse, aux Etats-Unis d'Amérique, le rapport de l'Institut de Médecine, qui date aussi de 1996, a conclu que les données scientifiques disponibles étaient

déjà suffisantes pour «procéder avec prudence» à des essais cliniques. Il était également recommandé de créer un organe consultatif (et non de réglementation) afin de veiller à ce que soient prises toutes les précautions nécessaires. En 1997, l'OMS a organisé une consultation internationale à l'issue de laquelle un certain nombre de recommandations ont été formulées, qui soulignaient, entre autres, le besoin d'une coopération internationale aux fins de la recherche, de la communication et de la standardisation des principes directeurs visant à réduire le risque de transmission des xénozooses non pas simplement chez les receveurs mais aussi chez leurs contacts et dans la population en général.

Des greffes de cellules et de tissus hétérologues pour le traitement de maladies courantes comme le diabète, la maladie de Parkinson et l'épilepsie ont déjà été réalisées. Ce type d'opérations a permis de comprendre certains aspects des xénogreffes, encore que sur le plan clinique, elles n'aient pas donné de résultats probants. En règle générale, lorsque les enjeux sont importants, par exemple, quand des recherches sont financées par des entreprises de biotechnologie à capital à risque, le désir est grand de se hâter pour développer cette technologie et procéder à des essais cliniques. Aux Etats-Unis d'Amérique, la Food and Drug Administration a déjà autorisé un certain nombre d'essais cliniques qui, jusqu'ici, concernent des cellules et des tissus et non des organes vascularisés entiers.

Dans la mesure où le risque d'infection n'intéresse pas seulement l'individu mais en un sens l'ensemble de la communauté, il serait fondé d'envisager une forme de consentement de la communauté. A ce jour, les enquêtes d'opinion sur les xénogreffes ont été peu concluantes, voire contradictoires.

Des études récentes ont montré que sur les dix malades qui avaient reçu il y a quelques années en Suède des ilots de Langerhans de porc, aucun n'a présenté de signe d'infection par des rétrovirus endogènes porcins. Toutefois, il convient de se rappeler que des études *in vitro* ont fait apparaître une infectiosité intercellulaire et que, en tout état de cause, l'absence de preuve d'infection n'est pas une preuve d'absence de risque.

Nous devons poursuivre, mais avec une grande prudence, notamment parce que le coût des xénogreffes sera très élevé au début et que seuls quelques receveurs pourront en bénéficier dans les premiers temps.

Resumen

Trasplantes de órganos de animales: ¿solución o nuevo problema?

En los últimos años se ha reavivado el interés por los xenotrasplantes. La opinión de los clínicos, especialistas científicos, expertos en ética, analistas de las políticas públicas e investigadores está actualmente dividida en lo que respecta al tema del riesgo de xenozoosis.

Algunos desean pasar a la acción y empezar ya los ensayos clínicos, mientras que otros prefieren poner primero en marcha estructuras de evaluación y de minimización de los riesgos. Casi todos, sin embargo, desean ser testigos de avances científicos en ese terreno.

A raíz del trasplante de un corazón de babuino a Baby Fae en California, en 1982, la alternativa del xenotrasplante tuvo gran repercusión pública, al principio positiva, pero más tarde, cuando la niña falleció, negativa. El Dr. Thomas Starzl, quien llevó a cabo dos trasplantes de hígado de babuino a receptores humanos en Pittsburgh a principios de los años noventa, llegó a la conclusión, tras la muerte de su segundo paciente, de que había que llevar a cabo nuevas investigaciones antes de realizar más ensayos clínicos. El trasplante de médula ósea de babuino a Jeff Getty, un enfermo de SIDA, fracasó, pero benefició en cierta medida al paciente.

La preocupación suscitada por las zoonosis ha llevado a exigir que se apliquen controles más rigurosos a los xenotrasplantes, sobre todo teniendo en cuenta la sospecha de que el VIH procede de simios y el hecho de que los retrovirus humanos pueden tardar muchos años en manifestarse. Ello ha conducido además a un amplio acuerdo en el sentido de que no debe utilizarse a primates no humanos como fuente de órganos para el hombre. En el Reino Unido, el informe Kennedy (1996) sostenía que el xenotrasplante a partir del cerdo podía ser éticamente aceptable. En el informe, no obstante, se recomendaba aplicar una moratoria efectiva mientras no se constituyera una autoridad nacional de regulación de los xenotrasplantes que estableciera normas, aceptara solicitudes y analizase los progresos en ese campo de la ciencia. Actualmente, para realizar cualquier ensayo clínico se debe presentar una solicitud a la Autoridad Provisional de Regulación de los Xenotrasplantes del Reino Unido, que aconsejará al Ministro de Salud si debe o no dar su autorización. En los Estados Unidos, por el contrario, en el Informe del Instituto de Medicina (también de 1996) se resolvía que había base científica suficiente para justificar que se pasara «con las debidas precauciones» a realizar ensayos clínicos. Se recomendaba la creación de un órgano asesor, más que de un órgano regulador, para velar por que se observaran las precauciones necesarias. En una reunión consultiva internacional organizada por la OMS en 1997 se formularon diversas recomenda-

nes que resaltan la necesidad de cooperación técnica en materia de investigación, comunicación y normalización de directrices a fin de reducir al mínimo el riesgo de zoonosis, no sólo entre los receptores sino también entre sus contactos y el público en general.

Ya se han realizado xenotrasplantes de células y tejidos contra enfermedades comunes como la diabetes mellitus, la enfermedad de Parkinson y la epilepsia. Esas operaciones han ayudado a profundizar en el conocimiento de determinados aspectos de los xenotrasplantes, pero aún no han tenido gran trascendencia clínica. En general, cuando es mucho lo que está en juego, por ejemplo en las investigaciones financiadas por empresas de biotecnología de capital de riesgo, hay gran interés en potenciar el desarrollo de esas técnicas y en pasar a realizar ensayos clínicos. En los Estados Unidos, la Administración de Alimentos y Medicamentos ha autorizado ya varios ensayos de ese tipo, que sin embargo hasta ahora se han realizado sólo con células y tejidos, no con órganos enteros vascularizados. Dado que el riesgo de infección afecta no sólo a los pacientes sino, teóricamente, al conjunto de la comunidad, parece lógico que deba preverse algún tipo de consentimiento informado por parte del público. Los resultados de las encuestas de opinión pública sobre los xenotrasplantes han sido hasta ahora contradictorios y no permiten extraer conclusiones.

Estudios recientes han mostrado que los diez pacientes que recibieron islotes pancreáticos porcinos en Suecia hace unos años no presentan signos de infección por retrovirus endógenos porcinos, según los análisis realizados con las actuales técnicas diagnósticas. Sin embargo, debemos recordar que los estudios *in vitro* realizados han revelado signos de infectividad intercelular, y que en cualquier caso la inexistencia de pruebas no demuestra la inexistencia de riesgos asociados a esos u otros agentes infecciosos.

Es necesario seguir adelante, pero con mucha cautela, sobre todo considerando que el costo de los xenotrasplantes sería inicialmente muy alto, y que sólo un reducido número de pacientes podría beneficiarse de ellos en los primeros años.

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