Pontifical Academy for life prospects for xenotransplantation scientific aspects and ethical considerations

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Introduction

Transplantation represents a highly successful means of treating a variety of human illnesses. However, the number of transplants performed is limited by a shortage of human organs and tissues[1]. Xenotransplantation, the transplantation of organs, tissues or cells from one species to another, if applied to man, would offer the possibility of a huge supply of organs, tissues and cells for transplantation thereby relieving the «chronic» shortage of human donors.

However, before xenotransplantation becomes a clinical reality, there are practical challenges that must be overcome. One is rejection, the process by which the body of the transplant recipient attempts to rid itself of the transplant. Another is to ensure the correct functioning, across species barriers, of the transplant in its new host. Also, there is the need to minimize the likelihood of the introduction of new infectious agents into the human population via the transplant.

In addition there are concerns about xenotransplantation that require theological, anthropological, psychological and ethical considerations, as well as an examination of legal issues and procedural matters.

First Part: Scientific Aspects

Historical background

1. To date, there is only very limited experience in transplanting xenogenic organs or tissues to humans. The attempts made in the 1960s and early 1970s used immunosuppressive therapies on the recipient to prolong survival of the organ. The most striking success was the nine-month survival of a chimpanzee kidney transplanted into a human by REEMTSMA and colleagues[2]. In the 1980s, a baboon heart was transplanted to a baby (Baby Fae) that survived briefly[3]; however, rejection occurred within a few weeks. In the 1990s, baboon livers were transplanted in two patients by STARZL and colleagues[4]. Those patients

1 Cf. Evans R., Orians C., Ascher N., The potential supply of organ donors; an assessment of the efficacy of organ procurement efforts in the United States. JAMA 1992; 267: 239-46.

2 Cf. Reemtsma K., McCracken B.H., Schlegel J.U., et al. Renal heterotransplantation in man, Ann Surg, 1964, 160: 384.

3 Cf. Bailey L.L., Nehlsen-Canarella S.L., Concepcion W., et al. Baboon-to-human cardiac xenotransplantation in a neonate, JAMA, 1985, 254: 3321.

4 Cf. Starzl T.E., Fung J.J., Tzakis A.G., et al., Baboon-to-human liver transplantation, Lancet, 1993, 341: 65.

survived for 70 days in one case and 26 days in the other.

The first patient was placed on an oral diet on the fifth post-transplant day and spent most of his time in a regular ward, leaving the hospital briefly on one occasion[5]. However, in one of the two cases, a baboon pathogen (cytomegalovirus) was apparently transferred to the patient, even though this did not result in a disease process[6]. However, in both patients there was evidence of an adequately functioning liver mass, sufficient to sustain life. The baboon livers led to the presence of baboon proteins synthesized by the liver; in some cases those proteins assumed the blood levels that are characteristic of the baboon and not of the human. Possible molecular incompatibility of those proteins poses a potential problem of functionality for humans.

Transplants have also been attempted using pig hearts (three cases) or livers (one case); in no case did the recipient survive more than 24 hours[7].

While non-human primates have been preferred in the past as source organs for humans, at present the scientific community and the regulatory agencies in those countries which are addressing the issue have ruled out the use of such source animals both because of the increased risk of transmission of infection and because of a variety of other ethical and practical concerns[8]. As a consequence many researchers have settled on the use of pigs as a potential source animals for xenotransplantation[9]. The use of genetic engineering has resulted in significant improvement in survival time for a pig organ in a non-human primate receiving immunosuppression[10]. However, the

5 Cf. Marino I.R., Doyle H.R., Nour B., Starzl T.E. Baboon liver xenotransplantation. In: Cooper D.K.C., Kemp E., Platt J.L., White D.J.G., eds. Xenotransplantation, The Transplantation of Organs and Tissues between Species. 2nd ed. Berlin: Springer-Verlag 1997: 793-811.

6 Cf. Michaels M.G., Jenkins F.J., St George K., Nalesnik M.A., Starzl T.E., Rinaldo C.R. Jr., Detection of infectious baboon cytomegalovirus after baboon-to-human liver xenotransplantation. J Virol. 2001; 75: 2825-8.

7 Cf. Taniguchi S., Cooper D.K.C. Clinical xenotransplantation - A brief review of the world experience. In: Cooper D.K.C., Kemp E., Platt J.L., White D.J.G., eds. Xeno-transplantation. The transplantation of Organs and Tissues Between Species. 2nd ed. Berlin: Springer-Verlag 1997: 776-792.

8 Cf. Allan J.F. Xenotransplantation at a crossroad: prevention versus progress. Nature Med. 1996, 2: 18-21; Hammer C., Linke R., Wagner F., Diefenbeck M., Organs from animals for man, Int. Arch. Allergy Immunol., 1998, 116: 5-21.

9 Cf. Hammer C., Linke R., Wagner F., Diefenbeck M., Organs from animals for man, Int. Arch. Allergy Immunol., 1998 116: 5-21; Cooper D.K.C., Ye Y., Rolf J.L.L., et al., The Pig as Potential Organ Donor for Man. In: Cooper D.K.C., Kemp E., Reemtsma K., White D.J.G., eds. Xeno-transplantation. The Transplantation of Organs and Tissues Between Species. 1st ed. Berlin: Springer-Verlag 1991: 481-500.

10 Cf. Loss M., Vangerow B., Schmidtko J., et al., Acute vascular rejection is associated with systemic complement activation in a pig-to-primate kidney xenograft model, Xenotransplantation 2000, 7: 186-96; Cozzi E., Bhatti F., Schmoeckel M. et al., Long-term survival of nonhuman primates receiving life-supporting transgenic porcine kidney xenografts, Transplantation 2000, 70: 15-21; Vial C.M., Ostlie D.J., Bhatti F.N. et al., Life-supporting function for over one month of a trasgenic porcine heart in a baboon, J. Heart. Lung Transplant 2000, 19: 224-9; Bhatti F.N., Schmoeckel M., Zaidi A., et al., Three-month survival of HDAF transgenic pig hearts transplanted into primates, Transplant Proc.

survival time of such organs does not yet approach that of human organs transplanted to other humans (allotransplantation). Therefore, certain barriers to xenotransplantation remain[11].

Further genetic engineering of source animals and/or use of additional/new immunosuppressive agents are the two approaches that are considered most likely to prolong the survival of a xenotransplant[12]. Clearly more research in xenotransplantation is needed and should be done.

Current Situation

Rejection: Immunology of Organ Xenografting

2. There are four immunological barriers that must be overcome for achieving successful organ xenotransplantation from pig to primate (human and non-human). First, hyperacute rejection, which is caused by xenoreactive natural antibodies and complement of the recipient acting against endothelial cells of the source animal organ. Second, acute vascular rejection caused by the combined effect of elicited xenoreactive antibodies and activated host natural killer cells and monocytes. In combination these stimuli (the anti-graft antibodies and the activated host cells) result in activation of the endothelial cells of the source organ. Endothelial cell activation leads to general inflammation with resultant thrombosis (platelet aggregation and activation of the coagulation cascade) resulting in organ rejection. Third, the xenograft counterpart of classical T cell mediated rejection of allografts (transplantation between individuals of the same species) will almost certainly occur. Finally, xenografts may also be subject to chronic rejection in a manner analogous to allografts.

Hyperacute Rejection: Recipient xenoreactive natural antibodies and complement are the two major factors that result in hyperacute rejection of an immediately-vascularized organ. Pre-existing xenoreactive natural antibodies bind with vascular endothelial cells of the pig organ[13]. These antibodies are directed primarily towards a sugar moiety, the Gal-a (1,3)-Gal-ß (1,4)-GlcNac antigens of the pig, also known as «a-gal»[14]. The bound antibodies fix and activate complement, with the combination of antibodies and

1999, 31: 958; Diamond L.E., Quinn C.M., Martin M.J., et al., A human CD46 transgenic pig model system for the study of discordant xenotransplantation, Transplantation 2001; 7: 132; Lin S.S., Weidner B.C., Byrne G.W., et al., The role of antibodies in acute vascular rejection of pig-to-primate cardiac transplants. J Clin Invest 1998; 101: 1745-1756.

11 Cf. Starzl T.E., Rao A.S., Murase N., et al., Will xenotransplantation ever be feasible?, J Am Coll Surg 1998, 186 (4): 383-7.

12 Cf. Auchincloss H. Jr., Sachs D.H., Xenogenic transplantation, Annu.Rev.Immunol. 1998, 16: 433-70.

13 Cf. Platt J.L., Fischel R.J., Matas A.J., et al., Immunopathology of hyperacute xenograft rejection in a swine-to-primate model, Transplantation 1991, 52: 214-220; Dalmasso A.P., Vercellotti G.M., Fischel R.J., et al., Mechanisms of complement activation in the hyperacute rejection of porcine organs transplanted into primate recipients, Am J Pathol 1992, 140: 1157-66.

14 Cf. Good A.H., Cooper D.K.C., Malcom A.J. et al., Identification of carbohydrate structures which bind human antiporcine antibodies: implications for discordant xenografting in man, Transplant Proc 1992, 24: 559-60; Sandrin M.S., Vaughan H.A., Dabkowski P.L., et al., Anti-pig IgM antibo-

activated complement leading to endothelial activation which result in thrombosis, rapid graft ischemia and rejection. Elimination of xenoreactive natural antibodies provides one method to overcome hyperacute rejection[15]. Hyperacute rejection has also been overcome by methods that inhibit complement[16].

Among the different approaches for achieving inhibition of complement, the one that has proven most effective is based on in vitro experiments in which a human protein that inhibits human complement activation is introduced into the membrane of pig endothelial cells. The molecule first tested was human Decay Accelerating Factor, or hDAF. The presence of hDAF in the pig endothelial cells prevented lysis of those cells and would thus, presumably, prevent the activation of the cells[17]. These findings suggested that the production of transgenic pigs expressing hDAF might provide an approach for overcoming hyperacute rejection of pig organs transplanted into primates.

Certain research groups have produced such transgenic pigs and have demonstrated that organs from these pigs usually do not undergo hyperacute rejection[18]. Based on these results with

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dies in human serum react predominantly with Gal(a1-3 Gal epitopes, PNAS 1993, 90: 11391-5.

15 Cf. Leventhal J.R., John R., Fryer J.P., et al., Removal of baboon and human antiporcine IgG and IgM natural antibodies by immunoadsorption: Results of in vitro and in vivo studies, Transplantation 1995, 59: 294-300; Cooper D.K.C., Lexer G., Rose A.G., et al., Effects of cyclosporine and antibody adsorption on pig cardiac xenograft survival in the baboon, J. Heart. Transplant. 1988, 7: 238-46; Latinne D., Soares M., Havaux X., et al., Depletion of IgM xenoreactive natural antibodies by injection of anti-mu monoclonal antibodies, Immunol Rev 1994, 141: 95-125; Rydberg L., Hallberg E., Bjorck S., et al., Studies on the removal of anti-pig xenoantibodies in the human by plasmapheresis/immunoadsorption, Xenotransplantation 1995, 2: 253-63.

16 Cf. Gewurz H., Clark D.S., Finstad J., et al., Role of the complement system in graft rejections in experimental animals and man, Ann. NY Acad. Sci., 1966, 129: 673-713; Pruitt S.K., Kirk D.A., Bollinger R.R., et al., The effect of soluble complement receptor type 1 on hyperacute rejection of porcine xenografts, Transplantation 1994, 57: 363-70; Kobayashi T., Neethling F.A., Koren E., et al., In vitro and in vivo investigation of anticomplement agents FUT-175 and K76COOH, in the prevention of hyperacute rejection following discordant xenotransplantation in a nonhuman primate model, Trans Proc 1996, 28: 604; Kroshus T.J., Rollins S.A., Dalmasso A.P., et al., Complement inhibition with an anti-C5 monoclonal antibody prevents acute cardiac tissue injury in an ex vivo model of pig-to-human xenotransplantation, Transplantation 1995, 60: 1194-202.

17 Cf. Bach F.H., Turman M.A., Vercellotti G.M., et al., Accomodation: a working paradigm for progressing toward clinical discordant xenografting, Transplant Proc. 1991; 23: 205-7; Dalmasso A.P., Vercellotti G.M., Platt J.L., Bach F.H., Inhibition of complement mediated endothelial cell cytotoxicity by decay accelerating factor. Potential for prevention of xenograft hyperacute rejection, Transplantation 1991; 52: 530-3.

18 Cf. Diamond L.E., Quinn C.M., Martin M.J., et al., A human CD46 transgenic pig model system for the study of discordant xenotransplantation, Transplantation 2001; 7: 132; Cozzi E., White D.J.G., The generation of transgenic pigs as potential organ donors for humans, Nature Medicine 1995, 1: 964-6; Fodor W.L., Williams B.L., Matis L.A., et al., Expression of a functional human complement inhibitor in a transgenic pig as a model for the prevention of xenogenic hyperacute organ rejection, Proc Natl Acad Sci 1994, 91: 11153-7; McCurry K.R., Kooyman D.L., Alvarado C.G., et al., Human complement regulatory proteins protect swine-to-primate cardiac xenografts from tumoral injury, Nature Med 1995, 1: 423-7; Cowan P.J., Aminian A.,

transgenic hDAF-expressing pigs, it appears that hyperacute rejection can be overcome, which is the first major triumph of gene therapy in the field of organ transplantation.

Another possible solution to hyperacute rejection is to eliminate, or greatly reduce the expression of «a-gal» from pigs by knocking out the 1,3 galactosyl transferase gene, which is needed for the expression of «a-gal»[19]. This has not yet been accomplished in pigs, although present-day cloning technology could make this possible.

Acute Vascular Rejection: Acute Vascular Rejection is precipitated by elicited xenoreactive antibodies and by the possible infiltration of host inflammatory cells, monocytes and natural killer cells, that invade the xenograft[20]. Endothelial cells are activated resulting in thrombosis, compromised blood flow and rejection[21]. Acute vascular rejection now represents the principle immunological barrier to successful xenotransplantation. Studies of acute vascular rejection in animals has shown that the use of immunosuppression leads to organ survival for a far greater length of time than is seen in untreated cases[22]. An alternative approach for overcoming acute vascular rejection is further genetic engineering animals/organs[23]. A number of genes that may suppress the inflammatory response that appears to cause acute vascular rejection are now being studied.

T Cell Response: If acute vascular rejection can be overcome, it is expected that there will be a xenograft counterpart of the allogeneic T cell rejection response[24]. There are disagreements whether the xenogenic T cell response will be more difficult to overcome than the allogeneic one, which today is easily controlled. In addition to the use of immunosuppression, there is the possibility that in pig-to-primate transplants we might achieve tolerance (non-reactivity of the immune system of the recipient to pig antigens

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Barlow H. et al., Renal xenografts from triple-transgenic pigs are not hyperacutely rejected but cause coagulopathy in non-immunosuppressed baboons, Transplantation 2000, 69: 2504-15; Lavitrano M., Forni M., Varzi V., et al., Sperm-mediated gene transfer: production of pigs transgenic for a human regulator of complement activation, Transplant Proc 1997;29: 3508-9.

19 Cf. Sandrin M.S., Fodor W.L., Mouhtouris E., et al., Enzymatic remodeling of the carbohydrate surface of a xenogenic cell substantially reduces human antibody binding and complement-mediated cytolysis, Nature Medicine 1995, 1: 1261-7.

20 Cf. Soares M.P., Lin Y., Sato K., et al., Pathogenesis of and potential therapies for delayed xenograft rejection, Opin Organ Transplant 1999 4: 80-8.

21 Cf. Hancock W.W., Delayed xenograft rejection, World J. Surg. 1997, 21: 917-23; Platt J.L., Lin S.S. and McGregor C.G.A., Acute vascular rejection, Xenotransplantation 1998, 5: 169-175.

22 Cf. Cozzi E., Bhatti F., Schmoeckel M. et al., Long-term survival of nonhuman primates receiving life-supporting transgenic porcine kidney xenografts, Transplantation 2000, 70: 15-21; Vial C.M., Ostlie D.J., Bhatti F.N. et al., Life supporting function for over one month of a transgenic porcine heart in a baboon, J. Heart. Lung Transplant 2000, 19: 224-9.

23 Cf. Bach F.H., Xenotransplantation: problems and prospects, Annu.Rev.Med.1998, 49: 301-10.

24 Cf. Yamada A., Auchincloss H. Jr., Cell-mediated xenograft rejection, Current Opinion in Organ Transplantation 1999, 4: 90-94.

without immunosuppression)[25]. Such tolerance is the hope of transplantation in general and may be aided in the xenogenic arena by further genetic engineering of the source animal.

Chronic Xenograft Rejection: There is evidence that - as with allotransplants, - even when a transplant survives all the above rejection phases, there is the possibility that it will be rejected months or years later[26]. This is referred to as «chronic» rejection. The main pathology of chronic graft failure involves smooth muscle cell proliferation and obliteration of the lumens of blood vessels.

Experimental Models

3. Xenotransplantation of organs has been studied primarily in small animal models and in pig-to-nonhuman-primate combinations.

Small animal models. The principal model used involves transplantation of hamster or mouse hearts to rats. For the most part, the rejection of a hamster heart by a rat is similar to the rejection of a mouse heart. However, the rat does not have sufficient preformed xenoreactive natural antibodies to reject a mouse or hamster heart hyperacutely; thus rejection is dependent on the synthesis of anti-graft antibodies that, together with recipient complement, lead to rejection of the organ[27]. Transplantation of mouse or hamster hearts to rats is therefore thought to be a good model of acute vascular rejection. The preliminary findings that have emerged from small animal transplants are the following: administration of immunosuppression to the rat can lead to long-term survival of hamster hearts[28]. In this sense, rejection of a hamster organ transplanted to a rat appear to differ from acute vascular rejection of a pig organ in a nonhuman primate in which hyperacute rejection has been overcome. In the pig-to-nonhuman-primate model, immunosuppression alone is currently unable to lead to long-term survival. The second finding in the hamster or mouse heart transplants to rats has been the achievement of «accommodation»[29]. Accommodation refers to the survival of an organ in the presence of anti-graft antibodies and complement. Short-term inhibition of complement coupled with continuing inhibition of T cells leads to long-term survival in these two situations. An interesting finding regarding accommodation is that the surviving organ

25 Cf. Auchincloss H. Jr., Sachs D.H., Xenogeneic transplantation, Annu.Rev.Immunol. 1998, 16: 433-70.

26 Cf. Bach F.H., Ferran C., Soares M., et al., Modification of vascular responses in xenotransplantation: inflammation and apoptosis, Nat. Med 1997. 3: 944-8.

27 Cf. Soares M.P., Lin Y., Sato K., et al., Pathogenesis of and potential therapies for delayed xenograft rejection, Opin Organ Transplant 1999 4: 80-8; Hasan R.I.R., van den Bogarde J., Forty J., et al., Prolonged Survival of Hamster to Rat Heart xenografts with Cyclophosphamide Therapy, Transplant Proceedings 1992, 24: 517-518.

28 Cf. Hasan R.I.R., van den Bogarde J., Forty J., et al., Prolonged Survival of Hamster to Rat Heart xenografts with Cyclophosphamide Therapy, Transplant Proceedings 1992, 24: 517-518.

29 Cf. Soares M.P., Lin Y., Sato K., et al., Accommodation, Immunol Today 1999, 20: 434-7.

expresses genes in its endothelium and smooth muscle cells that protect the organ from rejection[30]. To what extent these protective genes can be used therapeutically to aid pig organ survival in primates is not clear. Isolated cases of accommodation have been described in human allogeneic transplants as well[31].

Large animal models. The principal model today remains transgenic pigs expressing hDAF[32] and, in some cases, other human genes inhibiting complement cascade, coupled with immunosuppression in order to achieve survival. In most cases, normal pig organs are rejected hyperacutely by non-human primates, and thus, more rapidly than transgenic pig organs expressing hDAF[33]. Even when hyperacute rejection is avoided, the hDAF transgenic organs are rejected in non-human primates by a process that mimics acute vascular rejection, although rejection can be very much delayed[34]. Transgenic pig hearts have been shown to survive for up to 99 days when they are not asked to do life-supporting work (heterotopic transplant)[35]. When placed in the position of having to support life (orthotopic transplant), the longest survival periods have been a month for a cardiac xenograft[36] and 78 days for a renal xenograft[37]; most organs are rejected in a shorter period of time. Scientists propose two different approaches, which can be combined for achieving longer survival periods of pig organs in primates. The first is to try different immuno-

30 Cf. Soares M.P., Lin Y., Sato K., et al., Accommodation, Immunol Today 1999, 20: 434-7; Lin Y., Soares M.P., Sato K., et al., Accommodated xenografts survive in the presence of anti-donor antibodies and complement that precipitate rejection of naive xenografts, J Immunol. 1999 Sep 1; 163(5): 2850-7.

31 Cf. Alexandre G.P.J, Latinne D., Gianello P., et al., Preformed cytotoxic antibodies and ABO-incompatible grafts, Clin Transpl 1991; 5: 583-587.

32 Cf. Cozzi E., Bhatti F., Schmoeckel M. et al., Long-term survival of nonhuman primates receiving life-supporting transgenic porcine kidney xenografts, Transplantation 2000, 70: 15-21; Vial C.M., Ostlie D.J., Bhatti F.N. et al., Life supporting function for over one month of a transgenic porcine heart in a baboon, J. Heart. Lung Transplant 2000, 19: 224-9.

33 Cf. McCurry K.R., Kooyman D.L., Alvarado C.G., et al., Human complement regulatory proteins protect swine-to-primate cardiac xenografts from tumoral injury, Nature Med 1995, 1: 423-7; Cozzi E., Yannoutsos N., Langford G.A. et al., Effect of transgenic expression of human decay-accelerating factor on the inhibition of hyperacute rejection of pig organs. In: Cooper D.K.C., Kemp E., Platt J.L., White D.J.G., eds. Xeno-transplantation. The Transplantation of Organs and Tissues Between Species. 2nd ed. Berlin: Springer-Verlag 1997: 665-682.

34 Cf. Cozzi E., Bhatti F., Schmoeckel M. et al., Long-term survival of nonhuman primates receiving lifesupporting transgenic porcine kidney xenografts, Transplantation 2000, 70: 15-21; Bhatti F.N., Schmoeckel M., Zaidi A. et al., Three-month survival of HDAF transgenic pig hearts transplanted into primates, Transplant Proc. 1999, 31: 958; McCurry K.R., Kooyman D.L., Alvarado C.G., et al., Human complement regulatory proteins protect swine-to-primate cardiac xenografts from tumoral injury, Nature Med 1995, 1: 423-7.

35 Cf. Bhatti F.N., Schmoeckel M., Zaidi A. et al., Three-month survival of HDAF transgenic pig hearts transplanted into primates, Transplant Proc. 1999, 31: 958.

36 Cf. Vial C.M., Ostlie D.J., Bhatti F.N. et al., Life supporting function for over one month of a transgenic porcine heart in a baboon, J. Heart. Lung Transplant 2000, 19: 224-9.

37 Cf. Cozzi E., Bhatti F., Schmoeckel M. et al., Long-term survival of nonhuman primates receiving life-supporting transgenic porcine kidney xenografts, Transplantation 2000, 70: 15-21.

suppressive protocols, and the second is to produce pigs that express additional transgenes that might inhibit rejection factors associated with acute vascular rejection.

Xenozoonoses: the Transmission of Infectious Agents from one Species to another

4. Over sixty porcine infectious agents with a potential to cause disease in humans have been identified[38]. Development of «clean» lines of source animals, with a certified health status, is under way[39]. Control measures include the birth of pigs by hysterotomy (caesarean derived), carefully controlled environments and routine monitoring of pigs and their handlers. These steps appear to have excluded almost all known infectious agents of concern. However, it cannot be ruled out that an unknown porcine virus might exist which causes no pathology in pigs but which may cause disease in humans.

As is true for all other mammalian species, pigs have sequences in their DNA that encode retroviruses (PERV -Porcine Endogenous RetroViruses)[40]. Weiss and colleagues showed that pig retroviruses could infect human cells in vitro[41]. There are no satisfactory animal models to test the pathogenicity of these agents. The blood of 160 patients exposed to living pig tissues was studied for the presence of PERV. In 135 patients exposure was for only one hour or a little more. In a few of the remaining patients exposure was for longer periods, in one case for 460 days. None of the patients showed evidence of PERV infection, although pig cells containing retroviral sequences were found even several years after exposure to the pig tissue. It is a matter open to conjecture the extent to which one can take comfort from negative results in persons exposed for such short period of time, except for a few cases, and in any event to very few pig cells, as compared with the years of exposure that would presumably occur in an organ were it successfully transplanted into a human. Certainly, the elimination from pigs of all PERV, which represents a continuing concern and hinders the move to clinical trials, will remain a challenge for years to come.

Advances in Biotechnology and Molecular Genetics

5. The major advances in biotechnology that might favour further deve-

38 Cf. Onions D., Cooper D.K., Alexander T.J., et al., An approach to the control of disease transmission in pig-to-human xenotransplantation, Xenotransplantation 2000; 7: 143-155.

39 Cf. Iverson W.O., Talbot T., Definition of a production Specification for xenotransplantation, Ann. NY Acad. Sc. 1998, 862: 121-124.

40 Cf. Boeke J.D., Stoye J.P., Retrotransposons, endogenous retroviruses, and the evolution of retroelements, Chapter 8 In: Retroviruses. (J.M. Coffin, S.H. Hughes, and H.E. Varmus eds Cold Spring Harbor Press, Cold Spring Harbor, N.Y. 1997; 343-435.

41 Cf. Patience C., Takeuchi Y., Weiss R.A., 1997, Infection of human cells by an endogenous retrovirus of pigs. Nature Med 3: 282-286.

42 Cf. Paradis K., Langford G., Zhifeng L., Heneine, Sandstrom P., Switzer W., Chapman L., Lockey C., Onions D., THE XEN111 Study group, et al., 1999, Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue. Science 285: 1236-41.

lopment of xenotransplantation relate to producing transgenic pigs that express human genes which inhibit rejection. Two break-throughs are especially important. First, recent studies have led to the cloning of pigs[43], allowing for simple genetic manipulation compared with the methods currently available. With this procedure, at least in principle, new genes can easily be introduced into the DNA of the pig genome during the cloning process, and other genes «knocked out» so that they would no longer be functional. For instance, the gene that leads to expression of the «α-gal» antigen on porcine endothelial cells could be knocked out so that at least one of the causes of rejection would presumably be reduced.

Second, although still at the experimental level, methods to regulate the expression of transgenes have been devised[44]. It may well be that a certain transgene would be highly desirable at a given moment after transplantation while it would be undesirable at a different moment. Therefore, being able to regulate the expression of a transgene would represent a great advance in the development of xenotransplantation.

Moving to the Clinical Phase

6. Because transplanted cells and tissues are not immediately perfused with recipient blood after transplantation they are not hyperacutely rejected. Clinical trials using such transplants have therefore progressed further compared to clinical trials with solid organ transplants. Porcine pancreatic islets have been transplanted into a number of patients with diabetes[45] and foetal porcine neural cells have been injected into a significant number of patients (more than 50) suffering from Parkinson's Disease, Huntington's Disease or strokes[46]. Only limited clinical benefit has been reported to date. A significant number of patients with acute liver failure have taken part in multicentre studies using pig hepatocytes in artificial devices (bioartificial liver) with promising initial results[47].

There are considerable differences of opinion as to how long a pig organ should survive in a non-human primate before one proceeds to clinical trials involving the transplantation of pig

43 Cf. Polejaeva I.A., Chen S.H., Vaught T.D., et al., Cloned pigs produced by nuclear transfer from adult somatic cells, Nature. 2000, 407: 86-90; Onishi A., Iwamoto M., Akita T., et al., Pig cloning by microinjection of fetal fibroblast nuclei, Science. 2000, 289: 1188-90.

44 Cf. Harvey D.M., Caskey C.T., Inducible control of gene expression: prospects for gene therapy, Curr Opin Chem Biol 1998, 2: 512-8.

45 Cf. Groth C.G., Korsgren 0., Tibell, A., et al., Transplantation of Porcine fetal pancreas to diabetic patients, Lancet, 1994, 344: 1402-1404.

46 Cf. Brevig T., Holgersson J., Widner H., Xenotransplantation for CNS repair: immunological barriers and strategies to overcome them, Trends Neurosci 2000; 23: 337-44.

47 Cf. Mc Laughlin B.E., Tosone C.M., Custer L.M., Mullon C., Overview of extracorporeal liver support system and clinical results, Ann. NY Acad. Sci., 1999, 875: 310-325; Calise F., Mancini A., Amoroso P. et al., Functional evaluation of the AMC-BAL to be employed in a multicenter clinical trial for acute liver failure, Transpl. Proceed., 2001, 33: 647-649.

organs into humans. Some suggest that clinical trials on humans could begin only after routine survival periods of ninety days or more have been obtained for pig organs which are transplanted into nonhuman primates and which must perform life-supporting functions[48]. At present, survival periods for this type of xenotransplants vary from a few weeks to about three months, and three-month survival is certainly not routine[49]. Clearly, a significant improvement on current figures must be achieved before clinical trials using solid organ xenografts are warranted.

However, while survival of pig organs in non-human primates at present is not sufficiently long to consider transplanting such organs into humans as a permanent replacement organ, the option of using pig organs as «bridge' transplants may well be possible in a shorter time.

48 Cf. Cooper D.K.C., Keogh A.M., Brink J., et al., Report of the xenotransplantation advisory committee of the international society for heart and lung transplantation. The present status of xenotransplantation and its potential role in the treatment of end-stage cardiac and pulmonary disease. J. Heart Lung Transpl. 2000, 19: 1125-1165.

49 Cf. Cozzi E., Bhatti F., Schmoeckel M. et al., Long-term survival of nonhuman primates receiving life-supporting transgenic porcine kidney xenografts, Transplantation 2000, 70: 15-21; Vial C.M., Ostlie D.J., Bhatti F.N. et al., Life supporting function for over one month of a transgenic porcine heart in a baboon, J. Heart. Lung Transplant 2000, 19: 224-9; Bhatti F.N., Schmoeckel M., Zaidi A. et al., Three-month survival of HDAF transgenic pig hearts transplanted into primates, Transplant Proc. 1999, 31: 958.

Part Two: Anthropological and Ethical Aspects

Besides the scientific and technical aspects of xenotransplantation described in the first part of this document, anthropological and ethical considerations are also involved. The purpose of this second part is to explore these considerations, albeit by way of a brief overview.

Preliminary Issues

In addition to the problems raised by every transplant, it seems us that there are three issues specifically related to xenotransplantation: 1) the acceptability of man's intervening in the order of the creation; 2) the ethical feasibility of using animals to improve the chances for survival and well-being of human beings; 3) the possible objective and subjective impact that an organ or tissue of animal origin can have on the identity of the human recipient.

Human Intervention in the Created Order

7. To begin with, we would like to deal briefly with a fundamental question that, generally, is posed by the different religious traditions, albeit with different accents: this concerns the possibility itself that man may licitly intervene in the realities that exist in the universe in general and, more particularly, in those things that concern animals.

In view of the more specifically theological nature of such a question, we

deem it useful to offer a short summary of the Catholic position on this question, applying the language and the methods proper to theological anthropology.

By what right can humans, whom God created as female and male, and whose full human dignity must be recognized at every stage of life, intervene in the created order, perhaps even modifying some of its aspects? What criteria must be adopted and what limitations must be introduced?

From imagery of the account of creation «in six days»[50], it is evident that God established a hierarchy of values among the various creatures. Moreover, this hierarchy also emerges from a rational consideration of the transcendent richness and dignity of the human person.

Man, created «in the image and likeness of God», is placed at the centre and at the summit of the created order, not only because everything that exists is intended for him, but also because woman and man have the task of co-operating with the Creator in leading creation to its final perfection. «Be fruitful and multiply, and fill the earth and subdue it» (Gen 1: 28): this is the mandate that God gives to human beings, «dominion» over the created order, in his name. In this regard, Pope John Paul II writes in his encyclical «Laborem Exercens»: «Man is the image of God partly through the mandate received from his Creator to subdue, to dominate, the earth. In carrying out this mandate, man, every human being, reflects the very action of the Creator of the universe»[51].

This, therefore, is the deepest meaning of the action of man in relation to the created universe: certainly not that of arbitrarily «lording it over» the other creatures, reducing them to humiliating and destructive slavery in order to satisfy any whim that he may have, but to guide, through his responsible work, the life of the creation towards the authentic and integral good of man (the whole man and every man).

Certain documents of the Second Vatican Council had already affirmed this truth. In «Lumen Gentium», for example, we read: «Therefore, by their competence in secular disciplines and by their activity, interiorly raised up by grace, they (the laity) must work earnestly in order that created goods through human labour, technical skill and civil culture may serve the utility of all men according to the plan of the Creator and the light of his Word. May these goods be more suitably distributed among all men and in their own way may they be conducive to universal progress, in human and Christian liberty»[52]. Also the decree of the Second Vatican Council on the apostolate of the laity takes up this idea when it asserts that «this natural goodness of

50 The reference is made to the narrative scheme, of a theological-liturgical nature, used in Gn 1: 1-31; for a fuller understanding of the biblical anthropological context, from a protological point of view, the second account of creation, in Gn 2: 1-25, must also be taken into consideration.

51 John Paul II, Encyclical Letter Laborem Exercens, n. 4.

52 Second Vatican Council, Dogmatic Constitution Lumen Gentium, n. 36.

theirs (of the realities that make up the temporal order) receives an added dignity from their relation with the human person, for whose use they have been created»[53].

In summary, therefore, there should be a reaffirmation of the right and duty of man, according to the mandate from his Creator and never against the natural order established by him, to act within the created order and on the created order, making use as well, of other creatures, in order to achieve the final goal of all creation: the glory of God and the full and definitive bringing about of His Kingdom, through the promotion of man. The words of St. Irenaeus of Lyons still ring out with all their truth: «Living man is the glory of God and man's life is the vision of God»[54].

The Use of Animals for the Good of Man

8. For a theological reflection that will help to formulate an ethical assessment on the practice of xenotransplantation, we do well to consider what the intention of the Creator was in bringing animals into existence. Since they are creatures, animals have their own specific value which man must recognize and respect. However, God placed them, together with the other nonhuman creatures, at the service of man, so that man could achieve his overall development also through them.

It should be noted that this role of «service» rendered to man by other creatures occurs in different ways according to the cultural advances of humanity. Limiting ourselves to scientific and technological progress in the biomedical field, the service of animals to man represents a totally new application in xenotransplantation, which, therefore, in principle is not in conflict with the order of the creation. On the contrary, xenotransplantation represents for man a further opportunity for creative responsibility in making reasonable use of the power that God has given to him.

Furthermore, even if one limits oneself to a purely rational analysis, without desiring to make use of theological reasoning, one can reach the same conclusions on a practical level.

A simple look at humanity's long presence on the earth is sufficient to show an irrefutable fact clearly: it is man who has always directed the realities of the world, controlling the other living and non-living beings according to determined purposes. It is moreover in its relationship with man that the axiological measure (moral value) of every existing reality is revealed in a universal harmonic and orderly design that indicates all the fullness of the sense of reality.

In particular, man has always made use of animals for his primary needs (food, work, clothing, etc.) in a sort of natural «cooperation» that has constantly marked the different stages of progress and the development of civilization.

Such a position of «excellence» is a witness to and also demonstrates the

53 Second Vatican Council, Decree Apostolicam Actuositatem, n. 7.

54 Saint Irenaeus of Lyons, Against Heresies, Book 4, 20, 7.

ontological superiority of mankind over the other beings of the earth; this superiority is founded on the very nature of the human person, whose rational and spiritual dimensions place man at the centre of the universe, so that he may use its existing resources (including animals) in a wise and responsible manner, seeking the authentic promotion of every being.

To analyse more deeply the point under discussion, two issues of an ethical nature must be addressed. First, there is the question of the use of animals in order to improve man's chances of survival or to improve his health; the obvious starting point here is the particular way in which one views the relationship between man and animals[55]. Second, there is the question of the acceptability of breaching the barrier between animal species and the human species.

With regard to the first issue, contemporary thinking includes two opposing and extreme viewpoints[56]. There are those who believe that animals and man have equal dignity and those who believe that animals are totally at the mercy of man. In the former case, the use of animals is seen as species-ism or tyranny of man over animals. Even reducing human suffering could not justify the use of animals unless the contrary possibility was also allowed. In the latter case, man can use animals arbitrarily without being limited by ethical considerations.

9. From our point of view, supported by the biblical perspective that asserts, as stated above, that man is created «in the image and likeness of God» (cf. Gen 1: 26-27), we reaffirm that humans have a unique and higher dignity. However, humans must also answer to the Creator for the manner in which they treat animals. As a consequence, the sacrifice of animals can be justified only if required to achieve an important benefit for man, as is the case with xenotransplantation of organs or tissues to man, even when this involves experiments on animals and/or genetically modifying them.

However, even in this case, there is the ethical requirement that in using animals, man must observe certain conditions: unnecessary animal suffering must be prevented; criteria of real necessity and reasonableness must be respected; genetic modifications that could significantly alter the biodiversity and the balance of the species in the animal world must be avoided[57].

The theological and moral point of view sees no substantial problem in the utilization of different animal species (nonhuman primates or nonprimates), but leaves open the question of differing

55 Cf. Bondolfi A., I rapporti tra uomo e animale nelle tradizioni giudaico-cristiane e la sfida degli xenotrapianti, in L'arco di Giano, 1999; 21: 49-62; D'Agostino F., I diritti degli animali, in Bioetica nella prospettiva della filosofia del diritto, 1997, Giappichelli Ed., Torino, pp. 239-265.

56 Cf. Singer P., Animal Liberation, 2nd edit., 1995, Pimlico, London; Regan T., The case for Animal Rights, 1983, London, Routledge & Kegan Paul; Christian Medical Fellowship, Animal experimentation, 1997, (http: //www.cmf.org.uk, 10/7/2001).

57 Reflections on human responsibility for animal life may be found in Schockenhoff E., Etica della vita. Un compendio teologico, Brescia: Queriniana 1997: 407-451.

levels of sensibilities between animals of different species and that of equilibrium among species and within a species.

The point should also be made that Catholic theology does not have preclusions, on a religious or ritual basis, in using any animal as a source of organs or tissues for transplantation to man[58]. The question of the acceptability of an animal organ, - once it has been established that personal identity is not affected by xenotransplantation, and once all the general ethical requirements of transplantation have been met, - becomes one on the cultural and psychological level. Therefore, it may be possible to overcome initial misgivings by providing the necessary support in an effective manner.

Xenotransplantation and the Identity of the Recipient

10. In addition to considerations of a theological nature, and perhaps even before these are made, an ethical evaluation of the practice of xenotransplantation must be measured against current anthropological findings, especially that branch of philosophical anthropology that deals with personal identity[59]. Any ethical appraisal of xenotransplantation must ultimately address the question of whether the «introduction of a foreign organ into the human body modifies a person's identity and the rich meaning of the human body?» And if the answer is affirmative, one must ask up to what point is such modification acceptable.

Certainly, the concept of «personal identity» is replete with implications and subtleties of meaning, given the different contributions of philosophy and science[60]. More concisely, in keeping with the scope of this document, we can indicate personal identity as the relation of an individual's unrepeatability and essential core to his being a person (ontological level) and feeling that he is a person (psychological level). These characteristics are expressed in the person's historical dimension and, in particular, in his communicative structure, which is always mediated by his corporeality.

It must be affirmed, then, that personal identity constitutes a good of the person, an intrinsic quality of his very being, and thus a moral value upon which to base the right and duty to promote and defend the integrity of the personal identity of every individual.

We can therefore conclude that, in general, the implantation of a foreign organ into a human body finds an ethical limit in the degree of change that it may entail in the identity of the person who receives it.

11. Such a modification, as already noted, affects the historical dimension of

58 The Old Testament precept by which certain animals were held to be impure (cf. Lv 11: 3-8, 26-29), is considered abolished by Christ (cf. Mk 7: 14-23; Acts 10: 14-15; Rom 14: 14).

59 It should be noted that «identity indicators» in human beings are many (objective: name, sex, age, etc.; cultural: language, religion, ideology, etc.; group - social - professional).

60 Cf. Grinberg L. and R., Identità e cambiamento, Roma: Armando, 1992; Jervis G., La conquista dell'identità: essere se stessi, essere diversi, Milan: Feltrinelli, 1997.

the person, and thus the individual's communicative structure as mediated by his corporeality.

In light of a renewed appreciation of the body and of the symbolic understanding of it that much of contemporary anthropology offers, it should be observed that not all organs of the human body are in equal measure an expression of the unrepeatable identity of the person. There are some which exclusively perform their specific function; others, instead, add to their functionality a strong and personal symbolic element which inevitably depends on the subjectivity of the individual; and others still, such as the encephalon and the gonads, are indissolubly linked with the personal identity of the subject because of their specific function, independently of their symbolic implications. Therefore one must conclude that whereas the transplantation of these last can never be morally legitimate, because of the inevitable objective consequences that they would produce in the recipient or in his descendants[61], those organs which are seen as being purely functional and those with greater personalized significance must be assessed, case by case, specifically in relation to the symbolic meaning which they take on for each individual person[62].

12. The questions and issues connected with the defence of the personal identity of the recipient patient is a central point not only for philosophical anthropology but also for moral theology, as is demonstrated by certain official pronouncements of the Magisterium on xenotransplantation, which see this as one of the fundamental criteria for the moral legitimacy of xenotransplantation. First Pius XII (Address to the Italian Association of Corneal Donors, Clinical Ophthalmologists and Legal Medicine, 14 May 1956), and more recently John Paul II (Address to the Eighteenth International Congress of the Transplant Society, 29 August 2000, n. 7), have clearly upheld the moral legitimacy, in principle, of this therapeutic procedure, on the condition that «the transplanted organ does not affect the psychological or genetic identity of the person who receives it» and «that there exists the proven biological possibility of carrying out such a

61 We do well to specify that, while the encephalon is related to the personal identity of the subject insofar as it is the organ representing the «principal seat of psychological consciousness», and the «deposit» of existential memory, the gonads are likewise related, insofar as they are organs charged with gametogenesis (the production of gametes); they represent, in a manner of speaking, the «transmitter» - by means of procreation - of the subject's personal identity (genetic patrimony) to offspring. For this reason, while an hypothetical encephalon transplant can in no case be considered morally licit, neither can an eventual gonad transplant - if performed for the purpose of supplying the gametogenetic function - be morally acceptable. Different, however, is the case of a gonad transplant performed exclusively for hormonogenetic purposes (that is, to restore a sufficient hormonal function); once the integrity of the subject's personal identity has been ensured, and once the disassociation with procreation has been established, there would be no particular moral reservations. In this regard, see M.P. Faggioni, Il trapianto di gonadi. Storia e attualità, Med. Mor., 1998, 48, 15-46.

62 Cf. Cuer P., Quelques considérations éthiques, notamment sur l'identité lors de xénotrasplantations, Path Biol (Paris) 2000, 48: 426-428.

transplant with success, without exposing the recipient to excessive risks».

We may observe here that together with the defence of personal identity, these pronouncements of the Magisterium indicate a second criterion for the moral legitimacy of xenotransplantation: health risk. We shall discuss this in greater detail shortly.

With regard to all other issues, from the standpoint of moral theology, the ethical conditions required for every other kind of transplant apply also for xenotransplantation[63].

Bioethical Issues

Further investigation and clarification is needed for a wider bioethical analysis. The ethical evaluation of the practicability of xenotransplantation, in light of the current situation as summarized in the first part of this document, requires the consideration of a whole series of factors, some of which are derived from the general moral norms valid for all transplants, and others of which are more specifically related to xenotransplantation[64].

The Health Risk

13. As previously stated, one of the fundamental ethical questions that should be examined when judging the legitimacy of xenotransplantation is that of the health risk involved in such procedures. This risk is dependent on various factors which cannot always be predicted or assessed. Before going on, therefore, it may be useful to recall some general aspects of the ethics of risk.

63 Cf. also John Paul II, Address to the Participants at a Congress on Organs Transplantation (20 June 1991) in Insegnamenti di Giovanni Paolo II, XIV/1, 1991, p. 1711, 20/6/1991; Catechism of The Catholic Church (1994) n. 2296; John Paul II, Enc. Lett. Evangelium Vitae (1995) n. 86; Pont. Counc. Past. Assist. Health Care Workers., Charter for Health Care Workers (1995), nn. 83-91; John Paul II, Address to the Eighteenth International Congress of the Transplant Society, 29/8/2000.

64 For an overview of the current debate see: Caplan A.L., Is Xenografting Morally Wrong?, Transplantation Proceedings, 1992, 24: 722-727; Hanson M.J., The Seductive Sirens of Medical Progress. The case of Xenotransplantation, Hastings Center Report 1995, 25: 5-6; Nuffield Council of Bioethics, Animal-to-Human Transplants: the Ethics of Xenotransplantation, London: Nuffield Council of Bioethics, 1996; Mc Carthy Ch.R., A New Look at Animal-to-Human Organ Transplantation, Kennedy Institute of Ethics Journal, 1996, 6: 183-188; U.S. Institute of Medicine Committee on Xenograft Transplantation, Xenotransplantation: Science, Ethics, and Public Policy, Washington: National Academy Press, 1996; Bach F.H., Fishman J.A., Daniels N., et al., Uncertainty in Xenotransplantation: Individual Benefit versus Collective Risk, Nature Medicine, 1998, 4: 141-144; Hughes J., Xenografting: Ethical Issues, Journal of Medical Ethics, 1998, 24: 18-24; Vanderpool H.Y., Critical Ethical Issues in Clinical Trials with Xenotransplants, The Lancet, 1998, 351: 1347-1350; Clark M.A., This Little Piggy Went to Market: The Xenotransplantation and Xenozoonose Debate, Journal of Law, Medicine and Ethics, 1999, 27: 137-152; Comité Consultatif National d'Éthique pour les Sciences de la vie et de la santé (France), Avis sur l'éthique et la xénotransplantation, n. 61, 11 June 1999; Cooper D.K.C., Lanza R.P., Xeno, the Promise of Transplanting Animal Organs into Humans, New York: Oxford University Press 2000; U.S. Dpt. Health & Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, Source animal, product, preclinical, and clinical issues concerning the use of Xenotransplantation products in humans: guidance for industry (Draft, February 2001), (http: //www.fda.gov/ cber/guidelines.htm).

Risk - understood as an unwanted or damaging future event, the actual occurrence of which is not certain but possible[65] - is defined by means of two characteristics: the level of probability and the extent of damage. The probability of the occurrence of a certain damaging event in particular circumstances can be expressed as a risk percentage or as a statistical frequency. Furthermore, the presence or absence of certain chance factors of risk can sometimes alter the probability that a certain event will take place. The extent of the damage, in contrast, is measured by the effects that the event produces. Naturally, a very probable risk is easily tolerated if the extent of damage associated with it is very small; on the contrary, a risk that causes a high level of damage, however improbable, gives rise to much greater concern and require greater caution.

It is important to distinguish between a probable event (albeit with varying degrees of probability) and an event that is only hypothetical; this latter is an event which is not theoretically impossible but which is so improbable as to require no change in behaviour or choices.

Together, these two criteria - probability and extent of damage - define the acceptability of the risk, as reflected by the risk/benefit ratio. Only when a risk can be concretely assessed it is possible to apply criteria for evaluating its acceptability.

Lastly, it is necessary to distinguish acceptability from what we can define as the acceptance of the risk, as defined by the reaction of the individual or of the general public to the existence of the risk. This is a response that has a significant subjective component, one which is not always completely thought out and which is influenced by culture, by the information available and how it is understood, by the way in which the information itself is communicated, and by common sensibilities[66].

In the absence of data that allow a reliable assessment of such a risk, greater caution should be used; this does not necessarily mean, however, that a total «block» should be put on all experimentation. Indeed, to move from ignorance to knowledge, from the unknown to the known requires the exploration of new approaches which in all likelihood, especially during initial experimental stages, will not be without risks, at least potentially. In this situation, therefore, the imperative ethical requirement is to proceed by «small steps» in the acquisition of new knowledge, making use in experiments of the least possible number of subjects, with careful and constant monitoring and a readiness at every moment to revise the design of the experiment on the basis of new data emerging.

It is important to consider the distinction between risk assessment and

65 Cf. Schöne-Seifert B., Risk, in Reich T.W. (ed.), Encyclopedia of Bioethics, vol. 4, New York: MacMillan 1995 (revised edition), 2316-2321.

66 An overview of social reactions to different aspects of xenotransplantation: Appel J.Z., Alwayn I.P., Cooper D.K., Xenotransplantation: The Challenge to Current Psychological Attitudes, Prog Transplant 2000, 10: 217-225.

risk management. To achieve an ethical assessment, both elements must be carefully examined.

14. This general discussion of the ethics of risk must now be applied to the specific case of xenotransplantation.

First of all, we note that there are issues connected with xenotransplantation, such as the probability of rejection and the increase in the probability of infection because of immunosuppressive therapies, about which some degree of knowledge already exists, although further study is necessary. The data which the scientific community already possesses, together with new data being gathered, can help to establish the threshold of risk that must not be crossed if a transplant operation to be considered morally acceptable.

More complex and uncertain is the assessment and evaluation of risks connected to one specific aspect of xenotransplantation: the possible transmission to the recipient of infections arising from the xenotransplant (zoonoses) by known or unknown pathogenic agents which are not harmful to the animal but which are possibly dangerous for man. Such infections could escape detection, with the consequent possibility of the spread of the infection to those having close contacts with the patient, leading eventually to its being spread to the entire population.

Since clinical experience of xenotransplantation is quite limited and certainly insufficient to provide reliable statistics on the real probability of occurrences and spread of infections, any decision concerning clinical development of the new therapy can only be based on hypothesis. There is, therefore, an ethical requirement to proceed with the greatest caution.

When the moment for clinical application of xenotransplantation arrives, it will be necessary to select patients carefully, based on clear and well-established criteria[67], and to monitor the patient very closely and constantly. One must also contemplate the possibility of placing the patient in quarantine to prevent the epidemic spread of an infection. Arrangements for some kind of monitoring of those having close contacts with patient should also be made.

Moreover, during the experimental phase of clinical trials, patients should agree not to procreate because of the possible risk of genetic recombination that could affect the patient's germ cells. Sexual abstinence would also be necessary to avoid the venereal transmission of possible viruses.

In the clinical application of xenotransplantation, psychology should also play an important role. It should address the probable repercussions that the recipient could undergo in their psyche (e.g. because of the modification of one's «bodily schema») arising from the acceptance of a foreign organ[68], especially

67 Cf. Beckmann J.P., Xenotransplantation aus ethischer Sicht. Eine Skizze, Zentralbl Chir 1999, 124: 636-640; Welin S., Starting Clinical Trials of Xenotransplantation. Reflections on the Ethics of the Early Phase, J Med Ethics 2000, 26: 231-236.

68 In this regard, polls have been taken to ascertain the level of public acceptance of eventual xenotransplantation. See, for example, Mohacsi P.J., Blumer E.C., Quine S. et al., Aversion to Xenotrans-

when it comes from an animal[69]. In the post-transplant stage, psychology must also provide clinical support the for the patient in the process of integration.

Trangenesis

15. The use of organs from engineered animals for xenotransplantation raises the need for certain reflections on transgenesis and its ethical implications.

The term «transgenic animal» is used to indicate an animal whose genetic make-up has been modified by the introduction of a new gene (or genes). In contrast, the term «knock out» is used to designate those animals in which a given endogenous gene (or genes) is no longer expressed. In either case, such animals will express particular characteristics which will be transmitted to the offspring.

As we have already observed, the possibility of working out such genetic modifications, using genes of human origin as well, is morally acceptable when done in respect for the animal and for biodiversity, and with a view to bringing significant benefits to man himself. Therefore, while recognizing that transgenesis does not compromise the overall genetic identity of the mutated animal or its species, and reaffirming man's responsibility towards the created order and towards the pursuit of improving health by means of certain types of genetic manipulation, we will now enumerate some fundamental ethical conditions which must be respected:

1. Concern for the well-being of genetically modified animals should be guaranteed so that the effect of the transgene's expression, possible modification of the anatomical, physiological and/or behavioural aspects of the animal may be assessed, all the while limiting the levels of stress and pain, suffering and anxiety experienced by the animal;

2. The effects on the offspring and possible repercussions for the environment should be considered;

3. Such animals should be kept under tight control and should not be released into the general environment;

4. The number of animals used in experiments should be kept to a bare minimum;

5. The removal of organs and/or tissues must take place during a single surgical operation;

6. Every experimental protocol on animals must be evaluated by a competent ethics committee.

Informed Consent

16. In the ethical discussion on xenotransplantation, the subject of informed consent also deserves special attention[70].

plantation, Nature, 1995, 378: 434; National Kidney Federation, Survey reveals positive feelings on animal-to-human transplants, Dialysis and Transplantation, 1995, p. 677; Mohacsi P.J. et al., Patients attitudes to xenotransplantations, Lancet 1997, 349: 1031.

69 Cf. Crafen J., Rodin G.M., Psychiatric Aspects of Organ Transplantation, New York: Oxford Medical Publications, 1992.

70 Cf. Barker J.H., Polcrack L., Respect for persons, informed consent and the assessment of infectious disease risks in xenotransplantation, Med Health Care Philos 2001, 4(1): 53-70.

Given the animal source of the organs which will be transplanted, this issues concerns only the recipient and, secondly, his relatives. At the outset the recipient should be given every information regarding his pathology and its prognosis, the xenotransplant operation and subsequent therapy, and the probability of success and the risks of rejection. Special attention should be paid to making sure that the patient is informed about the real and hypothetical risks of zoonoses, in light of current data, and about the precautions to be adopted in the case of infection (in particular the possible need for quarantine, which involves avoiding physical contact with others while the risk of contagion is present). The patient must also be informed about the need to remain under medical supervision for the rest of his life, so that the necessary constant monitoring following the transplant may be carried out. In addition, adequate information on possible alternative therapies to xenotransplant therapy should not be withheld.

This informed consent on the part of the patient should be understood as personal. For this reason, minors and those unable to give valid consent are to be excluded from the experimental phase.

However, if a patient incapable of giving valid consent should find himself in a previously unforeseen situation where there is danger of imminent death, recourse may be made to a legal representative (e.g. in the hypothetical case of a life-saving xenotransplant as a temporary solution for a patient in a coma), provided that the medical procedures to be used offers a reasonable hope of benefit for the patient.

The patient's relatives should also be informed about what the transplant could entail regarding their contact with the patient and about the possible risks of contagion should an infection, as mentioned above, set in. In a strict sense, however, consent cannot be requested from them, since it is the patient who is ultimately responsible for the choices concerning his own health.

Allocation of Health Care Resources

17. Xenotransplantation certainly represents a form of possible treatment requiring a great outlay of both health care resources and economic resources[71]. For this reason, some people have expressed doubts about its ethical validity; given the large amounts of resources that it would take away from the other forms of therapeutic treatment and from other area of research, they consider both the uncertainty about its success and the risk entailed to be excessive. Faced with these doubts, it is important to remember that, even taken into due consideration the costs-benefits balance, the huge amount of health care resources used in this case is justified by the urgent need to try to save the lives of so many patients who would otherwise have no chance of survival.

71 Cf. Kress J.M., Xenotransplantation: ethics and economics, Food Drug Law Journal 1998, 53 (2): 353-384; Urruela Mora A., Workshop on the ethical, sociologic, economic and legal aspects of xenotransplantation, Law Hum Genome Rev 2000 Jan-Jun; (12): 245-6.

It should also be added that as long as xenotransplantation on man remains at an experimental stage it should not be subject to the criteria applied to treatment in strict sense; rather it should be evaluated according to the criteria used for trials. Therefore, the foreseeable collective benefits that it may accrue in the future should also be taken into account. We do well to recognize here that the research into xenotransplantation which has taken place so far has also brought about greater medical knowledge in the area of allotransplantation.

Patentability and Xenotransplantation

18. Research on xenotransplantation has hitherto in large measure been carried out largely by private pharmaceutical companies which have committed substantial economic resources to this endeavour; they have also been providing financing to public institutions for the purpose of obtaining better therapeutic results. It is therefore reasonable for them to expect an economic return on the investment made; one of the possible ways to do this is by acquiring patents.

From a formal point of view, there is no technical or legal obstacle standing in the way of the patenting genetically engineered animal organs intended for transplants[72]. It should be emphasised however that the norms drawn up by the European Community to regulate this matter could not, at the time they were being drafted, take into account the use of such organs for transplant from animal to man, since this therapeutic procedure had not yet been accomplished in clinical practice.

We therefore stress that, given the extraordinary financial commitment that has been made, now is the time to reconsider - or rather to be more precise about - the specific norms that apply.

We are aware of the broad debate underway on the basic question of whether the possibility itself of patenting living beings (even though genetically modified) or parts of them, especially when they contain genetic elements derived from humans (as is the case with animal organs genetically engineered for xenotransplantation into man), is ethically acceptable. We are also aware that there is a difference between a «discovery» (which cannot be patented) and an «invention» (which can be patented). Although it is our view that the transgenic animal as such - and all the more when they are used for transplantation into man - should be considered «nonpatentable», we nonetheless believe that it is not the purpose of present document to address this complex question directly.

Here, we shall limit ourselves to emphasising that, whatever answer may be given to this basic question, it is always necessary - as a bare minimum - to guarantee respect for the fundamental right of every person to equitable access

72 Cf. Trattato di Cooperazione sui Brevetti (Washington, 1970), art.33; Convenzione del Brevetto Europeo (Munich, 1973), 54-57; vedi anche Marchetti P., Ubertazzi L.C., Commentario breve al diritto della concorrenza, Padova, CEDAM, 1997: 1343.

to the health care they may be needed, without discrimination and without being impeded by excessive costs. This applies above all else to accessibility to treatment. This objective - in the hypothetical case of patents connected with xenotransplantation, a procedure which should be viewed from a therapeutic standpoint - can be reached by making appropriate legal requirements apply (for example, the introduction of compulsory licences), thus allowing «production» at accessible prices[73] which would hopefully be controlled by a supranational body specifically set up for this purpose.

Practical Guidelines

19. Bearing in mind all that has been said above, we can now present a practical approach which will guide the path of research and development in the area of xenotransplantation as applied to man.

Regarding the xenotransplantation of solid organs, it is of course necessary that pre-clinical experiments (from animal to animal) should continue for as long as scientists should require and until repeatable positive results are obtained, results which are considered sufficient to allow trials on man to begin.

When the moment arrives, it will be ethically correct, respecting the rules of informed consent indicated above, to involve initially only a restricted group of patients, patients who cannot be chosen - in the given circumstances - for allotransplantation (whether because of waiting lists or individual counter-indications), and for whom no better alternative treatment is available.

A commensurate moral imperative is that of ensuring careful and detailed monitoring of the individuals who receive a xenograft, a situation which could foreseeably continue for the rest of the patient's life, watching for any sign of possible infection caused by known and unknown pathogenic agents.

In addition, every experimental clinical trial should be carried out in highly specialised centres with proven experience in pre-clinical pig-to-primate models; these centres should be authorised and supervised by the competent health care authorities.

The results thus obtained, if unequivocally positive, would constitute the basis for extending the practice of xenotransplantation, making it an accepted surgical therapy.

20. The questions and issues related to xenotransplantation have implications of a very wide social character. There is thus an ethical need to acquire correct information on the topics of greatest public interest with regard to the potential benefits and risks. This information should be communicated to as large a segment of the public as possible. Moreover, by means of debates and public discussions in small

73 Cf. WIPO/OMPI, Introduction to Intellectual Property: Theory and Practice, Kluwer Law International, London 1998: 145-150; Accordo di Marrakech istitutivo dell'Organizzazione Mondiale del Commercio, Annesso lC: Accordo sugli aspetti della proprietà intellettuale relativi al commercio (Marrakech, 1994), art. 31.

and large groups, society itself, through its representatives, should help to identify the conditions under which they would find it acceptable to invest resources and hope in this new therapeutic approach, in light of the scientific uncertainties which are still present and the urgent need to increase the availability of organs which can be transplanted.

A serious ethical commitment on the part of scientists should not neglect to explore therapeutic paths which may represent alternatives to xenotransplantation, such as seem to be promised by many recent discoveries in the field of genetics, as in a longer period the therapeutic use of adult stem cells.

21. With respect to the specific fields of health-related policies and legislation on matters of xenotransplantation, it is our heartfelt hope that the considerations offered in the present document will provide a useful point of reference for all those who - at an international, national, regional and local level - are responsible for leading society. Many countries[74] have already developed guidelines to regulate this complex sector, offering helpful operational directives.

On our part, we do not believe that this document should enter into procedural political-legislative matters. We therefore limit ourselves to emphasizing the importance and desirability that a substantial convergence of international legislation in this area should be achieved as soon as possible, by means of a genuine coordination at the different levels. On the one hand such legislation must provide rules for the continuation of scientific research, guaranteeing its validity and safety; on the other hand it must watch over the health of the citizens involved and the potential risks (especially infective) connected with xenotransplantation. Furthermore it must offer criteria for organizing the necessary information campaigns aimed at the entire population.

We conclude this document with the sincere hope that the effort made on this study by those who have participated in it - scientists, jurists, theologians and bioethicists - will represent a concrete contribution to the development of the discussion on the important theme of xenotransplantation. May it also be seen as a further expression of the close attention which the Catholic Church pays on problems related to human disease and suffering.

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74 To give a few examples of some important organizations that have drafted guidelines in this area, we list the following: the Council of Europe, the Health Council of the Netherlands, the Swedish Committee on Xenotransplantation, the Spanish Xenotransplantation Sub-committee, the Argentine National Commission on Xenotransplantation, the U.S. Department of Health and Human Services Committee on Xenotransplantation, the United Kingdom Xenotransplantation Interim Regulatory Authority, and the Italian Xenotransplantation Commission. In France, the ethical aspects are currently being examined by the French National Ethics Committee and applications for clinical trials will need the approval of the newly formed Agency for the Security of Health Products and of the Ministry of Health. In Germany, the German Medical Council has established a committee to prepare guidelines on xenotransplantation. In Canada «Health Canada' has the authority to regulate xenotransplantation as a new technology.

* As is the custom, this document of the Pontifical Academy for Life is published under the editorship of the President and Vice-President.

In drafting its contents, the Academy received input from an international work group with specific expertise in the various disciplines connected with xenotransplantation; this work group met many times in the Vatican earlier this year.

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