Xenotransplantation

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Health Council of the Netherlands: Committee on Xenotransplantation

to:

the Minister of Health, Welfare and Sport

the Minister of Agriculture, Nature Management and Fisheries

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Preface to the English edition

In a letter dated 31 December 1996, the Minister of Health, Welfare and Sport asked for information on the current level of knowledge concerning xenotransplantation. A Committee on Xenotransplantation of the Health Council was formed to respond to the Minister's request. On 21 January 1998, I presented the Committee's report to the Minister. An English translation of my letter accompanying the report reads as follows:

On 31 December 1996 you asked for advice concerning the scientific, ethical and legal aspects of xenotransplantation.

A Committee that I installed for this purpose drafted the report 'Xenotransplantation'. Having consulted the Standing Committees on Medicine and on Medical Ethics and Health Law I herewith present you with this report.

The Committee concludes that xenotransplantation can be an alternative to transplantation of human organs, tissues or cells. Results of animal experiments indicate good progress in adjusting the technique for use in human patients. Nevertheless the Committee does not consider it possible to indicate when the first clinical trials can be performed. In particular the possible transfer of pathogens from the animal transplant to the human recipient and third parties is very worrisome. The Committee also suggests that, before xenotransplants on human patients are performed, a public debate is held on whether such medical treatments are desirable. I fully agree with these points of view, as I do also with the position that transplantation of human organs is by far preferable to xenotransplantation.

The Committee also indicates the legal position of xenotransplantation and the legislative gaps with respect to the technique. I would especially like to point at the recommendation, that was also given by the

Gene Therapy Committee of the Health Council, to develop dedicated laws that lay down rules for the quality and control of medical products being or consisting of living material (biologicals). I think that it is of utmost importance that clear regulations be drafted pertaining to such modern biotechnological developments.

Finally I would like to draw your attention to the recommendation of the Committee to give the Central Committee, that will be formed within the framework of the Medical Research Involving Human Subjects Act, the sole authority to judge on protocols for clinical xenotransplantation experiments. Also because of the ethical questions relating to xenotransplantation, I feel it to be of great importance that a central authority monitors the developments in this field and decides when experiments involving human beings are justified.

The present publication contains the English translation of the full text of the Committee's report.

JA Knottnerus,
Vice-president
of the
Health Council of the Netherlands

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Executive summary

Xenotransplantation is the transfer of organs from an animal of one species to an animal of another species (or to a human being). The technique is seen as a possible solution for the shortage of human donor organs caused by the fact that the demand for organs is rising faster than the supply. In this report, a committee of the Health Council of the Netherlands describes the present scientific status of xenotrans- plantation. A number of ethical issues are also considered in relation to the desirability and acceptability of research into and the possible clinical application of the technique. The report additionally includes a brief summary of the legislation which is relevant in this field.

The rejection of transplanted material is a major problem in relation to transplantations in general and xenotransplantation in particular. The evolutionary differences between humans and animals are sufficiently great that rejection begins within a few minutes, except in cases where organs are being transplanted to humans from non-human primates. Hyperacute rejection of this kind and the associated molecular processes are nowadays quite well understood. It would appear that the problem could be solved by effecting certain genetic modifications in the source animal, to make it more similar to the recipient. However, once the hyperacute rejection stage is past, another form of rejection manifests itself within a matter of days. The only way of preventing this second kind of rejection is to use immunosuppressive agents — substances which prevent or interfere with normal immune responses — in doses which are not

acceptable for humans because of the associated high risk for many and serious complications. There is no obvious solution to this problem at present.

Difficulties also exist in relation to the way the transplanted organ functions in the recipient's body. Here again, solutions must be found before xenotransplantation becomes a viable means of treating human patients.

At present, another obstacle to the use of xenotransplantation is the risk of infection. It is conceivable that agents such as viruses could be transferred to the recipient of the organ, causing disease. Indeed, once transferred to a human in this way, a disease might even be passed on to other people. Scientists do not yet understand anywhere near enough about the processes involved to enable them to estimate the associated risks.

Uncertainty regarding the questions outlined above presently remains too great for the Committee to reach any conclusion regarding the future viability of xenotransplantation as a clinical technique. Clinical experiments would not be appropriate until there is a good chance of operative success and until the rejection problems have been reduced to a level comparable with that currently associated with the transplantation of organs from human donors. The risk of infection must also be reduced to an acceptable level. To this end, there is a need for better understanding of the risk of pathogen transfer and for ways of ensuring that organs are free from highly infectious pathogens. Greater certainty is required both in relation to pathogens capable of causing relatively minor infections in large population groups (such as influenza viruses) and in relation to pathogens capable of causing serious diseases in small groups.

It is important that the ethical acceptability of clinical xenotransplantation — both from the human viewpoint and from the animal viewpoint — is considered while the technique is still at an early stage of development.

If xenotransplantation becomes clinically viable, the technique will be capable of alleviating the suffering of people with certain medical conditions and in many cases of prolonging life. The Committee therefore believes that, from a human point of view, xenotransplantation is ethically acceptable. Furthermore, the Committee is of the opinion that the interests of the people who might benefit from the technique are sufficient to justify the possible inconvenience to or infringement upon the integrity of the animals concerned and that the breeding of genetically modified animals for xenotransplantation purposes is therefore acceptable.

It is recognized that some people may, for cultural or religious reasons, disagree with the Committee's conclusions regarding the morality of using animals for xenotransplantation or implanting animal organs into humans. The Committee would consequently like to see information made available and the encouragement of public debate on these matters.

In view of the safety risks associated with the possible transfer of infectious pathogens, the Committee advises against obtaining organs from non-human primates for the time being. Scientific developments tend to suggest that the pig is currently the most suitable source animal for xenotransplantation.

The Committee considers it acceptable that pigs are kept in conditions appropriate for the breeding of specified pathogen-free (SPF) animals, provided that due consideration were given to the animals' welfare. The breeding of pathogen-free animals is complicated by the presence of endogenic viruses, i.e. viruses which are part of the host's genetic make-up and therefore not easy to eradicate. Recent research suggests that such viruses could make the transition from pig to man, but it is not yet clear whether they would cause disease in humans.

All possible avenues must be explored in the search for a way of ensuring that the demand for replacement organs is met. The Committee believes that the best course by far is to increase the supply of organs from human donors. In this context, great importance is attached to information campaigns, both aimed at the public and aimed at the medical professions. While welcoming the publicity activities organized in the framework of the revised Organ Donation Act, the Committee doubts whether these or other statutory activities will be sufficient to end the present shortage. Other options, such as gene therapy and artificial organs, are not expected to provide a solution in the short term, i.e. within the next few years. Preventive measures could reduce the incidence of organ function loss, but are not thought likely to reduce the demand for organs sufficiently. Indeed, as the population ages, the demand for organs is only likely to increase.

The report's brief summary of existing and future legislation pertinent to xenotransplantation indicates that not all relevant issues are or will be adequately or appropriately covered.

The use of animals is addressed by the Animal Health and Welfare Act, which regulates among others that the performance of biotechnological procedures, including genetic modification, is subjected to licensing based on an ethical judgement of the Biotechnology in Animals Committee. However, the Act does not control experimentation with (source) animals bred in other countries. The Committee therefore proposes to modify the Act in such a way that this is taken care of. As long as this is not the case the Committee asks scientists to take their social responsibility and to voluntarily present such experiments to the Biotechnology in Animals Committee.

Organs from genetically modified source animals and the recipients of such organs are covered by the legislation on genetically modified organisms (GMOs). This legislation is designed to protect the environment and human health from any adverse

effects which the production or use of GMOs might have. If clinical xenotransplantation were to become a reality, the recipient of a genetically modified animal organ would be regarded under this legislation as the carrier of a GMO. As such, the recipient would come within the scope of the Environmentally Hazardous Substances Act and the associated regulations. The Committee considers this undesirable, as this body of law was not formulated with medical applications in mind; it is intended to protect the population at large, rather than the health of individual patients. The Committee would therefore like to see the recipients of genetically modified animal organs explicitly excluded from the scope of the Act.

Furthermore, the Committee recommends most strongly that agreement should be sought within the EU regarding the application of GMO regulations in a way which specifically addresses the issues surrounding xenotransplantation.

According to the Committee, the government should act before clinical experimentation begins, to protect individual patients and public health against the risks associated with xenotransplantation, in particular the risk of possible pathogen transfer. One of the first requirements is further research into the risk of cross- infection between species. The government could then, on the basis of the results of this research, introduce organ quality requirements. It might also be appropriate for the government to impose specific quality requirements on all aspects of treatment associated with transplantation, in order to limit the risk of infection from unknown pathogens.

The expectation is that animal organs for xenotransplantation will be supplied on a commercial basis. It is therefore important that quality requirements applicable to such organs are included in product regulations. The Committee advises taking the necessary action before clinical experimentation begins. Given that the trade in organs will in all probability be international, the Committee is strongly in favour of uniform product quality standards, at least within Europe.

In the Committee's judgement, the Netherlands' existing medical product regulations are not adequate to regulate the trade in organs for xenotransplantation, mainly because they do not contain the desired quality standards or quality control requirements. The Committee therefore wishes to see new legislation introduced covering medical products that consist at least partly of living material (biologicals). This legislation should include quality standards for biological products in general and for particular product types. A new act could also serve as a vehicle for the harmonization of existing rules and the regulation of otherwise neglected areas. As indicated earlier, the quality standards included in any such legislation should be agreed with the Netherlands' European partners.

While recognizing that new legislation of the kind described cannot be introduced in the short term, the Committee would like to see regulations brought in quickly to

cover xenotransplantation involving human beings. It is accordingly suggested that, as an interim solution, organs for xenotransplantation should be brought within the scope of the legislation on medicines. Until the introduction of European quality standards, this move should be agreed with other EU member states.

The (forthcoming) Medical Research Involving Human Subjects Act will cover clinical xenotransplantation experiments and appears to provide a sound basis for the supervision of such activities. It is suggested that only the central ethical review committee (CeCo) whose establishment is provided for by the Act should have the authority to review protocols for research involving human xenotransplantation. As a national body, the CeCo would be well placed to monitor developments in this field.

The existing Hospital Provision Act does not lend itself easily to governmental control of clinical xenotransplantation. However, it would be possible to ban xenotransplantation or to introduce compulsory licensing under the Exceptional Medical Procedures Act that recently came in force. The Act could also be used to impose a moratorium.

Any patient offered an animal organ should be properly informed about the proposed procedure, and no xenotransplant operation should be performed without the recipient's informed consent. The information given to potential recipients should highlight the possibility of pathogen transfer and the consequent need for continual and extensive monitoring following the operation. Since an infection could be passed on to people with whom the transplant patient has contact, the health of such individuals would also have to be monitored. The voluntary and informed cooperation of the patient's friends and relatives is therefore an important aspect of the xenotransplant operation. Registration of the data collected during the postoperative checks is an essential prerequisite; there may, however, be problems reconciling public health interests with the individual's right of privacy. Nevertheless, it should always be made clear that further direct contact between the patient and anyone who declines to cooperate in this regard would not be possible. Furthermore, during the clinical experimentation phase at least, it will be necessary to restrict the number of people with whom a patient has contact following a transplant operation, so as to keep the postoperative monitoring programme to tolerable proportions. As a result, the organ recipient's freedom of movement will need to be restricted. Xenotransplant operations should not be made generally available until these problems are manageable.

Chapter 1

Introduction

1.1 Background

Loss of organ function is a major cause of illness and death. Increasingly, it is possible to treat such function loss by implanting an organ, part of an organ or certain organ cells, usually taken from a deceased human donor. However, demand for organs, which already exceeds supply, is rising. By way of example, Figure 1 shows how the number of people waiting for kidney transplants has risen in the area covered by Eurotransplant (Belgium, Germany, The Netherlands, Austria and Luxembourg).

In 1995, 384 kidney transplant operations were performed in the Netherlands using organs from deceased donors (post-mortem transplants) and a further ninety-six patients received kidneys from living donors (usually relatives). At the end of 1995, 1703 people were waiting to receive kidneys. In the same year, there were forty-eight heart transplants, although sixty-seven patients were referred for such operations (Cou97).

The most appropriate replacement for a malfunctioning or non-functional organ is currently an organ from a human donor; and by far the best way of tackling the shortage in donor organs is to increase the supply. Nevertheless, as long as a shortage exists, it is important to look for alternatives. Broadly speaking, there are two possible alternatives to human donor organs: man-made implants (e.g. artificial hearts) and animal organs. The transfer of organs from one species to another is known as

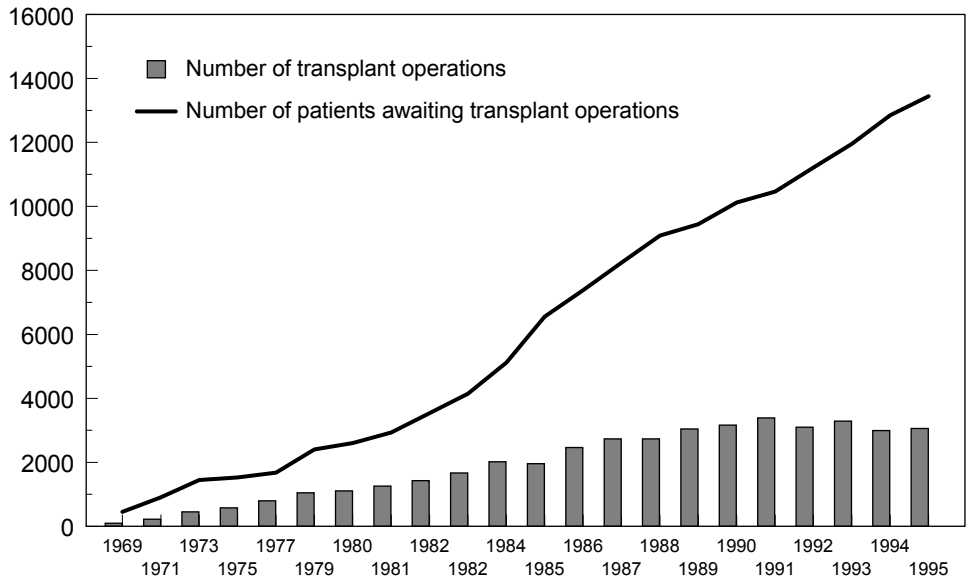

Figure 1 The length of the Eurotransplant kidney waiting list on 31 December each year and the number of kidney transplant operations performed each year, between 1969 and 1995. The growing number of people waiting for transplants is due partly to loosening of the referral criteria and partly to the increase in re-transplantation. (Source: Coh95)

xenotransplantation (xenos = foreign). Transplantation between two humans is also referred to as *allotransplantation* (allos = other).

The xenotransplantation of animal organs to humans is problematic for various reasons. First, the body naturally rejects tissue from another species. The farther removed the source animal* is in evolutionary terms, the more violent the rejection. However, recent scientific research has indicated that rejection phenomena can be reduced to a certain extent by genetically modifying the source animals. Second, xenotransplantation is potentially hazardous: organs taken from animals may contain pathogens which, even if they have no adverse effect upon the health of the source animal, are capable of causing disease in humans. It is possible that a disease transferred in this way might be contagious, i.e. capable of passing from the recipient of an animal organ to other humans. The nature and seriousness of such risks are not known. Third, doubt exists as to whether an animal organ would, in functional terms, be capable of replacing a human organ. The greater the evolutionary difference between the source species and homo sapiens, the greater the likelihood of significant physiological differences in organ function. Fourth, the ethical, legal and social

* It would not be appropriate to refer to an animal from which an organ is taken for transplantation as a donor animal, since donation is a voluntary act. Clearly no animal used for xenotransplantation can consent to participation.

acceptability of xenotransplantation is open to question. Is it acceptable to genetically modify animals with a view to using them to provide organs for human patients? And is a person's human integrity compromised if his or her life depends on an organ taken from an animal? Finally, it is unclear whether the law as it stands forms an adequate framework for regulating biomedical developments in the field of xenotransplantation. For several years, the pharmaceutical industry and other interested parties have done a great deal to secure progress in this field. As a result, the issues associated with xenotransplantation have a very international nature. Genetically modified — transgenic — source animals are bred (usually for commercial purposes) only in a small number of countries around the world. Consequently, international trade in such animals or their organs will inevitably develop. Under such circumstances, it is not always possible to regulate this trade using national legislation alone.

In recent years, partly as a result of the business community's involvement, scientists have made considerable progress in their efforts to reduce certain rejection phenomena which occur immediately after xenotransplantation. The publicity given to these developments has generated a great deal of public interest in xenotransplantation (Ano96, Lai96, Mor96, Nas95). Many patients see xenotransplantation as a potential cure for their problems and are pressing for the acceleration of scientific developments (Rog96). At the same time, the existence of commercial interests means that there is a danger of scientific information being suppressed for reasons of industrial politics. This makes it more difficult to obtain a proper, up-to-date overview of the present state of affairs in this field.

1.2 Ministerial request and composition of the Committee

In view of the circumstances outlined in section 1.1, the Minister of Health, Welfare and Sport asked the Health Council to prepare a report on the subject of xenotransplantation. The text of the Minister's request is reproduced in Annex A.

On 13 January 1997, the Council's vice-president established a Committee on Xenotransplantation (referred to in this report simply as 'the Committee'), whose remit was to prepare a report, as requested by the Minister. The members of the Committee are listed in Annex B.

1.3 Structure of this report

In this report, the Committee addresses the questions posed by the Minister and makes certain recommendations regarding resolution of the problems identified. In Chapter 2, a number of relevant reports published in other countries are discussed. The most

significant biomedical developments are then reviewed in Chapter 3, which also describes the rejection and infection problems associated with xenotransplantation. The following chapter deals with various animal and human welfare issues central to the debate on the social acceptability of xenotransplantation. Alternative ways of meeting the demand for replacement organs are also briefly considered. Chapter 5 is devoted to existing and proposed legislation pertinent to the various developmental stages: animal testing, experiments with humans and ultimately general clinical application. In the sixth and final chapter, the Committee presents its conclusions regarding the desirability of xenotransplantation.

Chapter 2

Reports published in other countries

In 1996 and 1997, three important reports were published on the subject of xenotransplantation: two in the United Kingdom and one in the United States. These reports helped to inspire the deliberations upon which the present report is based. The principal conclusions of the three foreign reports are discussed below.

2.1 The Nuffield Council of Bioethics

The UK's Nuffield Council of Bioethics concluded that it was ethically acceptable to breed and use pigs for xenotransplantation purposes, but not primates (Nuf96). The Council highlighted the risk of pathogen transfer and strongly urged the authorities to take appropriate preventive action. The report's main recommendation was the creation of an Advisory Committee on Xenotransplantation with a wide-ranging remit: collecting data on the risk of disease transfer and drawing up rules to minimize such risks, formulating guidelines on the medical supervision of xenotransplant recipients and the maintenance of a register of recipients, authorizing experiments with human subjects, determining the effects of xenotransplant operations on the patient and promoting debate on the issue. The Council recommended a moratorium on experiments with human subjects until the Advisory Committee had been set up and allowed to consider the acceptability of such experiments.

2.2 The Kennedy Committee

At about the same time that the Nuffield Council's report appeared, an Advisory Group on the Ethics of Xenotransplantation (otherwise known as the Kennedy Committee) set up by the British government completed its own deliberations (Ken96). Nothing was made public for a further six months, however, to allow the government to consider its response to the Committee's recommendations (Gov97). When they ultimately appeared, the Kennedy Committee's findings were largely in line with those of the Nuffield Council. The use of pigs as a source of organs for xenotransplantation was judged acceptable, as was the genetic modification of pigs with a view to reducing organ rejection problems. The Kennedy Committee considered it inadvisable to use primates as source animals, however, partly for emotional reasons, but mainly because of the greater risk of pathogen transfer. Experiments involving human subjects were not considered acceptable until more was known about the suppression of rejection phenomena and the risk of pathogen transfer. The Kennedy Committee echoed the call for a central body to supervise developments and to decide when clinical experiments should be allowed. The British government accepted the Committee's recommendations and duly established the UK Xenotransplantation Regulatory Authority (Ano97, Gov97, Nas97). A moratorium on the xenotransplantation of organs into humans was also announced.

2.3 The Institute of Medicine

Towards the end of 1996, the US Institute of Medicine published a report which recommended that the existing local Institutional Review Boards should be given responsibility for the assessment and supervision of xenotransplantation experiments (IOM96). The Institute envisaged making appropriate provisions under the federal regulations, which were published in draft form around the same time by the Public Health Service (PHS) (PHS96). The IoM placed considerable emphasis on the prevention of pathogen transfer and suggested that, once sufficient scientific progress had been made and the necessary safety measures were in place, the xenotrans-plantation of animal organs into humans would be justified and should therefore be permitted.

Like the IoM report, the PHS's draft guidelines firmly underlined the importance of safety. Even so, the document received a great deal of comment and criticism, especially on the issue of safety. In one response, forty-four scientists (most of them virologists) signed a letter stating that the use of primates as source animals was not acceptable because of the risk of pathogens being transferred to xenotransplant

patients, and the consequent risk of causing serious illness (Ben97). The PHS's assumption that it was sufficient to make provision for the early detection of any symptoms of disease was criticized on the grounds that by the time problems were detected, the damage had already been done. Some commentators were also unhappy with the suggestion that the (local) Institutional Review Boards should have the final word on whether xenotransplantation experiments with human subjects were to be allowed. It was felt that a central committee could summon greater expertise and would have a better overview of developments in the field. Perhaps predictably, the draft guidelines were criticized from the other side by transplant surgeons, who argued that the guidelines amounted to excessive government interference. A revised draft is expected from the PHS in early 1998.

Chapter 3

The state of science

3.1 Biomedical developments

3.1.1 Rejection

One of the main problems associated with transplantation is the process of rejection, whereby the recipient's immune system is activated and attacks the implanted foreign organ or tissue. The violence of the response is determined partly by the degree of difference between the tissue characteristics of the donor and those of the recipient and partly by the nature of the transplanted organ or tissue. For example, the transplantation of a (non-vascular) cornea barely provokes any immune response, while a transplanted kidney is liable to be violently rejected.

Immunological rejection, which is brought about by white blood cells (lymphocytes), takes several forms. First, there is rejection involving the production of antibodies by B-lymphocytes and their release into the blood; this process is known as humoral rejection. Antibodies can attack structures on the blood vessel endothelium (the cells which line the inner walls of the blood vessels) of a transplanted organ, thereby causing inflammation. Certain so-called complement system proteins circulating in the blood play an important role in this process. Complement proteins can also cause inflammation themselves, without the involvement of antibodies, by reacting with the blood vessel endothelium (see also 3.1.3). In either case, the result can be rejection of the transplant within a matter of hours or even minutes. Such rejection is known as hyperacute rejection. Another kind of rejection is caused by

T-lymphocytes: white blood cells which, once activated, can directly attack the cells of the foreign tissue, again resulting in inflammation. This form of rejection, known as cellular rejection, takes place over a period of days or months: acute and delayed acute rejection, respectively.

3.1.2 *Xenotransplantation*

Xenotransplantation is the transplantation of living material (cells, tissues, organs or parts of organs) from an organism of one species into an organism of another species. So far, research into the clinical viability of cellular xenotransplantation has focused mainly on the islets of Langerhans (with the aim of restoring insulin production in diabetes patients) (Gro94, Now94) and on brain cells (e.g. the transplantation of pig fetal brain cells into patients with Parkinson's disease, which involves function loss in certain brain tissues) (Dea97, Din97).

The organs in which xenotransplantation researchers are most interested are the kidneys, heart, lungs and, to a lesser extent, the liver and pancreas. A successful xenotransplant operation — i.e. one which resulted in the restoration of adequate organ function without serious rejection problems — would represent a major clinical breakthrough. However, while considerable success has been achieved in certain fields, it will be apparent from the paragraphs which follow that there is no immediate prospect of successfully transplanting an animal organ into a human being.

In this report, the Xenotransplantation Committee focuses on the xenotransplantation of organs. Nevertheless, the issues addressed (both the practical issues, such as rejection and infection risk, and the ethical or legal issues) relate equally to the xenotransplantation of cells or tissues.

3.1.3 *Discordance and concordance*

The degree of similarity between species determines the violence of the rejection process. In this context, a distinction is made between relatively dissimilar species (discordant species), such as humans and pigs, and relatively similar species (concordant species), such as humans and non-human primates (Mar94). Where discordant species are involved, the greatest obstacle to successful xenotransplantation has so far been hyperacute rejection, in which the complement system plays a key role. Complement, which is part of the humoral rejection system, consists of a series of consecutively activated blood-borne proteins (Law96). The binding of one of the first proteins in the complement series to the blood vessel endothelium (with or without the mediation of an antibody) triggers a complex process of complement protein binding and activation. This ultimately induces inflammation and would cause hyperacute

rejection in a xenotransplant recipient. Although the blood vessel endothelium is provided with complement-regulating proteins, which protect the blood vessel wall against complement activation, these are species-specific: they do not provide protection against the complement system of another species. Complement-regulating proteins appear to be the key to the problem of hyperacute rejection (Bha97, Dia97, Dor97, Kro97, Law96, Law97, War97, Zai97).

Xenotransplantation between concordant species would not cause problems with complement activation or, therefore, with hyperacute rejection. Thus, non-human primates would seem the best source animals for organ xenotransplantation.

3.1.4 Primates as source animals

Despite the advantages, there are a number of objections to using non-human primates as source animals.

First, the use of primates would create moral and legal problems. These are considered in chapters 4 and 5.

In addition, there are significant differences in body size and life expectancy. The heart of an adult baboon, for instance, would not have sufficient capacity to circulate blood around the body of an adult human, which would typically be twice as heavy. It is not known whether a baboon heart could grow or provide adequate life expectancy if given to a child.

Another important reason for not using primates as source animals is the risk of pathogens being transferred to the recipient and possibly via the recipient to other people. The likelihood of pathogen transfer is much greater between concordant species than between discordant species. Both HIV and the Marburg virus originated in primates, and serve as examples of the potential threat to human health. This particular safety problem is considered more closely in section 3.2.

3.1.5 Pigs as source animals

In view of the objections outlined above, researchers have for several years concentrated on the pig as a possible source of organs. Pig organs are similar in size to human organs, although pigs do not generally live as long as people. Another advantage is that pigs, unlike non-human primates, can be bred in large numbers relatively quickly.

Since pigs and humans are discordant species, hyperacute rejection would be the first obstacle to the use of pigs as source animals for xenotransplantation. Thereafter, there would be the problem of acute and delayed acute rejection in the period from a few days to a few months after transplantation. Finally, the possibility of chronic

rejection (which can occur several months or even years after transplantation) would have to be addressed. Animal experiments suggest that acute and chronic rejection are generally much more violent and serious after xenotransplantation than after allotransplantation (Bha97, War97, Zai97).

Before pigs can be considered suitable source animals, not only must the question of rejection be addressed, but it must also be established that a pig organ can adequately take over the function of a human organ. Pig organs transplanted into non-human primates have not always functioned properly. With the heart, the main problem is size; if the new organ is too small, it will not be able to pump enough blood around the body, but if it is too big (assuming it will even fit in the rib cage), it will pump too much blood, possibly leading to hyperaemia and oedema in the lungs and thus to loss of lung function (Sch97). Following the transplantation of discordant kidneys, anaemia is often a problem, because the new organs tend not to form enough of the hormone erythropoietin, which regulates the production of red blood cells (Koz97). Other researchers have observed that, when implanted in other species, pig kidneys do not always properly regulate blood concentrations of electrolytes such as sodium, potassium and calcium ions, which are important to the proper functioning of the body (Ham97a). Given the complexity of many liver functions, it is unlikely that a pig's liver could permanently take over from a human liver without function loss. However, the liver of a genetically modified pig has recently been used in isolation outside the body of a patient to give temporary assistance in a case of acute liver failure (Day97, Rog97).

Over the last few years, a number of experimental treatments have been performed, in which (fetal) pig islets of Langerhans were transplanted into humans. While rejection problems were successfully controlled by the use of high doses of immunosuppressing drugs, the amount of insulin produced was barely measurable (Tib97). It is worth noting that insulin from pigs was successfully administered to diabetics for decades before insulin produced with biotechnological methods became available.

3.1.6 Genetic modification

Significant progress has recently been made towards resolving the problem of hyperacute rejection.

First, the human genes which provide the code for various complement-regulating proteins were identified and isolated. Once this had been done, molecular biological techniques were used to introduce the relevant genes to pigs (Coz95). The process of transferring genes in this way is called transgenesis. Pigs whose genes have been modified in this way — transgenic pigs — carry human proteins which function just as

they do in people. Transgenic pigs with several human complement-regulating proteins are being bred in various countries (Bac97, Law97).

Another approach to the hyperacute rejection problem that is under investigation involves modifying certain cell membrane protein sugar groups, which act as recognition points for complement proteins, so that recognition is either prevented or impaired (LaV95, Pla95, Vau94). This kind of genetic modification is not transgenesis, since it does not involve the transfer of genetic material from one species to another. Researchers are now seeking to effect the same membrane protein sugar group modification in the transgenic pigs referred to above.

In very recent experiments, hyperacute rejection proved to be significantly reduced when the organs (hearts or kidneys) of transgenic pigs were transplanted to primates (Bha97, Dia97, Kro97, Law97, Zai97). Even so, immunosuppressant drugs were required in very high doses — up to ten times the maximum permitted for humans. The drugs were needed to control acute and delayed acute (cellular) rejection. Despite the success in controlling hyperacute rejection, it has not been possible to keep a primate alive with a functional pig's heart or kidney for longer than about three months. In cases where the organ was not rejected in an acute cellular response, the recipient animals died as a result of complications associated with the drastic immune suppression treatment (Bha97, Dia97, Zai97).

3.2 Risk of infection

From the survey above, it will be apparent that xenotransplantation still involves considerable risk for the recipient: not only may the transplanted organ fail to function or to function properly as a result of rejection or some other cause, but the immunosuppressing therapy necessary to prevent rejection may itself be hazardous. In addition to these risks, there is the danger that an infection could be transferred from the source animal to the recipient. Indeed, the threat of infection is particularly great because of the need to suppress the patient's immune responses. One must also bear in mind the fact that such infections may not be confined to the recipient. Contact between the patient and his or her environment may result in the disease spreading through the general public.

At present, only non-human primates and genetically modified pigs are under consideration as source animals for use in xenotransplantation. The following discussion of infection risks is therefore restricted to these animals.

Whether non-human primates or pigs are used as source animals, xenotransplantation involves a high risk of human recipients becoming infected by known pathogens, in particular viruses. There is also a risk of infection by potentially pathogenic (micro)organisms or other, as yet unidentified, pathogens (All96, Cha95).

3.2.1 *Primates*

In relation to human beings, non-human primates are concordant animal species. It is therefore probable that the use of such animals for xenotransplantation purposes would entail a considerably greater risk of infection than the use of discordant source animals. For this reason, the Committee believes that clinical experiments involving the use of primates as source animals are not presently justified.

On the other hand, the xenotransplantation of primate organs into humans would not induce such serious rejection problems as the introduction of pig organs. Thus, primates may be regarded as more suitable source animals. The Committee does not therefore rule out the use of primates as a matter of principle; if the xenotransplantation of pig organs should prove impractical, the situation might have to be reconsidered. Before using primates for such purposes, however, the ethical considerations must be explored (see 4.2.2). If it should be judged acceptable to use primates as source animals, organs should be taken only from specified pathogen-free (SPF) animals.

3.2.2 *Pigs*

Transplantation between discordant species (such as pigs and humans) does carry a risk of pathogen transfer, albeit smaller than the risk of pathogen transfer between concordant species.

The health risks associated with parasitic, bacterial and fungal infections could probably be reduced to acceptable levels by operating efficient elimination programmes and keeping the animals under conditions which preclude the reintroduction of such infections. To this end, it would be necessary to develop and implement a good husbandry practice (GHP) regime which entailed retaining the animals within a barrier system. Such a regime would also have to provide for regular testing to check for the presence of infections (as an assurance of the source animals' SPF status) and for an accompanying registration system. However, one could never exclude the possibility that an SPF animal was carrying a pathogen whose nature and significance for human health could not be accurately estimated.

In relation to the xenotransplantation of pig organs, viral infections represent by far the greatest risk, as well as being the hardest to quantify or prevent.

Although it is possible to breed pigs which are free of particular pathogens, at least two problems exist which cannot yet be satisfactorily resolved (Swi96). First, there is the problem of viruses which scientists are not (yet) able to eliminate, such as endogenic retroviruses. The genetic material of these viruses is contained within the

genome of the host, making it very difficult to remove. *In vitro* experiments have shown that endogenic retroviruses from pigs can infect human cells (LeT97, Pat97). The second problem is that new viruses are emerging all the time, so that no test programme can ever be comprehensive.

In most cases, little is known about the extent to which pig viruses represent a threat to human health. Nevertheless, it may be assumed that the risk to patients experiencing prolonged exposure to such viruses through xenotransplantation while their immune responses are being suppressed would be relatively high. Antibodies to various pig viruses have been detected in the blood of patients who had received a kidney from a human donor and islets of Langerhans from a pig. However, none of the patients had developed symptoms of any associated illness (Tib97).

Clearly, there is a risk of pathogenic viruses being transferred to the recipient, and of then being passed on to the recipient's environment. A further worry is that, partly as a result of immune suppression treatment, a xenotransplant recipient is an ideal environment within which viruses can adapt (by mutation or recombination with viruses already carried by the host) to infect humans. By such processes, initially harmless viruses can become a threat to human health.

The likelihood of prion infections being transferred to humans by the xenotransplantation of pig organs is probably quite small, certainly if a GHP regime and SPF animals are used. Furthermore, it would only be the recipient who was at risk, since there is at present no evidence that prions can be transferred by contact between individuals. From what we know of bovine spongiform encephalopathy (BSE, or 'mad cow disease') and its human equivalent, Creutzfeld-Jacob's disease, it appears that prion diseases only manifest themselves after quite long incubation periods. So the recipient of an animal organ would only be at risk if he or she lived for a considerable time following the transplant operation. In any case, prion diseases are presently unknown in pigs. On the other hand, medical science currently offers very limited scope for the detection of such diseases, certainly during the incubation period. It would therefore be necessary to establish special prion monitoring programmes in order to assure the SPF status of source animals. This would have to involve the histopathological examination of brain tissues from randomly selected animals. Research into the transfer of prions between pigs would probably be needed as well.

3.3 Conclusions

Xenotransplantation has yet to progress beyond the experimental stage. However, rapid advances have been made over the last few years. It now appears possible to prevent hyperacute rejection by genetically modifying the source animal so that it carries

certain proteins found in the recipient. Nevertheless, solutions must still be found to the problems of acute and chronic cellular rejection, which are much more serious with xenotransplantation than with allotransplantation. Cellular rejection can presently only be controlled using immunosuppressing medication in doses which would be unacceptable for human patients, because of the risk of numerous and serious complications.

Even if the rejection problems can be overcome, doubt remains as to whether an animal organ could function properly in a human recipient. There is evidence that the functionality of xenotransplanted pig organs cannot always be relied upon.

Given the considerations outlined above, the Committee believes that the clinical xenotransplantation of whole organs, even on an experimental basis, would currently be premature. The likelihood of success would be too small. It is unclear how soon clinical application might be in order. However, experimental xenotransplant operations should not be performed until there is a reasonable prospect of success, and certainly not until the risk of rejection has been reduced to a level comparable with that associated with allotransplantation.

Furthermore, the Committee is of the opinion that experiments involving the clinical xenotransplantation of whole organs, or indeed of cells or tissues, would be inappropriate at the present time, since insufficient guarantees could be made regarding the safety of the recipient or the protection of public health. For similar reasons, the Committee is for the time being against other applications involving close contact between an animal organ and a human, such as the use of a pig's liver located outside the patient's body to take over his or her liver function pending the availability of a human organ for transplantation. Clinical application should be deferred until preclinical studies can provide a better understanding of the infection risks and the means by which such risks may be minimized. The Committee would particularly like to see the following undertaken:

- a detailed inventory of pig viruses
- research into the possibility of eradicating from pigs persistent viruses, including endogenic retroviruses
- research into the transfer of pig viruses to non-human primates and humans and into the implications for the health of the new host
- definition of a good husbandry practice regime and the arrangements for monitoring the specified pathogen-free status of genetically modified pigs intended for use as source animals.

Even if research should in due course indicate that, provided certain precautions were taken, the risk of infection could be reduced considerably, uncertainty would always

exist regarding the threat from unknown infectious agents. Consequently, it will never be possible to estimate the level of infection risk very accurately. The potential benefits of xenotransplantation will have to be weighed up against the estimated infection risk to the individual patient, to his or her contacts and possibly to the general public. Any such assessment should take into account both pathogens capable of causing relatively minor illnesses in large numbers of people (e.g. influenza viruses), and pathogens which might cause serious disease in a small group of people.

Chapter 4

Social issues

4.1 The use of xenotransplantation in the treatment of humans

4.1.1 Acceptability

When considering the arguments for and against xenotransplantation, much depends on the way we view the human body. While no (absolute) distinction can be made between the body and the soul, medical science frequently treats the body as a mere object in a technical procedure. The tendency is to regard the body as a machine and the doctor as a mechanic. Many bodily problems indeed have a clear physiological cause, which can be addressed by the use of medication or some other treatment. Certainly, impaired organ functionality is normally attributable to a physiological cause. A patient suffering such impairment cannot be helped by talking; treatment is required — the doctor as mechanic. The question is: is it acceptable to replace a failing organ with a non-human body part? In other words, does the inclusion of an organ from another species compromise our humanity?

Medical science has long made use of artificial devices, such as man-made joints and even completely artificial organs, including hearts. Furthermore, the medical use of materials taken from animals is well established: pigs' heart valves are used as an alternative to artificial valves and insulin from pigs was successfully administered to diabetics for decades before insulin produced with biotechnological methods became available.

Having studied the detailed ethical deliberations of both the Nuffield Council of Bioethics and the Kennedy Committee, the Xenotransplantation Committee shares the conclusions set out in the two groups' reports (Ken96, Nuf96) and feels that there is little to be gained from reiterating the various arguments at this point. In the Committee's opinion, human dignity is not diminished by the implantation of living organs, tissues or cells taken from an animal any more than by the implantation of lifeless material. There is no objection in principle, therefore, to performing such implants with a view to correcting human ailments. Nevertheless, the Committee recognizes that, for religious, cultural or other reasons, not everyone will share this opinion. A public debate on the acceptability of using animals to obtain 'spare parts' for transplantation into humans and of making the appropriate genetic modifications to the source animals would therefore be in order. It is important to determine whether society at large would support the implantation of animal organs into humans. The Committee welcomes the initiatives made by the Animal Protection League in this respect, but does not endorse the call for a two-year blanket moratorium on xenotransplantation research (Ham97b). If it should prove that most people were in principle in favour of allowing xenotransplantation, it would of course ultimately remain up to the individual patient whether to accept implantation of an animal organ.

4.1.2 Clinical experimentation

As indicated in Chapter 3, the Committee feels that clinical xenotransplantation experiments would not be justified at the present time. It would not be acceptable to transfer living animal tissue to a human patient until the conditions referred to in section 3.3 had been met. The treatment of a human patient using a technique which remained quite inappropriate would indeed be an injure to human dignity.

4.1.3 Clinical treatment

Several new issues will come to the fore if xenotransplantation should reach the point at which it is ready for application in the course of regular medical practice. While identifying a number of potential problems, the Committee considers the proposal of solutions to be beyond its remit.

First, there is a possibility that, if organs were more readily available, the criteria applied in the referral of patients for transplant operations might be relaxed. This in turn could conceivably lead to a reduction in the success rate achieved by such treatment.

The availability of resources is another possible area of concern. If the demand for organs could be met, would it actually be possible to treat everyone who needed one?

Is there sufficient theatre capacity; are there enough specialists and, most important, are there sufficient financial resources? Commercially interested parties are very keen to patent biotechnological 'inventions', such as transgenic animals or organs. But even without patenting, transgenic organs will acquire a market value, and this will have implications both for the ready availability of such organs and for the cost of health care.

If organs from source animals acquire a market value, human donor organs may also become a tradeable commodity. In the Netherlands, however, the sale of human organs would be illegal under the Organ Donation Act (Stb96c).

A general belief that xenotransplantation will be possible in due course could lead the public to think that (post-mortem) organ donation is no longer necessary. The Committee, however, believes that such a conclusion would be quite unjustified; by far the best way of resolving the shortage in organs for transplantation is to increase the supply of human donor organs. This issue is addressed in more detail in section 4.3. The proposed initiatives to provide both the public and the medical professions with information regarding the amendment of the Organ Donation Act are therefore highly desirable (Bor97).

4.2 The use of animals

4.2.1 Health and welfare

In the 1981 policy document entitled 'The National Government and Animal Protection', it was acknowledged that animals deserved protection and that it was one of the government's duties to provide such protection. According to this document, animal protection policy 'should be based upon recognition of the intrinsic value of the individual animal. Policy must be designed to afford animals as much protection as possible against human activities which threaten their physical and ethological welfare. In practice, this means that people are always accountable for the acceptability of their activities with animals.'

By recognizing the intrinsic value of the animal, the government effectively accepted that animals should not be regarded as objects whose only value is as an exploitable resource. It therefore follows, and is enshrined in law, that instrumental exploitation of animals is permissible only where sufficient justification exists. The use of animals for xenotransplantation or research into the viability of xenotrans- plantation would certainly be classed as instrumental exploitation and must therefore be justified.

The law lays down rules on the use of laboratory animals and their genetic modification (see Chapter 5). Under these rules, proposals regarding the conduct of experiments on animals require the approval of an Animal Experimentation Committee and, if genetic modification is involved, the Biotechnology in Animals Committee.

Both xenotransplantation experiments involving animals and the breeding of animals to provide transplantable organs would inevitably involve a degree of distress or suffering for the creatures concerned. However, such suffering must be minimized and proportionate to the aim of the activity. Similar criteria apply to the breach of individual integrity necessarily associated with transgenic experiments. The Committee sees no objection to breeding pigs which carry a small number of human genes, provided that the modifications made are without detriment to their physiology, functionality or welfare. Nevertheless, it must be recognized that it is not possible to determine in advance to what extent a particular transgenic experiment will affect the welfare of the animals concerned. Consideration of the welfare issues relating to proposed experiments must be individually evaluated by the Biotechnology in Animals Committee and the Animal Experimentation Committees.

4.2.2 Which species?

If it is accepted in principle that there is sufficient justification for the use of animals to provide replacement organs for humans, and thereby for the research which must necessarily precede such use, the question arises: is it equally acceptable to use any animal species?

As indicated in Chapter 3, the high risk of pathogens (particularly viruses) being transferred to humans makes the use of primates as source animals unacceptable. However, if the safety problems associated with primate use should ever be overcome, it will then be necessary to decide whether the involvement of these animals raises special ethical issues. In the context of this report, discussion is best restricted to a few points which are relevant to the argumentation:

- Emotionally speaking, the instrumental use of animal species which are relatively close to humans in evolutionary terms is more problematical than the use of more distant species. This may be because people see more of themselves in closely related species. It is also harder to kill animals which appear from the complexity of their behaviour and from their social interactions to possess greater individualism and consciousness.
- Being kept and bred mainly in the type of (highly sterile) environment necessary to assure a specified pathogen-free status would appear more distressing for primates than for animals which have traditionally been kept on farms.

- The use and killing of animals from rare or endangered species are not considered acceptable. However, not all non-human primates come under this category.

4.2.3 The breeding of source animals

The breeding and accommodation of animals to provide organs for xenotransplantation could raise welfare problems, since the animals would have to be kept under conditions designed to prevent them from acquiring pathogens. This might well make it difficult for the animals to behave naturally.

However, assuming that the pig becomes the preferred source animal, the Committee believes that it is acceptable to keep such animals under conditions designed to assure the production of specified pathogen-free individuals. While it is true that pigs bred under such circumstances would not lead very natural lives, there seems no reason why the animals' welfare should be unduly affected, given sufficient effort and investment. So long as pigs are commonly bred in a similar way in the agricultural industry, there seems no very good reason why pigs bred for purposes other than consumption should be entitled to a more natural life or more 'animal-friendly' treatment. Nevertheless, the Committee would point out that the policy document 'The National Government and Animal Protection' suggests that animal husbandry, for whatever purpose, is only justified if due consideration is given to the animals' natural habits.

4.3 Solutions for the organ shortage

4.3.1 Human donor organs

As indicated in section 4.1, the Committee believes that the shortage of replacement organs is best addressed by increasing the supply of human donor organs. It is recognized, however, that the scope for doing so is limited. One problem is the proportional increase of the ageing population, which is pushing up the demand for organs while reducing the supply. At the same time, supply is affected by the fact that road accident deaths are falling. Legal provisions, such as those in place in Belgium and Austria, where everyone is considered to have consented to post-mortem organ donation unless they indicate otherwise, can increase the supply of donor organs. Figure 2 shows the number of post-mortem donors per year per million people in several European countries between 1989 and 1996. Distinction is made between countries with an 'opt out' system and countries where donors have to explicitly consent. On average, countries with opt out systems have more donors than countries where donors must opt in. However, many other factors can affect the number of

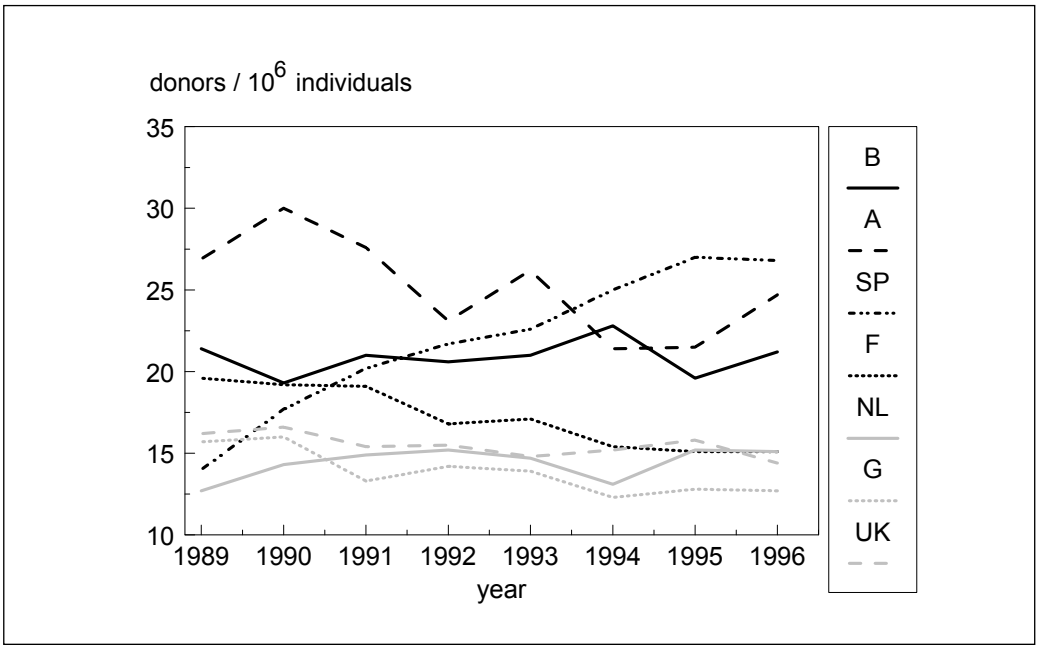

Figure 2 Numbers of post-mortem donors per million members of the population in various European countries between 1989 and 1996. The lines for countries with an 'opt out' system (Belgium, Austria, Spain and France) are in black. Grey lines are used for countries where explicit consent is required from donors (the Netherlands, Germany and the United Kingdom). (Sources: Cou96, Cou97, Per97)

donors, one being the number of transplant coordinators; Spain, for instance, has a relatively high number of coordinators, and this appears to benefit the level of supply.

Although an increase in the supply of donor organs could reduce waiting lists significantly, high levels of supply alone do not guarantee short waiting lists. Figures 3 and 4 show this, in combination with the data from Figure 2, for the numbers of people waiting for kidney and heart transplants, respectively. When studying these figures, one should bear in mind that Belgium, Germany, the Netherlands and Austria (together with Luxembourg) work together through Eurotransplant. As a result, organs which become available in one of the participating countries can be used in any of the others, and this has an impact on waiting list length. (The percentage of organs involved can be anything between about 10 per cent and 40 per cent, since it varies from year to year, and differs from one organ type to another.) There are also differences in referral criteria; this is particularly clear from Figure 4, which shows the number of people joining the waiting list for heart transplants. Because of these and other factors, the legal arrangements in Eurotransplant member countries have less influence on the waiting list length than on the supply of donor organs. Consequently, while the Committee thinks that the revised Organ Donation Act may well increase the supply of donor organs in the Netherlands*, it is not expected to have a major impact on the shortage, especially since population ageing is set to push up demand still further.

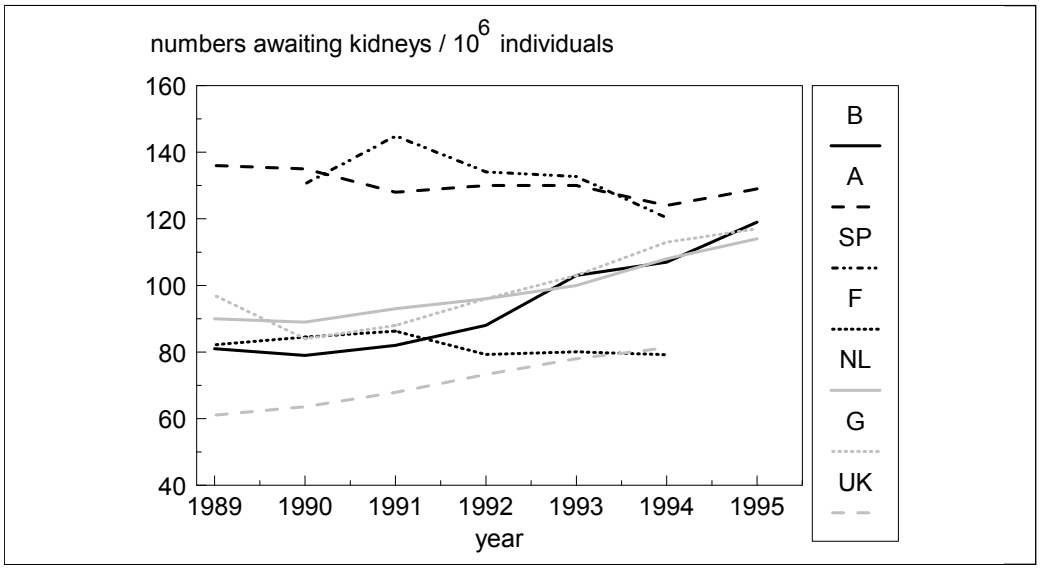

Figure 3 Numbers of people waiting for kidney transplants per million members of the population in various European countries between 1989 and 1995. The lines for countries with an 'opt out' system (Belgium, Austria, Spain and France) are in black. Grey lines are used for countries where explicit consent is required from donors (the Netherlands, Germany and the United Kingdom). (Sources: Coh95, Per97)

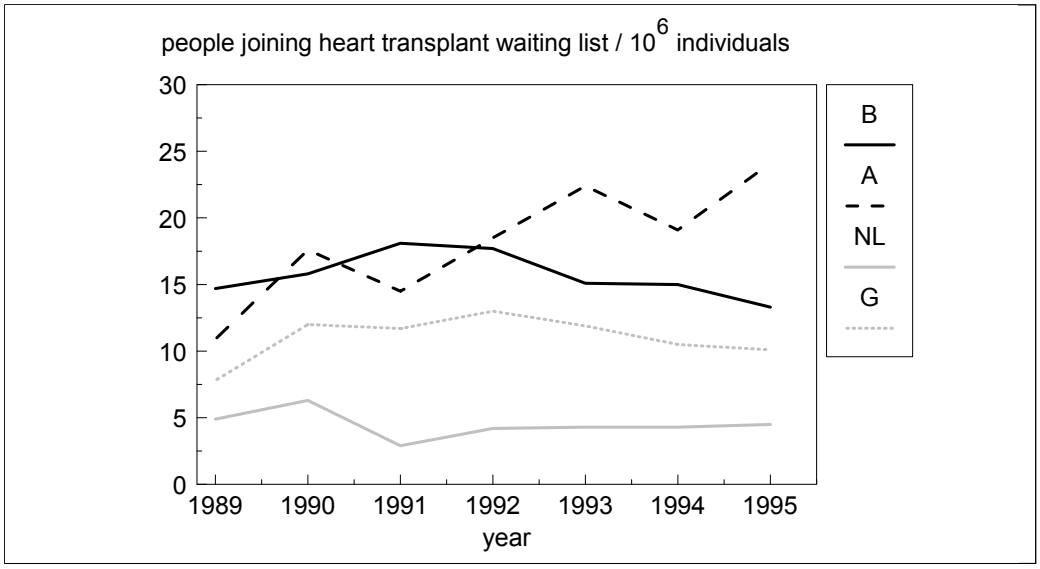

Figure 4 Numbers (re)joining the heart transplant waiting list per million members of the population in various European countries between 1989 and 1995. The lines for countries with an 'opt out' system (Belgium and Austria) are in black. Grey lines are used for countries where explicit consent is required from donors (the Netherlands and Germany). The numbers (re)joining in the Netherlands are relatively low because of the strict referral criteria. (Sources: Coh95, Per97)

4.3.2 *Other options*

Given the factors outlined above, the shortage of replacement organs cannot be met entirely by increasing the supply of human donor organs. Additional measures will be needed, and xenotransplantation is one of the possibilities. The Kennedy report identifies a number of other options which might in time help to resolve the situation, including gene therapy and the use of artificial organs (Ken96). However, no significant contribution can be expected from either option in the short term, i.e. within a few years. The advantages and limitations of these approaches are not considered in this report; readers are referred to the Kennedy report and the Health Council's recent report on gene therapy (GR97).

It is also important that the health benefits of preventive measures and the promotion of such measures are not overlooked in this debate. Life style changes, such as not smoking, reducing fat consumption and taking more exercise, would certainly reduce the incidence of heart disease, while the reduction of alcohol intake could help to cut the frequency of liver failure. While believing that the encouragement of healthy living could help control the incidence of organ function loss, the Committee does not expect that the impact of such a policy would ever be sufficient to correct the imbalance between the supply of and demand for replacement organs.

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* All people in the Netherlands of 18 years of age and older will receive a form on which they can indicate whether they want to be registered in a central registry as tissue/organ donor or not, or that they leave the decision to donate up to their relatives. If the form is not returned, the latter approach is followed.

Chapter 5

The legal position

The adequacy of existing and forthcoming legislation as a framework for regulating the development and possible application of xenotransplantation is the subject of consideration in this chapter.

The need for regulation is a corollary of the government's responsibility to protect public health. Product quality control and procedural safety in the field of xenotransplantation both require central regulation to ensure protection of the personal integrity and privacy of patients receiving animal organs (either in the context of an experiment or in the context of normal treatment) and the respectful treatment of the animals used. The government is also responsible for overall management of the nation's health care system. Xenotransplantation is important in this context as well, since its development and application have implications for the direction, planning, financing and supervision of health care.

Five existing and forthcoming bodies of legislation are pertinent to xenotransplantation:

- the law on the use of animals
- the law on genetically modified organisms
- product law
- care sector law
- patent law.

Each of these five legal areas is described in turn below and problems which might arise in relation to xenotransplantation are identified.

5.1 The use of animals

Two acts of parliament are relevant in relation to the use of animals:

- the Experiments on Animals Act
- the Animal Health and Welfare Act.

5.1.1 Animal experiments

The conduct of animal experiments must comply with the provisions of the Experiments on Animals Act (Stb92). Under this act, institutes can obtain a general licence to perform animal experiments. A licensed institute then has to submit details of each project involving animal experiments to an Animal Experimentation Committee (Dutch initials: DEC) for approval. Until such approval is obtained, the institute is not permitted to go ahead with the experiments. DECs assess proposals on the basis of various scientific, animal-welfare and ethical criteria. Ethical assessment involves carefully weighing up the degree of distress likely to be suffered by the animals against the scientific and social significance of the research. If a DEC refuses to approve a proposal, the licensee can appeal to the Central Committee on Animal Experiments. If the latter committee rules in favour of the licensee, the experiment can go ahead after all.

5.1.2 Biotechnical procedures

Animal experiments that involve biotechnical procedures, such as genetic modification, are covered not only by the Experiments on Animals Act but also by Sections 66 to 72 of the Animal Health and Welfare Act (Stb96a). (Naturally, the Act's general rules regarding protection of the health and welfare of the animals apply as well.) The basic principle applied is that biotechnical procedures involving animal subjects are forbidden unless licensed by the Minister of Agriculture, Nature Management and Fisheries. Before granting a licence, the Minister seeks the advice of the Biotechnology in Animals Committee, which assesses the proposed procedure against two criteria:

- the procedure must not have any unacceptable implications for the health and welfare of the animals
- no serious ethical objections to the procedure must exist.

Thus, the Biotechnology in Animals Committee would have to assess any xenotransplantation research proposal which involved genetic modification (transgenesis) of the source animals.

The said sections of the Animal Health and Welfare Act came into force on 1 April 1997, with the exception of Section 66, clause 1, subclauses c and d (Stb97a). The second of these subclauses, which applies to the importation of transgenic animals, has been held in abeyance so as not to create a barrier to trade within the European market. As the law stands, the Biotechnology in Animals Committee would not have to be consulted about an experiment to be performed in the Netherlands using transgenic animals bred abroad. However, the Xenotransplantation Committee would like to see a new clause added to Section 66 of the Animal Health and Welfare Act making it necessary to obtain a licence for xenotransplantation experiments involving the use of organs, tissues and cells from transgenic animals bred outside the Netherlands, since any such experiment would entail the application of transgenesis in a way that might arouse public disquiet. Pending the addition of such a clause, the Committee would call upon researchers to recognize that they have a moral responsibility to voluntarily submit proposals for such experiments to the Biotechnology in Animals Committee.

5.2 Genetically modified organisms

Animals subjected to biotechnical procedures for xenotransplantation research purposes and transgenic animals created in the course of such research would be covered not only by the relevant sections of the Animal Health and Welfare Act, but also by the laws on genetically modified organisms (GMOs). The laws in question are designed to protect human health and the environment against the possible adverse effects of producing and using GMOs.

Dutch legislation in this area incorporates two European directives.

Directive 90/219/EEC (EU90a) on the contained use of genetically modified organisms focuses mainly on the research phase. It includes requirements regarding the facilities and methods used in laboratories handling GMOs. The directive is implemented in Dutch law through two pieces of legislation:

- the Environmental Management Act (Stb94a) and the associated Environmental Management (Premises and Licences) Decree (Stb93a)
- Section 2 of the Genetically Modified Organisms Decree issued pursuant to the Environmentally Hazardous Substances Act (Stb93b) and the associated ministerial regulations (the Regulations on the Contained Use of Genetically Modified Organisms (Stc93)).

The other European directive concerned (90/220/EEC) (EU90b) lays down rules on the deliberate introduction of genetically modified organisms to the environment. It regulates all activities with GMOs which do not take place in institutions of the kind

covered by EC directive 90/219. (Such activities are referred to as 'the introduction of genetically modified organisms to the environment'.) Distinction is made between the marketing of products containing GMOs and all other activities with such organisms (including the treatment of patients). The directive is implemented in Section 3 of the Genetically Modified Organisms Decree.

Under the Genetically Modified Organisms Decree, the genetic modification of organisms and xenotransplantation activities involving GMOs have to be licensed under the Environmental Management Act. The licensing authority can refer to the Genetic Modification Committee (Dutch acronym: COGEM) for advice.

The laws on GMOs cover not only genetically modified animals used to provide organs for xenotransplantation, but also the organs obtained from them and even the recipients of these organs. Hence, the law as it stands would regard a patient receiving a genetically modified organ in a clinical xenotransplantation experiment as the carrier of a GMO. Consequently, such a patient would come within the scope of the Environmentally Hazardous Substances Act and the associated regulations. The Committee considers this an undesirable prospect, since neither the Act nor the regulations were drawn up with medical applications in mind; they are designed to protect the general public and not the health of individual patients. If the time comes when clinical experiments and perhaps, in due course, regular medical application are considered in order, the Committee would wish to see the law amended so that the carriers of genetically modified organs are explicitly excluded from compliance with the Environmentally Hazardous Substances Act. The (forthcoming) Medical Research Involving Human Subjects Act offers a much better framework for the regulation of clinical experiments in the field of xenotransplantation (see 5.3.2).

The Committee also strongly recommends that agreement is sought within the EU regarding application of the regulations on GMOs in relation to xenotransplantation.

5.3 Quality and safety of products and treatments

As discussed in section 3.2, there is a risk of pathogenic organisms being transferred from source animals to humans as a result of xenotransplantation. The Committee believes that the government should take appropriate preventive measures to protect individual patients and public health. First, as indicated in section 3.3, animal experiments should be performed to increase scientific understanding of the risks involved. Such research might, for example, indicate that it was necessary to ensure that organs intended for xenotransplantation were free from certain pathogens. The government could then set appropriate quality requirements before allowing clinical experiments. To obtain organs which were free from certain pathogens, source animals

would have to be bred under specified pathogen-free conditions within the framework of a good husbandry practice regime (see section 3.2), following the principles of GLP (Good Laboratory Practice) and GMP (Good Manufacturing Practice). Every animal organ should be checked for pathogens prior to transplantation.

With a view to controlling the risk of infection by unknown pathogens, the government should also introduce special quality requirements regarding the transplantation procedure itself. During and following a transplant operation, both the recipient of the xenotransplanted organ and everyone with whom he or she has direct contact must be constantly monitored so that any new illness can be detected and treated as early as possible. Monitoring arrangements should include a central registration system. The transplant operation and the monitoring activities should follow the principles of GCP (Good Clinical Practice).

5.3.1 Product law

Animal organs for xenotransplantation will in all probability become available on a commercial basis. The quality requirements which such organs must meet should therefore be set out in product law.

The Committee does not anticipate that source animals will be bred in the Netherlands in the near future. It is more likely that, once clinical application is in order, organs or source animals will be imported. The Committee is therefore strongly in favour of uniform product regulations, at least within the EU. It is most undesirable that different countries each develop their own quality requirements and monitoring system.

In the Committee's judgement, existing Dutch law on medical devices is not sufficient to cover animal organs for xenotransplantation. The main shortcoming is the absence of a suitable quality control system.

As things stand, the most far-reaching quality control requirements are contained in medicinal product law, under which the relevant parties have to perform thorough quality control procedures and post-marketing surveillance, based on the principles of GMP, GLP and GCP. Special rules exist covering medicines created using high-level technologies, such as genetic modification. Before any such product may be marketed, it must be licensed in accordance with both Dutch GMO law and European law (EU93).

However, medicinal product law is not intended to deal with products which consist of or contain living material or with the associated quality requirements. In consequence, many provisions of medicinal product law are not applicable to such products. In other words, there are gaps in the law, which will need to be filled by the

introduction of new legislation. Amendment of existing medicinal product law would make the legal position very complex, which the Committee considers undesirable.

The Committee therefore wishes to see new legislation introduced specifically to cover medicinal products which consist of or contain living material. Such a move would be in line with the recommendations of the recent Health Council report on gene therapy (GR97). The latter report coined the term 'biologicals'. An organ intended for xenotransplantation would fit the definition of such a product. Any new legislation could include quality standards for biological medical products in general and for certain product types. The creation of such a legal framework would allow for harmonization of all the matters which are presently either not covered by the law or covered by diverse legal provisions. These matters include the safety of genetic modification, working with GMOs and their introduction to the environment, special requirements regarding working under SPF conditions, a follow-up system and a registration procedure. As indicated earlier, quality standards should ideally be agreed at the European level.

If there were a single legal framework covering biological medical products, the law would be more comprehensible and transparent. Furthermore, the government would be able to respond quickly to new developments in medical biotechnology.

New legislation of the kind described could not be introduced very quickly. However, the Committee believes that some form of legal control of xenotransplantation involving humans is required in the short term. No clinical experiments should be conducted until all the conditions already referred to have been satisfied and until it is decided which product laws apply to organs for xenotransplantation. Accordingly, the Committee suggests that such organs should temporarily be brought within the scope of medicinal product legislation. Similar arrangements would need to be made at the European level, pending development of European quality standards.

5.3.2 Medical procedures

Legislation on medical procedures has three main functions:

- protection of the patient
- ensuring the quality of care and professional practice
- the organization, planning and financing of health care.

Protection of the patient

The (forthcoming) Medical Research Involving Human Subjects Act (Dutch initials: WMO) will apply to clinical xenotransplantation experiments and appears to provide a suitable framework for their regulation (EK97).

Clinical experiments will not be permitted unless the conditions set out in the WMO can be met. Under the Act, it is illegal to perform an experiment involving one or more human subjects until an independent committee has approved the research protocol. By reference to generally accepted standards and criteria (only some of which are explicitly named in the Act), a special local Medical Ethics Committee or a national Central Committee (CeCo) considers whether the proposed research is reasonable and whether it is ethically and scientifically acceptable. The Act makes provision for certain categories of research to be referred to the CeCo as a matter of course. Accordingly, the Committee believes that Section 2, clause 2, subclause 4, of the WMO should be used to give the CeCo exclusive authority to approve protocols for xenotransplantation experiments with human subjects. As a national body, the CeCo is better placed than any local committee to monitor developments in the field of xenotransplantation.

If xenotransplantation can at some stage be offered as a regular medical treatment, it will come within the scope of the part of the Civil Code covering medical treatment contracts (WGBO) (Stb94b). The Committee does not anticipate that this should prove problematic.

The right to information is important in relation to xenotransplantation, both in the context of experimentation and in the context of regular treatment. Patients must be informed of the nature of the procedure, its consequences, the associated risks and other relevant matters in a way which is clear and comprehensible to the individuals in question. Researchers and practitioners would need to bear in mind the fact that patients are likely to see xenotransplantation as a last resort. Indeed, this may be relevant to the ethical acceptability of xenotransplantation in its experimental stage, since it is essential that would-be subjects are able to make completely free and informed decisions.

The risk of pathogen transfer should be fully detailed in the information given to prospective transplant recipients. In particular, attention should be drawn to the fact that an infection could conceivably be passed on to the people with whom the patient has contact (see section 3.2). In view of this possibility, both the patient and his or her immediate contacts would have to be constantly monitored. Hence, the voluntary and informed cooperation of such contacts would also be required. Registration of the data collected during the postoperative checks would be an essential prerequisite; there

might, however, be problems reconciling public health interests with the individual's right of privacy. Nevertheless, it should always be made clear that further direct contact between the patient and anyone who declines to cooperate in this regard would not be possible. Furthermore, during the clinical experimentation phase at least, it would be necessary to restrict the number of people with whom a patient had contact following a transplant operation, so as to keep the postoperative monitoring programme to tolerable proportions. As a result, the organ recipient's freedom of movement would need to be restricted. Xenotransplant operations should not be made generally available until these problems are manageable.

Quality of care and professional practice

In the Committee's opinion, the Quality of Care (Institutions) Act (Stb96b) and the Individual Health Care Professions Act (Dutch initials: Wet BIG; Stb93c) provide sufficient assurances regarding the quality of care and professional practice in relation to xenotransplantation both in the context of experimentation and in the context of normal treatment.

Organization, planning and financing of health care

The Hospital Provision Act (in particular Section 18) provides a framework within which it is possible to set requirements regarding hospital provisions and to control the application of emerging technologies (Stb71). However, the Act offers little scope for the regulation of clinical xenotransplantation. Now that the Exceptional Medical Procedures Act (Dutch initials: WBMV) is in force, this would appear to be a better vehicle for regulation (Stb97b). Under this Act, the government could prohibit xenotransplantation or introduce compulsory licensing. The WBMV could also be used to impose a moratorium, during which clinical experiments or certain procedures were prohibited pending public debate and political review.

5.4 Patent law

Patent law can be used to protect biotechnical 'inventions'. Generally speaking, neither animal breeds nor biological procedures for producing animals of a given breed can be patented. However, microbiological procedures and the products of such procedures form an exception in this regard (EU64, EU75, Stb95). It would appear from a ruling passed by the European Patent Office's Technical Board of Appeal in the case of the 'Harvard Oncomouse' that an individual animal can be patented, even though a breed cannot. This case has now gone before the European Patent Office's Opposition

Division, however, so the Board of Appeal's ruling may not prove to be the final word on the matter. No decision is expected in the short term.

In response to the growing interest in patenting biological 'inventions', the European Commission has been working on an appropriate directive. The first draft was rejected by the European Parliament in March 1995, because MEPs considered it ethically unacceptable to grant patents on genetically modified biological material (EU95). A revised draft was subsequently approved by the parliament (Com95). One of the main features of the directive is that it opens the way for patenting biological material, including animals and parts of animals created using procedures which are not manifestly biological, but excluding plant varieties and animal breeds. Manifestly biological procedures for producing animals would remain unpatentable. Under the directive, it would be possible to patent ways of using animal breeds and procedures necessary for producing animals of a given breed. The EU's Council of Ministers is due to decide where it stands on this issue, after which the directive will receive a second reading in the European Parliament. The expectation is that the directive will be passed by 1 January 1999. Once in force, the new directive should lead to uniform application of the existing rules on what can and cannot be patented, as well as to an unambiguous interpretation of patents granted in the field of biotechnology.

Chapter 6

Conclusions

On the basis of the assessment outlined in the previous chapters of the report, the Committee concludes that xenotransplantation can probably be developed into a viable clinical technique, but not in the near future. It will be quite some time before the serious rejection and safety problems associated with xenotransplantation can be overcome.

It is important that the ethical acceptability of clinical xenotransplantation — both from the human viewpoint and from the animal viewpoint — is considered while the technique is still at an early stage of development.

If xenotransplantation becomes clinically viable, the technique will be capable of alleviating the suffering of people with certain medical conditions and in many cases of prolonging life. The Committee therefore believes that, from a human point of view, xenotransplantation is ethically acceptable. Furthermore, the Committee is of the opinion that the interests of the people who might benefit from the technique are sufficient to justify the possible inconvenience to or infringement upon the integrity of the animals concerned and that the breeding of genetically modified animals for xenotransplantation purposes is therefore acceptable.

It is recognized that some people may, e.g. for cultural or religious reasons, disagree with the Committee's conclusion. The Committee would consequently like to see information made available and the encouragement of public debate on these matters.

The Committee feels that this is not yet the time to bring xenotransplantation to the clinic. While it appears that a solution to the problem of hyperacute rejection may well be within reach, another form of rejection, which begins within a few days of a transplant operation, seems more intractable. Currently, the only way to prevent such rejection is to administer immunosuppressant drugs in doses which would be unacceptable for humans. Not only is a solution to this problem some considerable way off, but serious doubt also remains regarding the functional ability of an animal organ to take over from its human equivalent.

At present, another obstacle to the use of xenotransplantation is the risk of infection. In the Committee's view, scientists do not yet understand anywhere near enough about the processes by which infectious agents might be transferred from an animal organ to its human recipient — and perhaps subsequently transmitted to others — to enable them to estimate the associated risks.

Clinical experiments would not be appropriate until there is a good chance of operative success and until the rejection problems have been reduced to a level comparable with that currently associated with the transplantation of organs from human donors. The risk of infection must also be reduced to an acceptable level. To this end, there is a need for better understanding of the risk of pathogen transfer and for ways of ensuring that organs are free from highly infectious pathogens. Greater certainty is required both in relation to pathogens capable of causing relatively minor infections (such as influenza viruses) in large population groups and in relation to pathogens capable of causing serious diseases in small groups.

In view of the uncertainties outlined above, it is not yet possible to say whether xenotransplantation will ever become a clinically viable technique and, if so, when.

Finally, the Committee wishes to see legislation drafted in anticipation of the possible clinical application of the technique, with a view to regulating the production and use of animal organs for xenotransplantation. Given that any future trade in such organs is likely to be of an international nature, appropriate product regulations should be established at the supranational level.

The xenotransplantation of animal organs into humans, even on an experimental basis, should not be permitted until an adequate legal framework is in place. The Committee believes that the Central Committee which is to be set up under the (forthcoming) Medical Research Involving Human Subjects Act should have exclusive authority to approve protocols for xenotransplantation experiments with human subjects. As a national body, the CeCo would be well placed to monitor developments in this field.

Rijswijk, 21 January 1998,
on behalf of the Committee,
(signed)

E van Rongen,	AJ Dunning,
secretary	chairman

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A The request for advice

B The Committee

Annexes

Annex **A**

The request for advice

In a letter dated 31 December 1996 (reference: CSZ/ME-9615719), the Minister of Health, Welfare and Sport asked the President of the Health Council to report on the present scientific status of xenotransplantation. The text of the Minister's letter was as follows:

I have noted that professional journals, the mass media and political commentators are devoting increasing attention to the subject of 'xenotransplantation', i.e. the transplantation of an organ from an individual of one species to an individual of another. Indeed, the first clinical xenotransplant operation (between an animal and a human) may not be very far away. I am aware that the Health Council has been following developments in this field for some time with a view to producing a report. I therefore thought it appropriate to announce to the Lower House during the 1997 budget debate that I intended shortly thereafter to formally ask the Council to prepare a report on this subject.

Accordingly, I hereby request that the Health Council prepares a report on the present scientific status of xenotransplantation, giving particular attention to the following questions:

1 Do the scientific and medical developments of recent years give reason to believe that xenotransplantation will within a reasonable period become a useful and responsible alternative — on various grounds, including quality and safety — to the transplantation of organs from (deceased) human donors? If so, which organs might be replaced in this way, and would such replacement be more or less permanent or merely a temporary solution? Before any clinical experiments are conducted with human patients, I believe a proper overview is needed of the potential benefits of and objections to xenotransplantation. In my opinion, the following matters deserve particular attention in this regard:

a The acute and chronic rejection of transplanted organs, and the pharmaceutical and genetic scope for controlling rejection, as well as the scope for making life-saving provisions available, either in the form of technical resources or human donor organs;

b The length of time a xenotransplanted organ might last if obtained from an animal which would not normally be expected to live nearly as long as a human being;

c The risk of persons directly involved with a xenotransplant operation (i.e. both patients and medical personnel) and of indirectly involved members of the public (e.g. patients' relatives) becoming infected with organisms which are (potentially) pathogenic for humans, and the scope for treating such infections, including those which are capable of causing serious illness.

2 Is it ethically acceptable to breed animals, and transgenic animals in particular, with the intention of using them to provide replacement organs for humans? If so, what conditions or restrictions should apply? I am aware, incidentally, that before long questions of this kind regarding the acceptability and ethicality of specific procedures planned with animals and involving the use of biotechnological techniques (including procedures to be performed for xenotransplantation purposes) are to be addressed by the Committee on Biotechnology in Animals, which is to be convened in accordance with Section 69 of the Animal Health and Welfare Act. This committee, which I expect to be able to begin its work quite soon, will also be responsible for assessing applications for permits to perform such procedures from various angles and in relation to various disciplines, including ethics.

3 Given that for several years to come expertise in the field of xenotransplantation will remain limited, how can a considered guiding judgement be made regarding the ethical acceptability of clinical research involving human subjects before a concrete research protocol has been submitted for assessment?

4 Taking account both of existing provisions and of legislation presently being prepared, is there an adequate legal framework for the regulation of xenotransplantation during its development and implementation? If not, what modifications are required? In my view, particular attention should be given in this regard not only to the matters addressed in questions 1 to 3, such as the position of the animals involved, of patients and experimental subjects and of medical professionals, but also to the position of the institutions concerned and the role of the government in relation to the nature (including quality and safety), direction, planning, financing and supervision of xenotransplantation. All legal provisions must, of course, be consistent with any existing or anticipated international obligations which might be pertinent to xenotransplantation in practice.

If possible, I would like to receive your report by the autumn of 1997. Should the Council consider it appropriate in view of developments in the field of xenotransplantation, I would be pleased to receive a brief preliminary report prior to completion of the full document.

The Minister of Health, Welfare and Sport
(signed)
E Borst-Eilers

Annex **B**

The Committee

- AJ Dunning, *chairman*
  emeritus professor of cardiology, University of Amsterdam
- FWA Brom
  ethicist, Catholic University of Brabant, Tilburg, and Utrecht University
- F Claas
  professor of transplantation immunology, Leiden University
- Tj de Cock Buning
  biologist/philosopher and professor of ethics, alternatives and history of animal experimentation, Leiden University
- FG Grosveld
  professor of molecular cell biology, Erasmus University Rotterdam, and member of the Scientific Advisory Board of Imutran Ltd (Novartis) in the UK
- CCE Koning
  radiotherapist, Westeinde Hospital, The Hague
- RL Marquet
  immunologist, Erasmus University Rotterdam
- F Moss
  lawyer, Royal Dutch Society for the Advancement of Pharmacy, The Hague
- ADME Osterhaus
  professor of virology, Erasmus University Rotterdam and Utrecht University, and member of the Safety Advisory Board of Imutran Ltd (Novartis) in the UK

- GG Persijn
  medical Director of the Eurotransplant Foundation, Leiden
- J Prop
  physician, Groningen University Hospital
- OT Terpstra
  professor of general surgery, Leiden University Hospital
- LP the Waal
  transplantation immunologist, Blood Transfusion Service Central Laboratory, Amsterdam
- FCB van Wijmen
  professor of medical law, University of Maastricht
- LFM van Zutphen
  professor of laboratory animal science, Utrecht University
- PCM de Greeve, *advisor*
  inspector, Chief Veterinary Inspectorate, Rijswijk
- GJ Olthof, *advisor*
  Ministry of Health, Welfare and Sport, Rijswijk
- ECM Keijser, *advisor*
  lawyer, Health Council of the Netherlands, Rijswijk
- E van Rongen, *scientific secretary*
  cellular biologist, Health Council of the Netherlands, Rijswijk