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ORIGINAL COMMUNICATION

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Ethical guidelines for the use of human embryonic or fetal tissue for experimental and clinical neurotransplantation and research

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Abstract Recently a Network of European CNS Transplantation And Restoration (NECTAR) has been founded, aimed at a concerted effort to develop efficient, reliable, safe and ethically acceptable transplantation therapies for neurodegenerative diseases, in particular Parkinson's and Huntington's disease. Owing to the use of human fetal brain tissue in such studies, usually obtained from elective abortions, ethical concerns have been focused on the relationship between abortion and transplantation activities. There is no uniform code on the retrieval and use of human embryonal or fetal material for experimental and clinical research or application in Europe. NECTAR has therefore formulated self-restraining ethical guidelines for its European member groups. These guidelines consist of a series of restrictions intended to prevent the use of grafts from encouraging induced abortions and to maintain high standards of respect for life and human dignity. In order to support applications for human embryonal or fetal neurotransplantation studies of NECTAR member groups to local or national medico-ethical committees, and to stimulate the goal of obtaining European legislation on this issue, the guidelines are here presented. They are followed by extensive explanatory notes. Only in this public manner can the lines of thought behind these NECTAR guidelines be addressed critically by those working in the fields of biomedical ethics and legislation as well by politicians and the general public.

Key words NECTAR · Ethical guidelines · Human fetal tissue Neurotransplantation

Introduction

Parkinson's disease is a common and severe neurodegenerative disorder which is due to a progressive loss of dopamine neurons in the nigro-striatal system of the brain. Current medical therapy, which is based on drugs that increase dopamine in the affected areas (e.g. levodopa), is effective in the early stages of the disease, but after 4–10 years, as the disease progresses, the efficacy of drug treatment is limited by severe side-effects in the majority of cases [34]. During the past decade techniques for dopamine replacement by intracerebral cell transplants into the striatum have been developed in animal models of Parkinson's disease, first in rodents and later in primates. On the basis of these techniques, which showed that transplanting a preparation containing fetal mesencephalic dopaminergic neurons induced long-term recovery of motor deficits, clinical trials in patients were initiated in several research centres in Europe, Central and North America and China [19, 26, 31, 38–40, 43, 49, 64, 68]. The prospect of therapeutically effective dopaminergic cell transplantation in Parkinson's disease and consequently in other neurodegenerative disorders [22, 55] has recently led to the formation of a joint transnational network to coordinate clinical trials and methodological developments

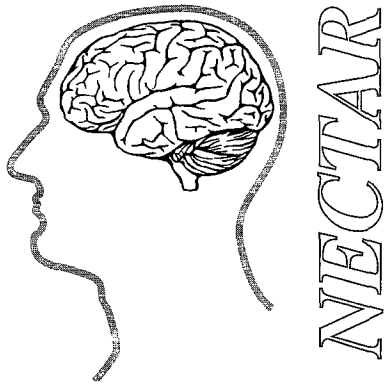
in Europe. At the inaugural meeting of this Network of European CNS Transplantation And Restoration (NECTAR) in Le Vésinet (near Paris, France) on 10–11 May 1991, representatives of 13 groups from 11 European countries made a concerted effort to develop efficient, reliable, safe and ethically acceptable transplantation therapies for neurodegenerative diseases, in particular Parkinson's disease. More recently Huntington's disease has also become a focus of interest [29, 53].

An important aspect in neural transplantation in humans is the fact that it touches upon relatively new ethical questions in biomedical research concerning the retrieval and use of human embryonal and fetal material [2, 44]. So far, the donor tissue for the most promising treatment schedules became available through legally induced abortions. In principle, the possible use of embryonal and fetal organs or tissue would be analogous to the use of organs and tissue from deceased persons [20, 24, 41], for which legislation already exists. However, since the decision on therapeutic abortion might be influenced by the donation of tissue for a given therapy [24] and conception might even be brought about with the sole purpose of obtaining organs or tissue from embryonal or fetal origin, additional regulation is called for. If, moreover, transplantation were to become a standard therapy for certain common diseases, this could create a great demand for human fetuses or embryos, with the chance that they would then be debased to the status of organ or tissue sources. Therefore, the ethical and legal regulations for the use and transplantation of embryonic and fetal organs or tissue cannot be completely separated from those concerning induced abortions [16, 27, 46, 54].

In most European countries political and legal debates have resulted in legislation on elective abortions, ranging from strictly pro-life to a qualified pro-choice [7, 18, 70]. Still, the tissue remains debatable in all countries, since there is no unanimity among the population about the moral judgement. It is not surprising, therefore, that critical questions have been asked and strong protests raised about the use of human embryonal organs and tissue, obtained through artificial abortion, for experimental work including neurotransplantation. Some pro-life critics have denounced the use of embryos or fetuses from elective abortions as complicity after a murder sanctioned by law [8, 11]. Other critics have said that the ethical questions are too often approached only from a scientific and technological perspective with the rationale that scientific research is important and beneficial to mankind, because in the end it may cure or prevent illnesses in numerous human beings. Consequently, they said, norms have been established that impede research as little as possible [36]. Such statements are belied by the growing body of publications on the ethical aspects of using embryonal and fetal organs and tissue, especially those showing complete openness on the part of the scientific community [28, 47, 62]. A full ethical judgement, however, generally lags behind scientific developments: indeed, ethical issues are often raised through scientific achievements. Therefore, ethical issues on the use of human embryos or fetuses will remain continuously open and under discussion.

Currently, there is no European country (apart from Spain) with complete legislation on the use of human embryos and fetuses for scientific, diagnostic, therapeutic, industrial and commercial purposes [63, 70]. But in Europe (as elsewhere in the world [65, 71]) guidelines have been published or proposed by many national health or ethical committees [13, 15, 16, 27, 51, 52] as well as the Parliamentary Assembly of the Council of Europe [57, 58]. These guidelines expressed considerably different views [66]. One of the aims of NECTAR, therefore, was to formulate self-imposed ethical guidelines for the use of human embryonic and fetal tissue for scientific and therapeutical purposes, including their rationale. It would then ensure a uniform code of conduct for the European member groups and would guide and support any application for human embryonal or fetal neurotransplantation studies in local or national medico-ethical committees. In addition it could serve as a source for the future determination of national or European legislation on this important issue. The importance of qualified information and final legislation is further emphasized by the fact that the European Commission (EC) has recently installed a Working Group Human Embryo Research to work on these ethical and legal questions [70].

The present paper reports on the guidelines as they crystallized after discussions at NECTAR meetings in Le Vésinet, France (10–11 May 1991), Milan, Italy (24–26 January 1992) and most recently in Brussels, Belgium (27–29 August 1993). In this presentation we will first list the set of guidelines adopted by NECTAR and subsequently explain the rationale behind the propositions. Four general moral principles served as the basis for the discussions: (1) human beings and their autonomy should be respected, (2) what is good should be done ("beneficence"), (3) what is bad should be avoided ("non-maleficence") and (4) what is just should be based on the fair distribution of the available means, on respect for human rights and on morally acceptable legislation [4].



Guidelines adopted

NECTAR ethical guidelines[1] for the retrieval and use of human embryonic or fetal donor tissue for experimental and clinical neurotransplantation and research

Clinical and experimental groups or institutions that are members of NECTAR will obey the present ethical guidelines, irrespective of the fact that national legislation may permit them to deviate from these guidelines and provided national legislation allows them to follow these guidelines.

1. Tissue for transplantation or research may be obtained from dead embryos or fetuses, their death resulting from legally induced or spontaneous abortion. Death of an intact embryo or fetus is defined as absence of respiration and heart beats.

2. It is not allowed to keep intact embryos or fetuses alive artificially for the purpose of removing usuable material.

3. The decision to terminate pregnancy must under no circumstances be influenced by the possible or desired subsequent use of the embryo or fetus and must therefore precede any introduction of the possible use of the embryonic or fetal tissue. There should be no link between the donor and the recipient, nor designation of the recipient by the donor.

4. The procedure of abortion, or the timing, must not be influenced by the requirements of the transplantation activity when this would be in conflict with the woman's interests or would increase embryonic or fetal distress.

5. No material can be used without informed consent of the woman involved. This informed consent should, whenever possible, be obtained prior to abortion.

6. Screening of the woman for transmissible diseases requires informed consent.

7. Nervous tissue may be used for transplantation as suspended cell preparations or tissue fragments.

8. All members of the hospital or research staff directly involved in any of the procedures must be fully informed.

9. The procurement of embryos, fetuses or their tissue must not involve profit or remuneration.

10. Every transplantation or research project involving the use of embryonic or fetal tissue must be approved by the local ethical committee.

[1] These guidelines were officially adopted at the second NECTAR meeting in Milan, Italy (24–26 January 1992) and were published in the NECTAR Newsletter no. 3, April 1992. Minor textual changes have since been included.

Explanatory notes

Status of guidelines

NECTAR has been initiated to stimulate collaboration of research groups with a mutual interest in the development of neurotransplantation as a possible therapy in brain diseases. The idea behind this collaboration is not that if there are ethical objections to experimental transplantation studies in one country, these studies should be carried out in another country where obtaining permission will not cause any problems. The ethical issue concerning the use of human embryos and fetuses available from legally induced abortions as well as from spontaneous abortions is considered to be universal. Therefore all NECTAR group members should adhere to the present guidelines in order to make NECTAR a credible network within the European communities.

In Europe, legislation on elective abortion, in particular, differs widely from country to country [7, 18, 70] and can even change rapidly within one country as a result of dramatic political changes, as was the case in, for example, Poland (J. Dymecki, personal communication). Moreover, there is always constant pressure on the prevailing views on elective abortion, since moral judgements differ among people, for instance on religious grounds [72]. The ethical views on the use of embryonal and fetal organs and tissue are less controversial within and among European nations, but are, as stated above, influenced by the views on elective abortion. It is the aspect of the use of legally obtained human embryonal or fetal material that is covered by the present NECTAR guidelines.

The NECTAR guidelines will obtain the status of a standard and a useful reference in any application for the use of embryonic and fetal tissue if each member group fully agrees with the directives given and adopts them as common practice. In that case they might also serve as a background for formal legislation on the issue in the various countries or even at the European level in the Council of Europe and the European Union (EU). The presently formulated self-adopted guidelines must not be seen as the final or definitive statement of NECTAR. Ethical aspects will remain under continuous evaluation as a result of both practical experience and further discussions with those outside the field of (neuro)transplantation.

The present ethical guidelines cannot be followed in countries where their application will lead to prosecution, but NECTAR groups from countries where legislation is more liberal than the NECTAR guidelines should still comply with the latter.

Definitions

Embryonic state is defined as between 15 days and 8 weeks post-conception of a pregnancy. In the absence of

more precise information (i.e. menstrual cycle length), conception is presumed to have taken place 2 weeks after the beginning of the woman's last menstrual period. At 8 weeks the rudiments of nearly all the main structures have been laid down and there is a general appearance of a mammal-to-be with four limbs and a head. However, the 8-week dividing line is still arbitrary, since a firm scientific basis for the transition to the fetal stage is lacking [56]. The *fetal stage* is taken to be the subsequent period between 8 weeks and the time the baby is born, at approximately 38 weeks post-conception (40 weeks post-last menstrual period). The distinction of the 15-day stage as the beginning of the embryonic stage is not arbitrary: the pre-embryo or zygote is not isomorphic with the later developmental stages, since cells cannot yet be defined as contributing to the embryo or to the extra-embryonic tissue [30], and complete implantation has not yet been accomplished [56]. The possible use of *zygote* or cells thereof (as well as of fertilized human egg cells) is not discussed within the present framework of neurotransplantation research and therapy.

Death before use (1)

Because of the basic ethical requirement of respect for the human being, the use of live, though non-viable, embryos or fetuses is generally not acceptable. In other words, even if the conceptus is pre-viable or non-viable outside the womb, the organism can still be seen as a human being to be. Intact embryos are non-viable outside the uterus as are fetuses – at the present stage of sophisticated technology of neonatal intensive care – until about 24 weeks post-conception [66]. A fetus without congenital disease that has passed the latter stage may be capable of continued "independent" existence without any connection with the mother [15] and according to "beneficence" no measures should be taken other than promoting its development and autonomous existence [14]. Out of respect for human life the non-viable embryo or fetus ex utero can be seen as a prematurely born baby and should be treated as such. This does not mean that no research can be done on the non-viable living embryo or fetus, but that in such cases the ethical rules for human experiments will have to be followed. This approach circumvents the difficult question of when human life, or when personhood, truly begins. This has been regarded as a time point up to which the fetus is only seen as living biological material not requiring any protection as a human being [67]. There are, however, no straightforward answers to this question, only a "complex of amalgams of factual and moral judgements", since the embryo or fetus cannot express itself in a way that we are able to understand [12, 46, 46].

Neurotransplantation does not require vivisection on living embryos or fetuses (see below). However, the source of viable brain tissue is not necessarily restricted to the occasion of elective abortion through vacuum aspiration which results in a collection of body and tissue fragments, so that death is obvious. An intact live but non-viable embryo or fetus could be available, though in a limited number of cases, as a result of a spontaneous abortion, surgery following ectopic pregnancy or elective abortion by the use of prostaglandins or, rarely, hysterotomy [21, 24, 66]. Death must then first take place and be established on the basis of indisputable criteria.

If embryos or fetuses are to be regarded as dying human beings, the way in which they are handled should spare them stress and respect human sentiment [24]. Two questions can therefore be raised: (1) Do we just wait for the embryo or fetus to die and under what conditions? (2) What criteria of death are ethically justified in view of the practical difficulty of monitoring physiological parameters without restraint? It is surprising that question (1) is hardly discussed [46], whereas question (2) has been given considerable attention in the advice provided by some national medico-ethics committees [13, 27]. In all publications and reports, death is defined as death of the brain, or more specifically as brainstem death [12, 45, 66]. However, application of the test battery for brainstem death developed for children is not possible in embryos and early-stage fetuses. That is why the irreversible arrest of cardiac and lung functions has been chosen as a practical, reliable and indisputable criterion for establishing death of the organism without stressful handling protocols. Hypothermia has been discussed as a complicating factor [27, 46]. However, it is futile to attempt to maintain physiological levels of body temperature of the non-viable embryo or fetus. With respect to waiting for death of the living but non-viable embryo or fetus, it has been argued that measures taken to shorten life are in conflict with respect for human life [14]. However, there may be better approaches than simply not doing anything, without obstructing the basal ethical principles of "beneficence" and "non-maleficence". Forms of anaesthesia and sedative medication could certainly diminish the potential stress of the embryo or fetus, who is going to die. A comparison can be made with the way hopeless newborns or terminal patients are handled.

The death of an embryo or fetus is not merely the death of its cells. When organs or tissue cease to function in an integrated manner with communication between the constituent cells, the cells themselves may still be alive and remain so under appropriate culture conditions. The principles of fetal neurotransplantation are based on this fact, since grafts obtained several hours after death still form highly functional implants [5].

No artificial rearing (2)

The developmental stage of a donor embryo or fetus may not entirely match the stage required for its use in trans-

plantation research or therapy. In cases where intact living but non-viable organisms are available, one might wish to keep the extrauterine embryo or fetus alive artificially for a considerable period to let it reach a later stage of maturation. However, such actions would be in conflict with the proposed ethical rule that no other measures should be taken than those aimed at promotion of the development and autonomous existence of the embryo of fetus. Artificial rearing is in fact based on the assumption that the organism can be regarded as simple laboratory material [67]. This violates respect for the human being to be, while such life-sustaining measures may, moreover, be a heavy burden on the living non-viable embryo or fetus (although the capacity of a being with an immature CNS to suffer is questionable [47]). Therefore, no form of artificial rearing of the live though non-viable embryo or fetus should be applied for the purpose of using tissue or organs for transplantation research.

Artificial rearing of isolated organs, tissues or cells, i.e. the application of culturing techniques, can take place after the death of the embryo or fetus and is therefore not in conflict with the above moral viewpoints. This would enable more advanced stages of cell maturation to be obtained for transplantations, while at the same time making it easier to screen the quality of the tissues or cells that are actually implanted (see also remarks on transmissible diseases).

No link with decision on termination of pregnancy (3)

A prominent ethical concern is that the potential use of embryonal or fetal organ and tissues for transplantation might influence a woman's decision to have an abortion. It is argued that a woman who is ambivalent about a decision to induce abortion could be influenced to opt for terminating pregnancy if she were told that the organs or tissue of her conceptus could be used scientifically or therapeutically. The notion could arise that donation is a noble and selfless act for the benefit of mankind. In turn, the load of possible guilt and depression after abortion could be borne more easily. On the other hand, since a complex mix of personal, physical, emotional, financial and/or religious aspects play a role in a woman's decision to have an abortion [10, 17], it seems unlikely that knowledge about beneficial use will have a great impact on her decision [24, 41, 61]. Still, the above factors might increase the frequency of legally induced abortions [2, 24, 54]. This potential consequence is of considerable concern to those who find elective abortion unacceptable or only allowed in extreme cases of danger of maternal harm or death. Thus, the ethical issue of the ex utero use of embryos and fetuses cannot be separated completely from the ethical aspects of the decision on elective abortion [2, 41, 54].

A variety of views are possible on the above aspect [20]. At the one extreme it could still be argued that there is no moral problem involved in either elective abortion or the subsequent use of the embryo or fetus. According to this view therapeutic abortion is acceptable since the fetus is not entitled to protection of life as long as it is not viable ex utero [67]. It is then also morally acceptable for the abortion-seeking women to donate the aborted organism for a variety of purposes. At the other extreme it could be argued that abortion is unacceptable and that the use of the resultant material is tantamount to complicity in the act of elective abortion [8, 11]. The first approach completely denies the respect for human beings to be that are non-viable ex utero and regards them as merely an organ bank without intrinsic human values. The second approach gives the embryo or fetus an absolute worthiness of protection of life and makes the use of the resultant material a crime of "complicity after the fact" [8]. However, it is not logical to place a higher value on the life of an embryo or fetus than one does upon the life of an adult [24]. Transplanting the kidney of a murdered adult, for example, is considered entirely acceptable and does not imply complicity in the act that caused the death [46, 60, 61].

Current legislation on therapeutic abortions in European countries is based on various degrees of protection in the period that the conceptus is non-viable ex utero, which is most often related to intrauterine age [7, 70]. In some countries, the woman has a free choice up to 23–24 weeks post-conception. In other countries, elective abortion is freely permitted during the first 12 or 13 weeks of pregnancy, but thereafter up to 24 weeks it is allowed only under particular circumstances which are scrutinized during consultation with a medico-social committee. Yet, in other countries, such a consultation is always required. Permission for termination of pregnancy in the various countries is additionally based on different degrees of medico-social indications, but sometimes only on the indication of possible maternal death. Irrespective of all these differences, therapeutic abortion is a current fact in all countries. If the decision concerning abortion is taken independently of, and prior to, the decision on the possible donation of the conceptus, it would reduce the above-mentioned chance of an increase in induced abortions motivated by the subsequent use of the aborted material, and eliminate the "complicity before and after the fact" of those who wish to use the aborted conceptus [60]. If the transplantation team and the recipient have no role in the abortion process, it seems ethically sound to use the organs or tissue of the legally aborted organism, which would otherwise be discarded. This would then be similar the to well-accepted use of organs or tissue from deceased babies, children or adults.

The above arguments turn on the relationship between the decision to abort electively and the use of the aborted conceptus in the case of a woman as a self-reliant and autonomous person who is seeking termination of pregnancy for reasons of her own. If a therapy were to be

developed that is based on embryonal or fetal grafts, it is conceivable that a woman might seek abortion not to protect her own health but to help a relative suffering from a life-threatening disease. She might even initiate pregnancy specifically for this purpose [2, 16, 44]. In this latter case of "preconceived donation", pregnancy and abortion are a means to the end of using the embryo or fetus, so that one can speak about instrumental exploitation of the embryo or fetus in utero. No intrinsic human values are then attributed to the embryo or fetus, thus completely denying the principle of relative protection of a potential person [54]. Moreover, preplanned pregnancy for donation as well as donation of an embryo or fetus (non-viable ex utero) whose birth was originally desired but donated to a diseased relative might easily become subject to enforcements on the woman [45]. It could even become related to economic needs, if a market should emerge for embryos or fetuses. The only way to avoid these latter aspects without having to make the difficult judgement on women's individual motives for abortion is not to permit any link between the donor and the user and/or recipient of embryo or fetal material and not to allow the recipient to designate the donor [14, 20, 45]. Since it is legal in many European countries to donate organs and tissue to specific persons for medical reasons (e.g. kidney donation), specific legislation would be required to protect the designation of embryos or fetuses [24].

"Non-maleficence" of retrieval methods (4)

If a pregnancy is terminated, there will be a choice as to the method and time of embryo of fetus retrieval for subsequent use in, for example, transplantation. The procedure and timing of abortion is certainly important for obtaining particular pieces of tissue with optimal suitability for neurotransplantation [9]. From an ethical perspective the woman seeking abortion should be protected against riskier and more stressful protocols. The same applies to the embryo or fetus ("non-maleficence"). Although retrieval of usable tissue can therefore never be the primary focus of elective abortion, the abortion procedure may thus be adapted as long as it does not conflict with efficient medical handling of the woman and the embryo or fetus. Appropriate medical handling must prevail over the aims of research or the obtaining of the human biological material for research or transplantation.

The safest and easiest kind of therapeutic abortion seems to be suction curettage. This is practised throughout Europe. It is expected to cause instantaneous death of the embryo or fetus, and is generally but not always well-received by the women seeking elective abortion. In terms of the potential use of organs and tissue it is a rapid method, with the advantage of short post-mortem delays, which maximizes cell viability, but with the disadvantage that organs are structurally damaged and that it is often hard to recognize particular structures in the collected fragments. The use of catheters with slightly larger diameters to obtain larger fragments of 10- to-12-week-old aborted fetuses together with suction by hand under ultrasound control is an adaptation which is already applied and regarded by a local medico-ethics committee as not conflicting with the above-mentioned premises [68].

Therapeutic abortion is not universally performed through suction curettage. Prostaglandin treatment is also practised, especially with later abortions [46]. Together with spontaneous abortions and surgical termination of (life-threatening) extrauterine pregnancies, such cases produce intact embryos or fetuses, sometimes dead, sometimes still alive. Although they pose the problems of handling the conceptus until death (see before), these situations facilitate the identification and dissection of specialized tissue for further use. Given the above rationale it would, however, not be ethical to ask a woman to undergo a prostaglandin-induced abortion when a suction curettage is routinely indicated.

Also the timing of the abortion should be governed by the woman's interests. In practice the desire for an optimum time for obtaining embryonic or fetal tissue might pressurize the woman into speeding up her final decision or into postponing the actual abortion process or surgery. Influencing the woman's decision to terminate a pregnancy can and will be avoided by following the guideline that the decision to terminate pregnancy should "not be influenced by the possible or desired subsequent use of the embryo or fetus and must therefore precede any introduction of possible use" (see above). This would avoid additional pressure on the woman, who may be wavering during the difficult psychological process of taking the final decision as to whether to undergo an abortion. Similarly, itis important to avoid the situation where the woman is asked to delay the abortion for some time, in order to increase the chances of obtaining optimal embryonal or fetal material for transplantation. Her undesired pregnancy is then prolonged for external reasons and this could harm both her physical and her mental health.

Consent of the woman (5)

Unlike the living body, the body of a deceased person can be regarded as a legal object subject to property regulations. Within the confines of the last will of the deceased person but also those of the law (piety and public health considerations) the next-of-kin of the heirs become responsible for ("owners" of) the mortal remains. Any decision concerning donation of the body or parts of it – unless the last will contains explicit instructions not to donate – is therefore in the hands of the next-of-kin. Requests to use the (mortal) remains of an embryo or fetus after a *spontaneous* abortion are therefore at the discretion

of the parents. In cases of an *induced* abortion, it has been argued that the mother's decision abrogates her subsequent rights in relation to the embryo or fetus, so that her consent is not required in case of further use [8]. However, the woman is usually sensitive to the pain of that decision, which follows a complex process of balancing conflicting thoughts, and therefore elective abortion does not disqualify the woman in her relationship with her embryo or fetus [60]. Moreover, the principle of donating a body for educational, scientific and therapeutic purposes can be described as "giving and receiving are better than routinely taking and getting". If no consent is needed, this may even cause grave distress for the woman if she later regrets that she did not know what was going to happen to her embryo or fetus [27]. For these reasons, her consent to the use of the aborted embryo or fetus should be required (proxy consent).

Much advice on guidelines for the use of embryos or fetuses for research and other purposes states that consent should be obtained from the parents. The rationale for involvement of the father, however, is not always discussed or justified [57]. If the mother's consent is explicitly stated to be the only requirement [27], the argument is that the father's relationship with the conceptus is less intimate than that of the mother and, although his consent may be desirable, it should not be an additional requirement for the use of embryos and fetuses. The physical link may not be as direct for a man, but his psychological link may be as strong as that of the woman. Moreover, the equal legal position of men and women in European societies may give the father the same rights concerning consent for use. Several arguments have led NECTAR to propose that the ultimate consent be required of the mother. The woman may not wish the begetter of her child to be involved in the whole process of terminating the pregnancy. A poor or non-existent relationship with this man may well be behind the request for abortion. In that case the basic ethical rule of non-maleficence (from the perspective of the woman) may be more important than that of respecting possible legal rights of the father, so that it would be morally justified to obtain consent only from the woman. Only in the case of a mutual or legal relationship can the man's consent be sought. In this case there is a parallel with the process of deciding on an induced abortion. In some countries the father is consulted and involved in this just as much as the mother, even though it is ultimately the mother who decides. This protocol is followed because an induced abortion is an intervention concerning the conceptus (created by both), but also concerning the woman's body. The father's wish carries less weight here, in view of the ethics of respect for the autonomy of the woman.

The consent required for the use of the aborted embryo or fetus should be informed and free, i.e. the relevant information should be presented to the parents in a comprehensible and honest form so that they can make a proper and free judgement. There should not be any form of coercion or inducement. The purpose(s) for which the remains of the aborted embryo or fetus *might* be used should be made clear. A request for "carte blanche" permission does not fulfil these requirements. This latter type of consent has been proposed with the argument that since material from the embryo or fetus may be used for various purposes, there is no reason to burden the parents with all sorts of details, and that it is anyhow a priori unclear whether the material can be used [15]. It will not always be necessary to transmit a large body of information, but what is provided should be relevant and serve to reach a decision [4]. One advisory document concerning the possible rules for the use of embryos and fetuses [27] states that the informed consent procedure should be general and that the consent should cover all the possible ways in which the embryo or fetus can be used. The rationale for this "all or none" permission is to prevent the aspect of beneficial use from playing a role in the decision on elective abortion and to further exclude designation of particular donor organs or tissue for specific use by a chosen recipient. This problem is avoided when the decision to have an elective abortion is made prior to the suggestion of possible use of the embryo or fetus and there is no link between donor and recipient. The "all or none" and "carte blanche" positions are quite rigid and do not take into account the fact that some women may give permission only for a particular application and not for any other. For example, a woman may approve of the material being used to establish the prenatal developmental anatomy of humans, but be horrified at the prospect of its use for implantation in laboratory animals. Both types of use have been, and still are, beneficial to the understanding and treatment of human health problems. Consent following full information on one particular application (after the decision to terminate pregnancy has been made) is therefore not necessarily comparable with consent for a specific use designated beforehand by the mother or the parents. If it becomes possible to use embryonic or fetal tissue for therapeutic treatment of, for example, neurodegenerative diseases, and if this subsequently becomes common knowledge, it is then inevitable that this may influence the parents's decision on donation (and possibly also on the elective abortion itself [60, 61]). The rationale behind the "all or none" decision will then lose its validity.

While it would be morally ideal to ask for permission to use the embryonal or fetal remains after the abortion has actually taken place, there may not be sufficient time for the woman (or parents) to make a deliberate decision (owing to the pressure for a short postmortem delay if living cells are to be used). Furthermore, the time immediately following the invasive and emotional abortion process is inappropriate for requesting consent. Consent given in that situation might even be regarded as invalid. Whenever possible, therefore, informed consent should be

obtained before the abortion. It is obvious that in the case of a spontaneous abortion this is not always possible.

Written information about the possible subsequent use of the conceptus, presented after a final decision to undergo termination of pregnancy, is probably the best way to introduce the issue of donation. Sensitive timing guided by the personality of the woman as well as the degree of emotional distress experienced before and during the process of deciding on elective abortion will regulate any further steps to discuss consent. This may in a way be analogous with requests for donation of organs or tissue to the family of a comatose terminal patient. Taking this aspect into consideration, the best person to introduce the possible use of the remains of the abortion would perhaps be someone involved with the decision on the elective abortion. The woman might try to get in touch with a member of the team planning on using the embryonal or fetal remains. There are at present no reports on practical experience with such protocols.

Consent for tests of transmissible diseases (6)

The recipient of any embryonal or fetal remains needs to be sure that the donor material is not infected. The situation is analogous with the donation of blood by living persons or of the organs of young or adult deceased persons. Thus tests for the presence of transmissible diseases are required. When blood is donated, tests for the presence of viruses, such as HIV, hepatitis (B and C), CMV and HTLV-1, and syphilis are performed. Such tests can be carried out carefully after taking the blood and before using it without pressure of time. Transplantation techniques require a rapid screening process. Procedures for testing for the above infections that take only a few hours have indeed been developed, but they are based on the availability of blood [37, 50, 69]. If the remains of an aborted embryo or fetus are used there is usually not enough blood available to perform such tests, which means that maternal blood should be obtained. Given the characteristics of transmissible diseases, tests on the maternal blood should provide relevant results. These results are, moreover, relatively safe, since not all viruses pass the placental barrier in all cases. The only way to circumvent the need for testing maternal blood would be to test the embryonal or fetal tissue itself. Such tests require extensive culturing techniques which take weeks rather than days, and are not routinely performed in the clinic. Moreover, culture and freeze storage techniques of the organs or tissue of the aborted embryo or fetus that do not at the same time limit the viability of tissue or isolated cells have not yet been developed.

Testing for transmissible diseases in the mother requires her separate informed consent. As argued above for the question of possible donation, informed consent should be obtained prior to the actual abortion. This may then lead to screening well before the abortion so that there is also time for confirmation tests. Should the woman be informed about the test results? As part of the informed consent procedure, she should be made aware of the consequences a positive test might have for herself and her family (especially in the case of HIV infection). Prospective blood donors are not accepted if they do not wish to be informed about such test results, since the right not to know may lead to repeated useless blood-taking as well as additional costs. This argument does not apply in the case of donation of an aborted embryo or fetus, since the latter will normally be non-recurrent. So, after informed consent has been given for the test for transmissible diseases, it could be up to the mother whether or not she wants to know the test results. The physician who performs the tests may be left with the problem, namely, if one is positive, whether or not to inform relatives as a public health measure.

Brain fragments only (7)

Concern has been expressed that the transplantation of embryonal or fetal brain tissue could lead to a certain extent of "personality transfer" [66]. It is curious to note that the advice of some organizations does not mention this aspect as such [28, 58, 71], while others have proposed guidelines which tried to exclude this possibility by allowing the use of cell preparations or tissue fragments only [6, 27]. Is personality transfer by means of brain tissue implantation feasible anyhow? In view of current neurobiological knowledge, it seems unlikely that personality is determined by one or several types of nerve cells or brain tissue pieces as isolated for translantation. An individual's characteristics are most probably based on the complex interaction of integrated neural networks that are formed by, and based on, numerous nerve cells, often grouped or layered in various sites throughout the central nervous system. If personality transfer were possible at all, it would require the transplantation of large pieces of intact fetal brain, which, moreover, must be able to survive and to mature further and integrate as a network in an existing, fully developed (adult) brain. It is very unlikely that this would be technically feasible, since the optimal survival conditions upon transplantation are different for each type of cell involved [5]. NECTAR aims to develop therapies for neurodegenerative (and perhaps other neurological) diseases that cannot be cured or sufficiently alleviated otherwise. At present it seems that this can be achieved by supplementation of cells at sites where their function is partly or wholly lost or by grafting cells that can promote endogenous regeneration or inhibit degeneration.

Physiological characteristics of an individual, however, may be transferable by transplantation, and personality changes (not transfer) cannot be excluded. Animal

grafting experiments, for instance, have shown that the biological rhythms of the recipient animal can change following transplantation of the fetal nerve cells that compose the biological clock [59]. If this applies to humans as well it would probably represent a change due to physiological (e.g. hormonal) reasons rather than a transfer of personality. Personality changes are caused by some diseases (such as Parkinson's disease); the same holds true for certain medications. If in these cases potential personality changes upon treatment can be accepted or restore the premorbid personality, the same should apply for neurotransplantation. These aspects, however, involve a different ethical question, i.e. whether a particular brain grafting technique is morally acceptable in view of unwanted effects on the recipient. The improvement caused by neurotransplantation therapy should always outweigh the possible physiological side effects (see below).

Hence, although brain tissue transplantation cannot conceivably lead to a transfer of personality, NECTAR has chosen to adopt a cautious approach. Therefore, the present guidelines recommend that only cell suspensions or small fragments of the brain be used for transplantation. Anyhow, its use is a prerequisite for the survival of grafted nerve cells and their functional integration with the host central nervous system [5].

Complete information for personnel involved (8)

Just as the general public may differ in their moral judgements concerning the use of aborted embryos and fetuses, so the views of those directly involved in the retrieval and use of the aborted concepti will also vary. This concerns physicians, nursing staff, laboratory technicians and personnel of the outpatient clinic. In view of the lack of general consensus, the ethical delicacy and the high level of public concern concerning this issue, complete and open information on the use of embryonal or fetal organs or tissue should be given to the public and, in particular, to all personnel involved.

One report on the use of embryos and fetuses discusses whether staff should be given the option not to become involved [27]. It was recommended that the right of hospital staff not to participate should be restricted to those directly involved in actions using the tissue, i.e. the retrieval of the embryonic or fetal tissue and the operation involving the transplantation, and that those with an active role in pre- and postoperative care should not have this option. The latter makes sense, since otherwise the recipient of a fetal transplant could become a medical pariah.

No profit and remuneration (9)

Payment to the mother for the organs or tissue of the embryo or fetus derived from abortion would increase the chance of a pregnancy being initiated or terminated for the sole purpose of aborting the conceptus [24]. If payment were permitted, financial incentives could also come to play a role for those involved in the (separate) actions of abortion and of use of embryonal and fetal material for transplantation. It would be in their interests to promote an abortion or to obtain consent for use of the conceptus [2, 24]. This would decrease the chances of proper informed consent.

Payment for the use of embryos and fetuses or their organs or tissue should therefore be banned, and no financial gains should be permitted to persons involved in retrieval and use of the aborted conceptus other than normal fees (no invoice to the recipient for embryonic or fetal material or its values added). This ban should also exclude indirect financial incentives such as reimbursement of the abortion costs to the woman. These rules do not exclude reimbursement of the normal costs of careful retrieval, storage, transport, handling and transplantation.

Application to medical-ethics committees (10)

All currently published trials on the use of fetal mesencephalic tissue to alleviate the symptoms of Parkinson's disease have been evaluated and approved by local ethics committees routinely existing in medical centres in Europe and elsewhere in the world [32]. In many European countries ethics committees also work at a national level [70]. With their advice and reviews they contribute both to the local decisions and to the decision-making process on ethical issues at judicial/government level (public, politicians and government officials).

The questions concerning the retrieval and use of tissue of elective or spontaneously aborted embryos of fetuses represent only part of the ethical concern in the area of neurotransplantation applied to Parkinson's disease and possible future grafting in the nervous system in other neurodegenerative diseases. Most of the present guidelines deal with this aspect and it seems proper that ethics committees review these protocols in order to ensure ethical standards in the experiments of clinicians and researchers involved. The moral rights of graft recipients involved in any clinical trial are also those based on the four basic ethical principles mentioned before. This should guarantee that any participation is voluntary and not initiated when there is an a priori chance of morbidity (or mortality), that the nature of the experiment is fully explained to the patient involved, and that it is reasonable to expect benefit for mankind, which justifies further experiments on human beings. The latter implies that clinical research must be appropriately planned and checked so that meaningful data can be obtained. Several local medico-ethics committees have decided that these requirements were fulfilled in the protocols they received

on implantation of autografts of adrenal medulla tissue fragments (originally seen as an alternative source of dopamine replenishing cells) [1, 3, 23, 40, 42], and later also on implantation of fetal dopamine neuron-containing mesencephalic tissue in the brain of idiopathic and MPTP-induced patients with parkinsonism [19, 26, 31, 38–40, 43, 49, 68]. Until treatment achieves the status of accepted therapy, each experiment should be subject to re-evaluation, since the moral judgement on new aspects of the protocol or the protocol as a whole may change when the findings of previous clinical trials or those meanwhile obtained elsewhere are taken into account.

Concluding remarks

Neural transplantation research using embryonal or fetal tissues is merely one of the examples of potential use of the remains of human embryos of fetuses. Neuroanatomical and neurobiological studies using human prenatal material, performed for decades, have provided important knowledge about normal and abnormal human brain development. In other scientific fields data on the origin and functional maturation of various organs and tissues in early embryonic states have been similarly obtained. The results can be found in handbooks on embryology and intrauterine development. This basic knowledge has contributed to measures that have helped to safeguard early prenatal human life, and have increased the chance of survival of babies born pre-term [20, 24, 25, 35].

Comparable with neurotransplantation research are the attempts at fetal pancreatic tissue transplantation into patients suffering from juvenile diabetes mellitus and transplantation of fetal thymus or liver parts in patients with immune deficiencies [2, 25, 46]. Such studies depend heavily on the availability of human embryos and fetuses and therefore gain momentum from the occurrence of elective abortions. The moral aspects of the use of embryos and fetuses for neurotransplantation research fall, therefore, in the context of more general guidelines taking into account the diagnostic, therapeutic, scientific, industrial and also commercial purposes.

The need for national or international legislation in this respect has been stressed several times by both scientists and politicians. At the European level the Parliamentary Assembly of the Council of Europe recognized this and presented documents [57, 58] to the Council of Ministers in 1986 and 1989 asking them to take steps in this direction. The documents accept the principle of the use of organs, tissues and cells of legally aborted embryos or fetuses under a variety of restrictions. One of them is that therapeutic use should be limited to rare diseases. Since the most promising development of clinical neurotransplantation might be a therapy for Parkinson's disease, certainly not a rare disease in Europe, this statement could restrict present clinical research. However, so far the answer of the Council of Ministers to these documents has been a positive acknowledgement and the installation of an advisory committee which in 1989 gave advice on the 1986 declaration, but still has to do so on the declaration of 1989 [48]. Recently a Work Group Human Embryo Research of the EC was set up and issued a report concerning the use of, and experiments on, pre-embryos [70], but is working on a report on the use of embryos and fetuses (I. de Beaufort and J. Zimmer, personal communications).

One of the aims of NECTAR is to provide a firm ethical basis for neurotransplantation which will help participating groups to develop their research protocols in a morally acceptable manner. Since we may be on the verge of clinical neurotransplantation trials regarding other neurodegenerative diseases as well, NECTAR has drawn up its own self-restraining ethical guidelines for the retrieval and use of embryos and fetuses. Clinical research groups of NECTAR involved in neurotransplantation are considered to have adopted these guidelines, even if national regulations permit them to deviate from these rules. The guidelines should not be a mere declaration of intent, but a solid basis for actual clinical handling and thereby subsequently justifiable to the general public. However, the present guidelines are not rigid rules and should therefore continue to be a basis for further discussions, the underlying idea being that ethical judgements, although paramount, also have their own development.

As discussed above, a separate issue is the moral justification of clinical trials of neural grafting in patients. A sufficient number of animal studies must have been carried out before such trials on humans can be done. However, what level of animal results justifies the application of these techniques to human beings? At the first international meeting on neurotransplantation in 1984 (Lund, Sweden), at which a comprehensive account was given of the first intrastriatal autoimplantations of adrenal medullary tissue fragments in two patients with Parkinson's disease [3], some scientists voiced serious criticism since at that time the only basic studies that had been done were in rats. Fetal brain tissue had not been used in these patients, so that the criticism concerned the graft surgery itself. The critics considered it unethical to perform such human studies as long as no successful results of non-human primate work had been presented. Since then clinical grafting operations have continued in many research centres, but now in parallel with similar studies on Parkinson primate models, i.e. MPTP- and 6-hydroxydopamine-lesion monkeys. It seems, therefore, that the balance between, on the one hand, the risk-benefit ratio for severly diseased patients with Parkinson's disease who have become unresponsive to drug treatment and, on the other hand, the time and money needed and the animal suffering involved in the implantation studies on the MPTP primate model, has shifted to the view that human clinical trials of

implantation surgery are so promising that they should continue [71]. This is also the view of NECTAR, providing full collaboration and exchange of results on restricted and carefully controlled groups of patients suffering from neurodegenerative disease (at present only Parkinson's disease) can be assured. The ethical guidelines considered above concerning the interests and well-being of the recipient are not covered by the present NECTAR guidelines, since these may differ for each individual neurodegenerative disease. However, these will eventually need to be drawn up, as exemplified by the application of human fetal cortex grafting in schizophrenic patients [33], for which there is no scientific rationale. Although the moral principles concerning trials on the use of drugs and application of brain lesion therapies can certainly be applied, neuroimplantation surgery adds new aspects, which must be addressed.

NECTAR takes the view that the use of material from embryos and fetuses obtained through spontaneous abortions, surgical termination of ectopic pregnancies or elective abortions is justifiable in compliance with a series of restrictions. These restrictions primarily aim to prevent the use of grafts by encouraging induced abortions and to maintain high standards of respect for life and human dignity. Moral and ethical views on these aspects are pluralistic in Europe, which is why the present NECTAR guidelines are accompanied by extensive explanatory notes clarifying the underlying thoughts and motives above the abstract level. It is hoped that these notes will assist discussions on the issue at local, national, European and perhaps even worldwide levels, in order to formulate clear ethical guidelines that are incorporated in formal legislation. Only in this manner can public concern on the use of tissue or cells from human embryos and fetuses be acknowledged and addressed in an honest, adequate and public manner.

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Note added in proof The EC Workgroup Human Embryo Research has recently presented its second report. It includes recommendations about the use of post-implantation embryos and fetuses as well as a survey of the current state of practize and legislation in the various EC member states.

Working Group on Human Embryos and Research (HER) (1994) Second report, EC, Directorate General XII Science, Research and Development, Brussels