Presidenza del Consiglio dei Ministri

NATIONAL BIOETHICS COMMITTEE

“The Cellular Therapy of Huntington’s Disease through the Implantation of Fetal Neurons”

20th of May 2005

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The NBC's response to the question raised by Dr. Alessandro Nanni Costa, the Director of the National Transplant Centre regarding the ethical problems connected to the source of the cells used in the multicentre study "The cellular therapy of Huntington's disease through the implantation of fetal neurons" in which the National Neurological Institute of Milan "Carlo Besta" is participating. (Responsible: Dr. Stefano Di Donato, Medical Director of Level II, Director of the Operating Unit of Biochemistry and Genetics and Director of the Department of Experimental Research and Diagnostics).

PREMISE

HUNTINGTON'S DISEASE

Huntington's disease or Huntington's chorea is a degenerative disease of the Central Nervous System, of genetic origin and with a prevalence of about 1 in 10,000, which occurs in most cases around the age of 30-40 and is clinically characterized by motor signs (bradykinesia, and hyperkinesia) and psychiatric disorders (depression, irritability), and cognitive impairment. Cognitive deficits include attention disorders, difficulty in using their newly acquired skills and slowing of mental processes. The outcome of the disease is fatal within 10-20 years, during which the patient undergoes cachexia in a context of postural rigidity and dementia.

The gene responsible for the disease has been localized on the short arm of chromosome 4. The molecular defect is represented by the expansion of a CAG repeat sequence in the gene IT15 type that encodes a protein called 'huntingtin'. The function of this protein is still unknown, although it is supposed to intervene in some mechanisms related to apoptosis (programmed cell death).

Huntington's chorea primarily affects the degeneration of an area of the brain called *stiate* ; it is situated in the basal area where the "central command system" that coordinates body movement lies.

There is no effective treatment for this disease today. However, numerous clinical trials on mice, rats and non-human primates, have demonstrated that transplanted fetal striatal neurons are able to restore the clinical deficit on animals with induced neurodegenerative lesions. On the whole, the clinical trials confirm the therapeutic potential of the grafts of homologous fetal neurons in the case of induced neuron degeneration in the animal models with Huntington's disease.

With regard to man, the general elements on which the attempt to treat Huntington's disease with intracerebral implantation of fetal neurons were published in the international scientific journal *Neuroscience* (Peschanski et al., 1995). A first pilot study on this type of testing was published in the journal *Lancet* (Bachoud-Levi et al., 2000). The results of this first study - which have also served to organize the multicenter study on a larger number of patients which is the subject of the NBC opinion – have been encouraging: in five patients, three showed marked objective clinical benefits after two or three years, and also the positron emission tomography showed that the implant was operating. These improvements have affected both the motor symptoms (reduction of chorea and

increased speed of muscle movement) and cognitive deficits (improvement in the level of attention, executive function, attention, planning, memory and language).

In terms of overall functional, three patients recovered many capabilities which they had lost for many years. In a fourth patient a significant improvement occurred only transiently which then was lost due to the destruction of the implant, probably caused by microbleedings. In the last patient the graft appeared to be present but was not working for unknown mechanisms. There are also two other ongoing pilot clinical trials with promising results: the first in the United States (Hauser et al. Neurology, 2002, Greenamyre and Shoulson comment, *Neurology* 2002), the other in Great Britain (Rosser et al. *J Neurol Neurosurg Psych*, 2002).

THE MULTICENTRE PROJECT

The multicentre project concerns six clinical research centers that have already begun testing coordinated by the local Services of Neurology, or Neurosurgery. Five are located in France: the *Centre Hospitalier Universitarie (CHU) Henri-Mondor* of Créteil*,* the *CHU Rangueil* of Toulouse, the *CHU* of Nantes and Rennes together, the *CHU* of Lille, and the *CHU* of Angers. A center is located in Belgium, at the *Erasme* Hospital of Brussels.

In total, in these centers there will be 60 patients involved of both sexes aged between 18 and 65, of which 50 in France and 10 in Belgium. Other centers, in Germany and Switzerland, are also about to join the study.

The National Neurological Institute "Carlo Besta" intends to participate in the multicenter study with 10 patients. The research group has an extensive general and specific experience in the study of genetic degenerative diseases, and as pointed out by Dr. Alessandro Nanni Costa, Director of the National Transplant Center, it is at the highest level in the international scientific panorama in this field.

The aim of the experimentation that is the subject of the opinion drafted by the NBC, is to demonstrate the existence of a direct clinical benefit to patients, both as regards cognitive and motor skills, resulting from the replacement of degenerated striatal neurons in patients suffering from Huntington's disease with counterpart neurons from human fetuses, comparing a treated group with an untreated control group. The assessment of therapeutic effectiveness requires the use of a series of functional, physiological and anatomical criteria as described in scientific literature.

The treatment applied to patients consists in the graft of intra-striatal tissue (neurons, macroglia, microglia, endothelial cells and neuronal precursors and microglia) from the lateral ganglionic eminences of human fetuses during the period between the seventh and the ninth week after conception (see Law 194 / 78[1]). Two grafts are performed, the first in the striatum of the right cerebral hemisphere, the second, two weeks later, in the left striatum.

[1] Law No.194 of the 22nd of May 1978, "Regulations on the social protection of motherhood and the voluntary termination of pregnancy." Art. 4 - In order to undergo termination of pregnancy during the first 90 days, women whose situation is such that continuation of the pregnancy, childbirth, or motherhood would seriously endanger their physical or mental health, in view of their state of health, their economic, social, or family circumstances, the circumstances in which conception

For Italy, the fetal tissues are obtained from voluntary terminations of pregnancy performed at the Mangiagalli Clinic - Clinical Specialization Institutes of Milan, in accordance with the regulations in force. In any case, for each of the research centres participating in the project - including the National Neurological Institute "Carlo Besta" - the preparation of the product of cell therapy involves two different structures that operate independently: an obstetrics department in which voluntary interruption of pregnancy is carried out under the laws in force in different countries, and a cell therapy centre (or a biologist associated with the Department of Neurosurgery) that prepares the tissue to be grafted, that is, the dissection and fragmentation of ganglionic eminences, and the immersion of the obtained tissue in a special solution.

Voluntary interruption of pregnancy is performed by aspiration through a Karman cannula using ultrasound guidance.

The woman's right to privacy is guaranteed under the laws in force in different countries.

The virological checks made on the starting material are indirect in that the voluntary interruption of pregnancy procedure provides the possibility of carrying out a series of tests on the mother's blood (fetuses are only potential carriers of viral infections transmitted from the mother).

The use of fetal tissue requires the informed consent of the woman and its acquisition does not involve any form of remuneration or compensation, or any kind of economic incentive or any other sort of incentive.

THE QUESTION SUBMITTED TO THE NBC

The question submitted to the NBC only concerns an assessment of the ethical issues related to the source of the cells used in the project under examination. The question does not deal with the bioethical issues related to recruitment, consent and the safeguards for patients, nor does it deal with the therapeutic efficacy and the risks associated with the provided treatment, or any other ethical or deontological matter connected with the protocols of clinical trials. In this regard, the NBC acknowledges that all these aspects of the Project should be appropriately placed under the scrutiny of the apposite ethical Committees which it hopes will be as extensive and thorough as possible in relation to the particularly sensitive and critical nature of the experimentation in question.

Further clarification is also appropriate. The question does not concern an ethical evaluation of the voluntary interruption of pregnancy itself. The Opinion does not, therefore, make any direct reference to this devastating and dramatic bioethical issue.

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occurred, or the probability that the child would be born with abnormalities or malformations, shall apply to a public counselling centre established under item *(a)* of Section 2 of Law No. 405 of the 29th of July 1975 or to a social-health facility that is fully authorized by the Region, or to a physician of her choice.

RESPONSE TO THE QUESTION

The retrieval of fetal tissue from dead fetuses deriving from voluntary interruption of pregnancy and its use for scientific and / or treatment purposes, is regarded as bioethically acceptable in principle, however, it does raise some serious doubts regarding the risk that such practices could in some way constitute an incentive to abortion.

The NBC therefore considers that the bioethical acceptability of these practices should be subordinated first and foremost to the ascertainment of the full independence and distinct separation of the respective decision-making processes between medical staff and / or the health institution engaged in the voluntary interruption of pregnancy, and the researchers and/or the research institute conducting the scientific and clinical experimentation.

Once this independence has been asserted, that is to say, that there is the absolute guarantee that the carrying out of voluntary interruption of pregnancy is in no way intentionally aimed at the use of fetal tissue for experimental and /or therapeutic purposes, the retrieval of fetal tissue from voluntary interruption of pregnancy and its use for the aforesaid scientific and /or therapeutic purposes are to be regarded as *morally acceptable practices*, only, when complying with the following conditions[2]:

1. There should be no advantage, incentive or benefit of any form for those involved, that is, the medical staff and/or health institution carrying out the voluntary interruption of pregnancy and the researchers and/or the research institutes conducting the scientific and clinical experimentation.

2. The woman's consent, and where possible, that of both the parents, should be obtained after being adequately informed. This consent should only be requested after the voluntary interruption of pregnancy has taken place, in order to prevent that the foreseen use of fetal tissue for scientific and/or therapeutic purposes might constitute an undue inducement to resort to this practice.

3. The method and procedures of the voluntary interruption of pregnancy are not modified or adjusted, in relation to the need to retrieve fetal tissue and the scientific or therapeutic purposes. No preventive treatment functional to the scientific or therapeutic purposes of the use of fetal tissue may be carried out on the woman and/or on the fetus during the course of the pregnancy.

4. The right to privacy of the woman should be guaranteed by the laws in force.

5. The use of fetal tissue should only be for highly important scientific and/or therapeutic purposes for which no alternative methods with comparable requirements exist. In any case, where possible, it is always preferable to resort to fetal material from miscarried fetuses rather than from voluntary interruption of pregnancy.

6. Each project which foresees the retrieval of fetal tissue, deriving from voluntary interruption of pregnancy or spontaneous abortion and its use for scientific and/or therapeutic purposes, should be subjected to preventive ethical evaluation on behalf of the relevant competent committee. The evaluation also concerns the scientific reliability of the team proposing the research or application

[2] See also the NBC document on *Identity and Status of the Human Embryo*, 22nd of June 1996.

of treatments for therapeutic purposes, as well as the ascertainment of full independence of the medical staff and/or health institution engaged in the voluntary interruption of pregnancy, and the researchers and/or research institution engaged in scientific or clinical experimentation.

7. The donation of fetal tissue from interruption of pregnancy or spontaneous abortion for scientific and/or therapeutic purposes should not involve any form of commercialization, remuneration or compensation. Fetal tissue must not under any circumstances be bought and sold by the mother and third parties.

With regard to this last point, the NBC hopes for intervention on a national and European level, in order to impose a ban on the commercialization of fetal cells and tissues deriving from voluntary interruption of pregnancy or miscarried fetuses as soon as possible by means of specific and unambiguous regulations which consent to counter the growing and concerning phenomena of “fetal tissue brokers,” specifically, the “mediators of fetal tissue,” who **-** in the absence of rules, or the harmonization of rules within the territory of the European Union - derive substantial profits from procurement and storage of fetal tissue from abortions. This could surreptitiously induce significant changes in abortion techniques in order to facilitate the collection of certain types of fetal tissues and organs, and could provide an incentive, albeit difficult to quantify but nevertheless realistic, to the recourse to voluntary interruption of pregnancy.

NOTES

While agreeing in principle with the content of the Opinion on Cellular Therapy of Huntington's disease through implantation of fetal neurons, I must express my concern as to the use of fetal tissue deriving from voluntary interruption of pregnancy, since it is - in practice – difficult to attain total independence between the team performing the interruption of pregnancy and the team that works on the obtained tissue given the need to program the timing and methods of such intervention and the subsequent procedures of dissection and suspension of the tissue.

Maria Luisa Di Pietro

ATTACHMENT

1. The letter from Dr. Alessandro Nanni Costa, Director of the National Transplant Center, regarding the question submitted to the NBC.

2. The application for authorisation, with relative attachments, for a Phase II clinical trial of cellular therapy product without extensive manipulation entitled: "Cellular therapy of Huntington's Disease through the implantation of foetal neurons", addressed to the Ministry of Health by Dr. Stefano Di Donato (Medical Director of Level II, Director of the Operating Unit of Biochemistry and Genetics and Director of the Department of Experimental Research and Diagnostics, “Carlo Besta” National Neurological Institute of Milan).