EUROPEAN COMMISSION
SECRETARIAT-GENERAL

Group of Advisers on the Ethical Implications of Biotechnology
SG-C-1

THE ETHICAL ASPECTS OF GENE THERAPY

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1. Opinion N°4 from the Group of Advisers on the Ethical implications of Biotechnology on Ethical Aspects of Gene Therapy

OPINION OF THE GROUP OF ADVISERS
ON ETHICAL IMPLICATIONS OF BIOTECHNOLOGY
OF THE EUROPEAN COMMISSION

N° 4 Date 13.12.94

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THE ETHICAL IMPLICATIONS OF GENE THERAPY

Reference : Commission request for an opinion dated 23 September 1993
Rapporteur : Prof. Luis Archer

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The Group of Advisers on Ethical Implications of Biotechnology of the European Commission :

- Having regard to the request of the Commission of 23 September 1993 for an Opinion on gene therapy;

- Having regard to the Treaty on European Union and in particular articles 129, 129 A and Article F.2 of the Common Provisions;

- Having regard to European Regulations in particular the Council Directives on genetically modified (micro) organisms 90/219/EEC and 90/220/EEC and relevant product legislation;

- Taking account of the statements expressed by the European institutions, the Council of Europe, the UNESCO and other international or national ethics committees;

- Having heard the report on "Ethical Aspects of Gene Therapy" by the rapporteur Prof. Luis Archer;

considering that :

1.1. Scientists generally agree that somatic gene therapy is one of the most promising ways of allowing to alleviate, to cure or to prevent a growing number of genetic as well as acquired diseases, including cancer and even perhaps AIDS. Somatic gene therapy has indeed recently entered the clinical setting as a highly experimental therapeutic procedure. An important and long lasting research effort is still required before routinely performed medical applications can be envisaged.

1.2. As somatic gene therapy is highly experimental, the ethical principles to be respected are at the very least all those applying to good clinical practice concerning research involving human subjects (namely, informed consent of the patients, with special care for children and incapacited persons, review of research protocols by an independant and multidisciplinary body, such as an ethics committee, proportionality of risks and benefits, confidentiality, etc...). In this respect, there is, concerning gene therapy, a tendency in many countries to reinforce the initial action of local committees by national supervisory bodies.

1.3. Specific regulations concerning genetically modified organisms (directives 90/219/EEC and 90/220/EEC as well as product legislation) have been adopted to fulfill safety requirements. These regulations do apply to certain research and development aspects relevant to gene therapy, but not to clinical trials in the context of gene therapy.

1.4. At its present stage, gene therapy focusses on serious diseases for which there is no other effective available treatment. In the future, therapeutic indications may be widened.

1.5. Somatic gene therapy has not only short term, but also individual and social long term consequences. Its cost is at present high but could become much lower in the future. In this respect, it should also be kept in mind that rare diseases are of little interest for pharmaceutical industry compared to more frequent diseases. Both these points raise the problem of equal access to treatment.

1.6. As somatic gene therapy applications are in the long term bound to be quite important, the use of new therapeutical products will be of great interest for the development of European Union biotechnological industry. Public control of the production and distribution processes is already exercised in some European countries and will be influenced by the recently established European Agency for the Evaluation of Medicinal Products.

1.7. Germ line gene therapy, which implies the attempt to cure or prevent transmission to future generations of gene defects resulting in serious diseases, raises considerable and controversial ethical problems. Although many discussions are already going on in various fora, the scientific basis and the technical feasibility of germ line gene therapy are far from being established. The possible transmission of the modification to future generations raises specific philosophical questions. Therefore, no proposal for clinical experimentation of germ line gene therapy on humans is at present even contemplated.

1.8. There are high expectations raised by the prospect of treating or preventing serious and widespread diseases. The public has often either too high expectations or needless concerns.

The group submits to the European Commission the following opinion :

2.1. Somatic gene therapy should be encouraged at different necessary levels (basic research, clinical trials, biotechnology), by supporting research actions (especially at European level by means of the Community Research Programmes in Biomedicine and Health, involving also research on bioethics), organizing training and exchange programmes for researchers and students, and by any other appropriate means.

2.2. The ethical evaluation of somatic gene therapy protocols requires processes assuring quality, transparency and efficiency of this evaluation without introducing any unnecessary delays to the treatment of patients. In addition to local review systems, a national supervisory body is important to evaluate as thoroughly as possible this experimental technology.

The harmonization and partial standardization of all European evaluation processes could be helpful especially for research carried out at European level.

2.3. To consider the specific problems linked to the use of genetically modified organisms in the context of gene therapy implies a national or even European control of clinical trials. Relevant regulations for this purpose could be elaborated at a European level.

2.4. Because of its present risk assessment, somatic gene therapy should be restricted to serious diseases for which there is no other effective available treatment. The widening to other possible therapeutical indications could be considered, indication by indication, with an evaluation of the medical as well as ethical aspects.

2.5. Appropriate measures should be taken to assure equal access to gene therapy within the European Union. In addition, according to this equal access principle, a special status could be attributed at European level to orphan drugs and diseases as already done within the Biomedical and Health Research Programme of the European Commission.

2.6. To guarantee transparency and to fulfill the objectives of the European construction by involving the citizens, special regulations should provide for evaluation at European level of the risks and results of gene therapy technology. The conclusions of this evaluation must be regularly published to allow public scrutiny and encourage public debate.

2.7. Because of the important controversial and unprecedented questions raised by germline therapy, and considering the actual state of the art, germ line gene therapy on humans is not at the present time ethically acceptable.

2.8. It is of vital importance that, simultaneously, public information and education are promoted, so that the public gains an objective and correct picture of the possibilities and limitations of gene therapy and related developments. The issue of gene therapy requires a didactic as well as a democratic approach, involving a close participation of European citizens.

In accordance with its terms of reference, the Group of Advisers on the Ethical Implications of Biotechnology hereby presents this Opinion to the European Commission.

Signatures : The Members

The Chairman

2. Avis N°4 du Groupe de Conseillers pour l'Ethique de la Biotechnologie relatif aux aspects éthiques de la thérapie génique

AVIS DU GROUPE DE CONSEILLERS
POUR L'ETHIQUE DE LA BIOTECHNOLOGIE
DE LA COMMISSION EUROPEENNE

N° 4 **Date 13.12.94**

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LES ASPECTS ETHIQUES DE LA THERAPIE GENIQUE

Référence : Avis demandé par la Commission le 23 septembre 1993
Rapporteur : Prof. Luis Archer

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Le Groupe de conseillers pour l'éthique de la biotechnologie de la Commission Européenne

- vu la saisine de la Commission, du 23 septembre 1993, demandant un avis sur la thérapie génique,

- vu le Traité sur l'Union européenne, et notamment ses articles 129, 129 A et l'article F paragraphe 2 des Dispositions communes,

- vu la réglementation européenne, en particulier les Directives du Conseil sur les (micro)organismes génétiquement modifiés 90/219/CEE et 90/220/CEE et la législation relative à la sécurité des produits,

- vu les différents textes émanant des institutions européennes, du Conseil de l'Europe, de l'UNESCO et des comités d'éthique nationaux et internationaux, intéressant la thérapie génique,

- le rapport de M. Luis Archer sur "Les aspects éthiques de la thérapie génique" entendu,

Considérant les points suivants :

1.1 Les scientifiques s'accordent, en général, à considérer la thérapie génique somatique comme l'une des voies les plus prometteuses pour soulager, guérir ou prévenir un nombre croissant de maladies non seulement génétiques mais également acquises, y compris le cancer et peut-être même le SIDA. La thérapie génique somatique vient d'ailleurs d'entrer en phase clinique, mais en tant que procédure thérapeutique encore très expérimentale. Il faudra encore consentir un effort important et soutenu en matière de recherche avant de pouvoir l'envisager en tant que pratique médicale de routine.

1.2 Compte tenu du fait que la thérapie génique n'en est encore qu'à un stade très expérimental, les principes éthiques à respecter doivent englober au minimum tous ceux régissant les bonnes pratiques cliniques en cas d'expérimentation sur des sujets humains (à savoir, le consentement éclairé des patients, en tenant particulièrement compte des enfants et des personnes majeures vulnérables, l'agrément des protocoles de recherche par un organe indépendant et multidisciplinaire, tel qu'un comité d'éthique, la proportionnalité entre les risques et les bénéfices, la confidentialité des données médicales, etc.). A cet égard, plusieurs pays ont actuellement tendance, en matière de thérapie génique, à renforcer l'action des comités locaux par l'intervention d'organes nationaux de contrôle.

1.3 Une réglementation spécifique relative aux organismes génétiquement modifiés (les directives 90/219/CEE et 90/220/CEE ainsi que la législation relative à la sécurité des produits) a été adoptée pour satisfaire aux exigences en matière de sécurité. Ces dispositions ne s'appliquent cependant qu'aux aspects de la thérapie génique qui sont liés au développement et à la recherche, mais non aux essais cliniques.

1.4 Au stade actuel, la thérapie génique est réservée aux maladies graves pour lesquelles il n'existe pas d'autre traitement efficace. A l'avenir, les indications thérapeutiques pourraient cependant être étendues.

1.5 La thérapie génique somatique n'a pas seulement des conséquences à court terme, mais aussi des implications à long terme, pour la société comme pour les individus. Si son coût est actuellement encore élevé, il pourrait sensiblement diminuer à l'avenir. A cet égard, il convient de garder à l'esprit que, contrairement aux maladies les plus courantes, les maladies rares ne présentent guère d'intérêt pour l'industrie pharmaceutique. Ces deux considérations soulèvent le problème de l'égalité d'accès aux soins.

1.6 Etant donné que les applications de la thérapie génique ne manqueront pas vraisemblablement de devenir importantes à long terme, l'utilisation de nouveaux produits thérapeutiques issus de cette technique présentera un grand intérêt pour le développement de l'industrie de la biotechnologie dans l'Union européenne. Le contrôle public des processus de production et de distribution de tel produits, déjà assuré dans certains pays européens, sera influencé par la toute récente "Agence européenne pour l'évaluation des médicaments".

1.7 La thérapie génique germinale, qui a pour but de remédier à des altérations génétiques provoquant des maladies graves de manière à éviter leur transmission aux générations futures, soulève des questions éthiques très sérieuses et controversées. Bien qu'elle suscite déjà de nombreux débats dans différentes enceintes, les bases scientifiques et la faisabilité technique de cette méthode thérapeutique sont loin d'être établies. L'éventualité de la transmission à la descendance des modifications génétiques opérées dans le cadre de la thérapie germinale pose des problèmes philosophiques particuliers. C'est pourquoi, il n'est actuellement pas même envisagé de proposer une expérimentation clinique de la thérapie génique germinale concernant des êtres humains.

1.8 La perspective de pouvoir soigner ou prévenir des maladies graves et très répandues fait naître d'immenses espoirs. Cependant, l'opinion publique est souvent conduite à avoir soit des espoirs excessifs, soit des craintes injustifiées.

Le Groupe présente à la Commission européenne l'avis suivant :

2.1 Le développement de la thérapie génique somatique doit être encouragé aux différents niveaux requis (recherche fondamentale, essais cliniques, industries biotechnologiques) par la promotion d'actions de recherche (en particulier au niveau européen par le biais des programmes communautaires de recherche en biomédecine et santé, comprenant aussi la recherche en bioéthique), l'organisation de programmes de formation et d'échange pour les chercheurs et les étudiants et par tout autre moyen approprié.

2.2 L'évaluation éthique des protocoles de thérapie génique somatique exige des procédures garantissant la qualité, la transparence et l'efficacité de l'évaluation, en évitant tous délais inutiles dans le traitement des patients. Outre les systèmes d'évaluation locaux, il est important qu'il existe un organe de contrôle national chargé d'évaluer de façon aussi complète que possible cette technologie expérimentale.

L'harmonisation et, dans une certaine mesure, la standardisation des processus d'évaluation européens sembleraient opportunes, notamment s'agissant des recherches menées à l'échelle européenne.

2.3 La prise en compte des problèmes spécifiques liés à l'utilisation d'organismes génétiquement modifiés dans le contexte de la thérapie génique exige un contrôle national, voire européen, des essais cliniques. Des dispositions particulières devraient être prises à cet effet au niveau européen.

2.4 Compte tenu des risques qu'elle présente au stade actuel, la thérapie génique somatique devrait être limitée aux maladies graves pour lesquelles il n'existe pas d'autre traitement efficace. L'extension à d'autres indications thérapeutiques éventuelles devrait être considérée, indication par indication, après appréciation des aspects tant médicaux qu' éthiques d'une telle extension.

2.5 Toutes mesures appropriées doivent être prises pour garantir l'égalité d'accès à la thérapie génique au sein de l'Union européenne. En outre, conformément à ce principe d'égalité d'accès, il convient d'envisager de conférer un statut particulier, au niveau européen, aux médicaments et aux maladies "orphelins", à l'instar de ce qui est fait dans le cadre du Programme Communautaire de Recherche en Biomédecine et Santé.

2.6 Dans le souci de garantir la transparence des pratiques et conformément aux objectifs de la construction européenne d'assurer la participation des citoyens, il importe de prévoir des dispositions spéciales en vue d'une évaluation des risques et des résultats de la thérapie génique au niveau européen. Les conclusions de cette évaluation doivent être publiées régulièrement pour assurer l'information de l'opinion et favoriser le débat public.

2.7 En égard à l'importance et au caractère controversé des questions sans précédent soulevées par la thérapie génique germinale et en l'état des connaissances scientifiques, la thérapie génique germinale sur l'homme n'est pas actuellement acceptable d'un point de vue éthique.

2.8 Il est essentiel de promouvoir simultanément l'information et l'éducation du public afin qu'il puisse avoir une vision exacte et objective des possibilités et des limites de la thérapie génique et de ses développements futurs. La question de la thérapie génique doit être abordée en suivant une approche didactique et démocratique, implicant une étroite participation des citoyens européens.

Conformément à son mandat, le Groupe de conseillers pour l'éthique de la biotechnologie remet le présent avis à la Commission européenne.

Signatures : Les membres

Le président

3. Report on ethical aspects of gene therapy from Prof. Archer

GROUP OF ADVISERS ON ETHICAL IMPLICATIONS OF BIOTECHNOLOGY
OF THE EUROPEAN COMMISSION

N ° 4 *Date : 13.12.94*

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REPORT ON ETHICAL ASPECTS OF GENE THERAPY

Reference : Commission request for an opinion dated 23 September 1993.
Rapporteur : Prof. Luis Archer

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1. DEFINITIONS

Human gene therapy is the deliberate transfer of genetic material into a patient's cells with the purpose of curing or preventing a disease. Removal of existing genes from cells is not yet technically feasible in current clinical tests. Only their addition is possible.

Depending on the type of cells being the target of this gene transfer (somatic or germ-line cells), gene therapy is called somatic or germ-line gene therapy respectively.

Germ-line cells are spermatozoa or eggs and their precursor cells, as well as cells of the early stages of the human embryo, before differentiation of the germ-line. Somatic cells are all the other cells of the organism.

It is assumed that, in somatic gene therapy, the genetic changes introduced are not transmitted to the progeny, while they would be in the case of germ-line gene therapy.

Somatic gene therapy is being practiced, as experimental research in human subjects, in a growing number of clinical centers in the world, including several European, countries. Germ-line therapy is not yet available in a clinically useful form, but its ethical implications are being discussed.

Enhancement genetic engineering (the transfer of a gene into cells of a healthy human being with the purpose of improving desired characteristics such as height or memory, for instance) is closely related to gene therapy and utilises the same technology.
Enhancement genetic engineering can also be divided into somatic and germ-line engineering.

At present, somatic gene therapy techniques are considered ethically admissible only for the treatment or prevention of serious diseases (see below, under 2.2), the latter being defined as diseases which cause significant suffering and premature death (W. French Anderson, The J. of Med. and Phil.14 : 681-693,1989). Consequently, enhancement genetic engineering is presently excluded from the ethically admissible clinical trials and, for that reason, will not be considered in this Report. If, in the future, clinical and ethical indications arise for gene therapy of minor diseases or even for certain health improvements, the matter should be discussed on a case by case basis. Furthermore, a different and more philosophical discussion would then have to be opened in our society on the ethical acceptability or unacceptability of certain kinds of betterment of the human nature.

2. ETHICAL EVALUATION OF SOMATIC GENE THERAPY

As gene therapy is currently (and will stay for a considerable time) in an experimental stage, there is a consensus that the ethical principles to be respected are those applying to the research on human subjects.

Such principles, although sometimes formulated in slightly different forms, are essentially the same in all countries since the Helsinki Declaration (1964, 1975, 1983, 1989) and the Belmont Report (1978). For our purposes they can be summarized in the following way: (1) Benefits for the patient should be expected; (2) Disproportionate risks should be excluded; (3) The dignity or autonomy of the person should be respected; (4) Justice should be attained. We will follow this order in our discussion.

2.1 Benefits

For an increasing number of serious and lethal diseases (both genetic and acquired diseases) gene therapy offers the prospect of effective alleviation, cure or even prevention.

In addition to the adenosine deaminase (ADA) deficiency, other genetic diseases have been the object of gene therapy protocols, namely familial hypercholesterolemia, cystic fibrosis, Gaucher disease, glucocerebrosidase and hemophilia B. Acquired diseases, like AIDS, cardiovascular diseases, and cancer are also being contemplated by gene therapy. As matter of fact, cancer is the disease for which about two thirds of gene therapy protocols have been designed. Most of them attempt to interfere with the immune system of cancer bearing patients by transferring to tumor infiltrating lymphocites (TIL) or to tumor cells genes coding for cytokines or for foreign antigens. This strategy is becoming known as "vaccination". In other attempts, a "suicide" gene is transferred to tumor cells with the objective of rendering them sensitive to a drug which is otherwise non-toxic. Other protocols transfer the multidrug resistance gene to hematopoietic cells with the purpose of making them resistant to high dose chemotherapy.

Initially, somatic gene therapy was always performed ex vivo. This meansthat target cells were removed from the patient, grown in culture in vitro, genetically modified by the use of an appropriate vector, and then harvested and finally reimplanted in the same patient. More recently an in vivo strategy started being developed which involves direct administration of the gene-carrying vector into the patient's organism. As this latter strategy tends to be used more progressively, each of the individual clinical trials will be less dependent on sophisticated high-technology, and the ethical use of somatic gene therapy will become much easier and more widespread. It will then have a profound impact on medicine.

Disease prevention can be obtained by the appropriate gene transfer to individuals who show by pre-symptomatic genetic tests, the presence of a gene defect causing a late-onset disease. We could also call disease prevention the appropriate gene transfer to individuals who showed, by genetic testing, predispositions for a given disease, like breast cancer, ischemic heart disease (through low level of LDL receptor molecules in the liver) and others.

In addition, gene therapy may develop, in the future, into a sophisticated drug delivery system. Instead of giving a certain agent by repeated or even daily injections, it might be preferable to administer it by a one-time insertion of the patient's own gene-engineered cells.

The benefits of somatic gene therapy for alleviation, cure, or prevention of genetic and acquired diseases are, therefore, very promising. These benefits are of special relevance when alternative therapies for a given disease are poor or inexistent.

2.2 Risks

In order to evaluate risks, sufficient scientific knowledge on the physiopathology of the disease and on the molecular biology of the gene concerned, as well as of its vector, are required. This knowledge, together with animal experimentation (including that non-human primates), should show whether or not (i) the therapeutic gene is expected to be inserted at the right place in the target cells and to remain there long enough to be effective, (ii) the introduced gene is appropriately regulated, producing acceptable amounts of the product and (iii) there are no secondary effects.

This latter requirement is, presently, very difficult to assess. As mentioned by the U.K. "Report on the Ethics of Gene Therapy" (Clothier Report), the questions of safety "are heightened by the possibility of inadvertent and unpredictable consequences of gene therapy to the patient, and the possible long term consequences" (8.8). For example, the much used retroviral vectors integrate in points at random of the genome. If integration takes place in certain points, it may activate an oncogene, or inactivate an anti-oncogene, or block an essential gene[1]. It is important that the public is aware of these potential risks, so that the review and oversight of gene therapy protocols do not become too relaxed and when the first serious problems come, the public does not force a halt or significant slowdown of gene therapy research, which should, nevertheless, continue and be encouraged to the benefit of so many patients.

It is, in part, in order to outweigh the above mentioned risks and uncertainties that most regulations prescribe that the diseases initially selected for gene therapy should be serious, and lack effective alternative treatments[2].

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1 Even the optimistic W. French Anderson agrees that "over time, problems will arise. It is even possible that our worst fears will be realized and a patient develops a leukemia, a solid tumor, or some other serious pathology as a result of the gene transfer" (Human Gene Therapy, 2:194, 1991).

2 The Clothier Report speaks of "disorder which is life threatening, or causes serious handicap, and for which treatment is unavailable or unsatisfactory" (p.25).
The Guidelines of the European Medical Research Council mentions "diseases which are invariably fatal or severely disabling and for which current therapies (...) are not always feasible or carry a high level of risk" (Lancet June 4, 1988, p. 1271).
The 1993 Opinion of the French National Ethics Committee restricts somatic gene therapy to "disorders for which no effective treatment is available and for which the prognosis is sufficiently serious to warrant the risks entailed in the application of what is, as yet basically an experimental form of treatment.

The Medical Research Council Guidelines state (p.31) that only once the trials with devastating diseases have proven to be effective and safe, should other less burdensome diseases be considered, such as hemophilia and PKU, for which alternative treatments exist.

2.3 The dignity of the person

In first the place, the interests of the patient's health should always prevail over the research interests.

The rights to confidentiality and privacy, in their conventional forms, also belong to the duty of respecting human dignity.

In addition, informed consent of the patient should be obtained, noting that, due to the declared uncertainty implicit in experimental treatments, the standard of disclosure for patient involvement and authorization should be higher than the standard required for conventional treatments. The Clothier Report from the UK further requires that patients receive advice from an independent source, unrelated to the research team. The 1993 Opinion from the French National Ethics Committee develops the concept that information supplied to the families involved and to the public be "as objective, restrained, measured and realistic as possible".

As many gene therapy trials involve children, the informed consent given by their parents or guardians should assume a truly vicarious form : they are supposed to decide not according to their interests but according to what is presumed that the child would decide if he or she would be already competent. A specially difficult situation is that of foetal gene therapy, recommended cases of some genetic disorders which lead to irreversible and cumulative effects before birth. This issue is complicated by the conflicting views on the status of the embryo and foetus.

2.4 Justice

Access to gene therapy of every potential candidate is an important ethical concern. Because gene therapy was initially dealing with a few, very rare diseases, the problem was not acute. as soon as it is extended to other and more common diseases, the problem of fair selection of patients will have to be faced. It should be prescribed that the criteria used for selection of patients is included in the proposal to be reviewed by the ethics committee. A fair selection of the diseases to be treated should also be considered. Special care should be taken of "orphan diseases" (those affecting few patients) which are other given great social support but are of little or no interest to the medicinal industry.

A second problem of justice refers to the distribution of resources for health care. In contrast to a more utilitarian view in the US, most european countries defend that everybody's right to health care is equal. However, the debates on resource allocation have shown that, due to the fast increasing number of new biomedical technologies, scarcity of resources is becoming evident and choices in health care are therefore inevitable. In this same context, socialized medicine, which is traditional in Europe, has recently given some place to forms of medical privatization. These problems of choices in health care will soon affect gene therapy, specially because this new technology is, at the moment, still very expensive. Criteria for priorities in health care have to be globally studied, discusses and established[3]

A third problem of justice deals with the distribution of gene therapy centers among the different countries. It would not seem fair that the benefits of this new technology were restricted to industrialized countries. It would be advisable to develop a policy for the promotion of gene therapy applications in developing countries.

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[3] An example of such a study is the report "Choices in Health Care" ("A Report from the Dutch Governmental Committee on Choices in Health Care", Zoetermer, The Netherlands, 1992) where four criteria are given to inclusion of a given technology in the "basic package", namely a. Is it necessary care, from the community point of view ? ; b. Is it demonstrated to be effective ? ; c. Is it efficient ? ; d. Can it be left to individual responsibility ?"

3. ETHICAL REVIEW OF SOMATIC GENE THERAPY PROTOCOLS AND PRODUCTS

3.1 Review of protocols

Any somatic gene therapy protocol must be assessed as to the ethical aspects. The natural places for such assessment are the local research ethics committees. They are supposed to be advisory bodies, leaving the responsibility of any accident with the medical team. However, there is a tendency in several European countries, as well as in the United States, to look for a reenforcement of the action of the local committees by one or more national supervisory bodies.

In the United States, the biological safety of the gene therapy research protocols is reviewed by a local committee (Institutional Biosafety Committee, IBC) and by two federal agencies : NIH, through its Recombinant DNA Advisory Committee (RAC) and the Food and Drug Administration (FDA). However, only NIH-funded investigators or investigators who work in institutions receiving NIH funding are required to undergo RAC review. On the contrary, FDA review is mandatory for all investigators, regardless of the funding source.

In the United Kingdom, the Clothier Report (1992) recommended the establishment of an "expert supervisory body", acting in coordination with the local research ethics committees, with tasks of advising, receiving proposals and recommending them for approval, monitoring, oversight and providing advice to Health Ministers. The recommendations of the Clothier Report were accepted by the Government and a "Gene Therapy Advisory Committee" was set up, as a non-statutory advisory body to oversee the conduct of gene therapy in the UK.

In France, the National Ethics Committee declared, in its 1993 Opinion that somatic gene therapy protocols fall under the socalled "Loi Huriet (1988)" as well as under the law of 13 july 1992 on the use of genetically modified organisms. This means that the researcher must approach, in addition to his local research ethics committee, two other committees. In addition, "it is imperative that the results of these trials are closely monitored by a technically and scientifically competent assessment committee as well as by the Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé" (CCNE, Avis de 1993).

In the Netherlands, at least for the first submitted protocols (1991-1992), approval by the local research ethics committee was followed by a positive advice from the VCOGEM Committee (concerned with introduction into the environment of genetically modified organisms) and a decisive opinion from the central "Core Committee on Medical Research Ethics" (KEMO).

In Italy, the protocols were approved by the local research ethics committee and by the Italian Committee for Biosafety. The Italian National Committee on Bioethics published, in 1991, a report on "Therapia genica" which describes the conditions for approval of gene therapy protocols and suggests the creation of an authority uncharged of listing diseases which could candidate for gene therapy, developing criteria, and collecting information on gene therapy research.

In Germany, the "Central Committee for the maintenance of moral principles in reproductive medicine, embryo research, and gene therapy" works in close collaboration with the local institutional review boards, having an advisory role on the definition of the criteria for evaluation, but leaving the final decisions to the local ethics committees.

The 1988 Guidelines from the European Medical Research Councils recommend that "a national body should consider all proposals for human gene therapy and ensure the application of agreed national guidelines. Early trials should be monitored by a central body".

Since 1989, the Council of Europe has recommended "national or regional multidisciplinary bodies" with tasks of informing, guiding, monitoring, and evaluating results. At the First Round Table of Ethics Committees (Madrid,1992), the Council of Europe suggested that national ethics committees be consulted as an instance complementary to the local ethics committees, in regard to formulation of standards, support, oversight, and evaluation[4].

Directives 90/219/EEC and 90/220/EEC from the European Union apply to certain phases of the gene therapy protocols, but do not cover, for instance, the clinical trials. These are regulated, in some European countries, by specific legislation. It might be desirable to have, on this, a legal document at European level.

An important ethical requirement for the whole net of control mechanisms is that, in addition to the quality of the ethical argument, they are efficient and do not cause unnecessary delays. Illnesses will not wait for a more convenient time and the patients need any help that can be given to them now. For such efficiency, the harmonization and partial standardization of all European evaluation processes might be helpful.

Another important ethical requirement is the transparency of the evaluation processes. They should be regularly published, giving to the public an objective information on the scientific and ethical aspects of gene therapy developments, and promoting the close participation of European citizens in the democratic construction of our science, technology, and ethics.

3.2 Review of gene therapy products

It is expected that, within a 3-5 years period, products for gene therapy are ready to come on the market. The gene therapy market is expected to be, in the near future, very large and the economic impact on biomedical equipment and gene therapy consumables will be considerable. It is important, therefore, that the manufacturing, commercialization, and distribution of gene therapy products are appropriately regulated.

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[4] For a more detailed description of national and international evaluation instances, see M.A.M. de Wachter "Experimental (somatic) Gene Therapy : Ethical Concerns and Control", Institute for Bioethics, Maastricht, 1993.

The commercially manufactured products will be covered by Community legislation and evaluated on the basis of quality, safety and efficacy, criteria laid down in the legislation for biotechnological products. In addition, the code of "Good Clinical Practice for Trials on Medicinal Products in the European Community" has to be observed. . This code includes the requirements for informed consent of the subject taking part in the trial and for the review of the local, pluridisciplinary and independent ethics committee. Additional guidelines for specific quality and safety requirements in the manufacture and control of products for gene therapy will be available in 1995.

Products for gene therapy will also need a marketing authorization given by the centralized procedure of the European Agency for the Evaluation of Medicinal Products. This Agency will start work in London on January 1st 1995. Through this procedure, patients from all 12 member States will have equal access to medical products, since the products will be sold in all States of the Union. Manufacturers will be assisted in the preparation of the applications for marketing authorization by the Committee for Proprietary Medicinal Products (CPMP). The competent authorities of the member States are represented in the CPMP.

4. ETHICAL EVALUATION OF GERM-LINE GENE THERAPY

The present state of knowledge in germ-line gene therapy can be described as follows :

a) there is no sufficient experience and monitoring of somatic gene therapy as to clearly establish the safety and effectiveness of its use and, much less, of its extension to the self-perpetuating germ-line;

b) they are no sufficient animal studies on germ-line gene therapy applicable to humans;

c) there is not yet any clinically useful and clearly proposed protocol for germ-line gene therapy, defining, namely, the vectors to be used and the potential target cells (spermatogonia ?, eggs ?, embryos ?).

With such scientific uncertainties, some contend that a ethical evaluation is impossible. Nevertheless, we will attempt to apply to germ-line gene therapy the same ethical principals used for somatic gene therapy.

4.1 Benefits

Some argue that germ-line gene therapy will be useless. In fact, for the vast majority of the cases, only one of the parents is carrying the genetic defect. In such cases, it would be easier and safer to select healthy embryos, by preimplantation diagnosis, than to perform gene therapy on those which carry the defect. Only in the highly exceptional and unlikely cases of embryos produced by two individuals both being recessive homozygous for the same defect would gene therapy be useful, since all embryos would then be affected. It can be answered, however, that other and more frequent cases in genetics could be mentioned where preimplantation diagnosis is of no help[5]. The same applies to diseases due to mitochondrial gene defects[6]. In addition, it should be mentioned that embryos are not the only target of germ-line gene therapy. The European Patent Office received recently a patent request, coming from two researchers of the University of Pennsylvania, which deals with gene therapy of spermatogonia. Although the main applications are in the field of veterinary, the patent request explicitly mentions its applicability to humans (New Scientist 9, April 1994). Gene therapy of spermatogonia might be the only possible option for those who have serious ethical objections against preimplantation diagnosis and destruction of pre-embryos.

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5 This is the case of "parents who do not wish to have heterozygous children in order to spare them the difficult decisions they would have when they in turn came to have children. This situation is already becoming more frequent in genetics. It happens when one parent is homozygous recessive and the other heterozygous for the same disease; in this case 50% of the eggs will be affected, 50% will be heterozygous and preimplantation diagnosis will be unable to identify a non-heterozygous embryo", Pierre M. Lehn, Scientific Aspects of Gene Therapy, a report to be published, p. 35, 1994.

6 For diseases due to defects in the mitochondrial genome, different conditions apply. Peimplantation diagnosis is not an option, and "germ-line gene therapy" would consist of the replacement of the entire mitochondrial population rather than insertion of DNA into an existing genome. This approach would not carry the risks inherent in recombinant DNA techniques.

- Considering that germ-line gene therapy is the only technique able to perform a genetic change in all the cells of an individual, the XXIVth Round Table from the Council for International Organizations of Medical Sciences declared in Inuyama (1990), that germ-line therapy might be "the only means of treating certain conditions, so continued discussion of both its technical and its ethical aspects is therefore essential". A Report of the same Meeting concludes : "The option of germ cell gene therapy must not be prematurely foreclosed. It may some day offer clinical benefits attainable in no other way. Science has confounded many predictions about what is technically possible and what is not. Germ cell therapy might eventually permit more effective prevention of genetic disease, rather than treatment of its effects".

- Sometimes, germ-line gene therapy is even presented as a medical imperative. The moral mandate of medicine is to cure, to care, and to prevent diseases, alleviating suffering as much as possible. Considering that such possibility may be expanded by this self-perpetuating therapy, medicine has a prima facie moral duty to pursue and employ germ-line gene therapy as soon as it is safe[7].

- Another benefit is its prophylactic efficiency. By preventing transmission at the affected genes, germ-line gene therapy would dispense with the need to perform costly and risky somatic gene therapy in multiple subjects of successive generations.

4.2 Risks

The description of the present state of knowledge given above (under 4) shows that the conditions for risk evaluation, required under 2.2, are far from being met. The situation will persist that way for quite a number of years.

It is clear that without risk evaluation, specially considering that any negative effects would be indefinitely perpetuated, to start now any attempt of germ-line therapy in humans would be severely unethical and should be forbidden. This seems to be an unanimous position of all statements produced on the matter by a variety of institutions[8].

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[7] "Keeping diabetics alive with insulin, which increases the propagation of an inherited disease, seems justified only if one is willing to do genetic engineering to remove diabetes from the germ-line and thus to save the anguish and cost to millions of diabetics" (Daniel Koshland, CQ Researcher 1 (23) : 793, 1991)

[8] It is true that the Spanish law on techniques of assisted reproduction (Act 35/1988) in principle authorizes therapy on in vitro pre-embryos "to treat an illness or prevent its transmission" (13.1) "if influence is not being exercised on non-pathological hereditary characteristics" (13.3.d). However, the conditions then set for this authorization are precisely those which are not yet met by science. Therefore, the Spanish law does not seem to make an exception to the consensual interim prohibition of germ-line gene therapy.

The differences of opinion begin when we ask whether this is the only reason to oppose germ-line therapy. For some, the present uncertainty on risks and benefits is the only reason for prohibition or non authorization[9], while, for others (to be mentioned below), additional basic and non circumstantial objections exist, which lead to the condemnation of germ-line therapy not only in the present situation but per se, even if one day sufficient safety guaranties were at hand[10]

4.3 The dignity of the person

Let us assume that a day comes when sufficient data on germ-line gene therapy accumulated (including experimentation in non-human primates treated by the same vectors and procedures to be used in humans) which made possible an accurate evaluation of risks as well as of side-effects and these were shown to be negligible. How would then germ-line therapy be ethically evaluated ?

- The Resolution of the European Parliament adopted on 16 March 1989 states that any, even partial, modification in the genetic information of germ-cells represents an unacceptable and unjustifiable distortion of human identity. The Working Group on Ethical, Social and Legal Aspects of the Human Genome Analysis from the European Commission, in its 1991 Report, gives, as two of the causes of concern, the changes in the human gene pool and possible "eugenic" implications. The Report " Terapia genica" from the Italian national committee of ethics also evokes, against germ-line therapy, the "intangibility of the genetic pool". It is known, however, that, in a variety of ways, we have been constantly changing the human gene pool without incurring the tremendous risks of eugenics. In addition, from the analysis of these statements we conclude that they address germ-line therapy but really have in mind germ-line enhancement.

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9 In addition to positions already mentioned, we can add, as typical examples, the Spanish law on techniques of assisted reproduction (Act 35/1988), the Clothier Report, the 1990 and 1993 Opinions from the French National Ethics Committee, the Report from the Dutch Health Council's Commission on Heredity. Science and Society, the Declaration of Bilbao (1993) and the Draft Convention on Bioethics from the Council of Europe. In its Article 16, the Draft Convention states "An intervention on the human genome may only be undertaken for preventive, therapeutic or diagnostic purposes and as long as the aim is not to interfere with the germ cell line". The only reason given in the Explanatory Memorandum for the last part of this Article is that, "at the present stage of scientific knowledge, it was impossible to know all the effects that these interventions might have on following generations".

10 Along the same lines, the President of the UNESCO International Bioethics Committee made the following statement in her 1993 Report : "An agreement (albeit provisional) seems to have been reached on the need to prohibit recourse to this form of therapy (germ-line) as long as the scientific data enabling its control are unavailable and, consequently, as long as it comprises risks of uncontrolled alteration of the human genetic capital. The chapter on the debate surrounding germinal therapy is no doubt unfinished. There is no consensus about whether we should oppose it in the name of the inviolability or the integrity of the human race, or limit ourselves to the idea of a simple moratorium".

- A frequent objection uses the slippery slope argument : germ-line gene therapy would open the door to attempts at germ-line enhancement of human traits, leading us to impose on future generations certain characteristics according to our capricious choices, what certainly is an offensive instrumentalization of future human beings. The safest course in order to prevent such abuses would be the unconditional prohibition of germ-line therapy. It can be answered, however, that the same argument has been used in the past, by Jeremy Rifkin and his followers, against somatic gene therapy and it was nether succesful nor correct. Somatic gene therapy is being carried on with societal approval and considerable benefits, while no attempts are known of somatic enhancement engineering.

- Recommendation 934 (1982) from the Council of Europe states that "the rights to life and to human dignity (...) imply the right to inherit a genetic pattern which has not been artificially changed" but adds that the recognition of this right "must not impede development of the therapeutic applications of genetic engineering (gene therapy)". Recommendations 1046 (1986) and 1100 (1989) from the Council of Europe develop the same concept. Since these documents specially focus on the protection of the individuals against non- therapeutic applications, asking even for a "list of serious diseases which may properly (...) be treated by gene therapy" we conclude that these Recommendations are frontally against germ-line enhancement engineering but not against germ-line gene therapy. We might only regret that the issue is so phrased that the right to a healthy genome is not recognized as a basic principle, but only as an exception of the questionable right to an untouched genome. It is not clear why hazards of nature should necessarily be better than achievements of science.

- Some members of the German Bundestag Commission of Inquiry of genetic engineering, which published the Report "Risks and Chances of Gene Technologies" (1987) expressed the view that any changing of the germ-line, even for the correction of defects, is an act against nature. The same Report states : "The humanity of human beings rests at its core on natural development" and "the dignity of human beings is based essentially on their being born and on the naturalness of their origins" (187). This view overlooks the importance of artificial components in our lives and activities. We are artificial beings by our very nature. The human intelligence and the consequent capability of innovation and creativity also belong to nature.

- Assuming that germ-line gene therapy will be performed in *in vitro* embryos, the same "Risks and Chances of Gene Technologies" Report states that germ-line therapy techniques will imply the destruction of many embryos, thus making human life only a means to an end. On this point, there is certainly an unsolved world controversy. But, as we have already noticed, embryos are not the only target of germ-line gene therapy.

- A common objection is the lack of consent from future generations. Multiple human generations would be placed in the situation of unconsenting research subjects. This objection fully holds for germ-line enhancement engineering. But for the case of germ-line gene therapy of very serious diseases we can reply that such consent is presumed. According to the above mentioned Inuyama Report (1990), "descendants of those so treated would still agree with the decision generations later".

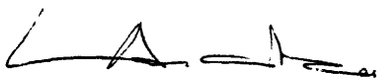
4.4 Justice

- Those who fear that germ-line gene therapy slips into enhancement genetic engineering of human traits, object that this would exacerbate problems of social discrimination based on those traits. We already took position (under 4.3) in regard to this slippery slope argument.

- Others have objected : on the basis of how to prevent social discrimination favoring elites through germ-line therapy ? But considering that there will be, at least initially, a limited number of situations which meet the clinical indications for this therapy, the problem will not be unsurmountable. In addition, abuses should not be impeditive of fair uses.

In conclusion, no decisive arguments could be found to prove, *a priori*, that any kind of germ-line gene therapy would necessarily affect human dignity and justice. The only solid reasons to oppose germ-line gene therapy for the time being are the scientific uncertainties which prevent us from evaluating benefits and risks. As long as this situation persists, any attempt of performing germ-line gene therapy in human subjects would be irresponsible and should be forbidden. As soon as the situation is scientifically clarified, it will have to be ethically reevaluated.

The Rapporteur



Luis Archer

4. European Commission press release presenting the Opinion on Gene Therapy

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COMISSÃO EUROPEIA
Serviço do Porta-Voz

IP/94/1185

Brussels, 12 December 1994

THE GROUP OF ADVISERS ON THE ETHICAL IMPLICATIONS OF BIOTECHNOLOGY GOES PUBLIC WITH ITS ADVICE TO THE EUROPEAN COMMISSION ON GENE THERAPY

The remarkable advances in scientific and medical research in the second half of the 20th century have paved the way for the development for biotechnology and genetic engineering, covering a wide range of processes whose applications – ranging from agriculture to industry and from the environment to health – are of concern to various instances in the European Community.

This is why, in December 1993, the White Paper on growth, competitiveness and employment ranked biotechnology among Europe's priority policy areas.

Although the rise of biotechnology has given rise to expectations – not to say enthusiasm – there is also some apprehension. The key point must be to control the scientific advances so as to enhance the quality of life and the standard of living of the people of Europe and to secure for them the highest possible standard of health in keeping with the values of our society.

The Commission is directly concerned with this important debate, as evidenced by the creation of the Group of Advisers on the Ethical Implications of Biotechnology in November 1991, in response to the wishes expressed by President Jacques Delors. Acting entirely autonomously, this Group formulates opinions designed to contribute to the Commission's policy-making work, including the legislative sphere.

In its first term of office (1991-93), the Group produced a number of opinions either on its own initiative (patentability of biotechnological inventions) or at the Commission's request (marketing of BST and application of the directive on products derived from human blood or plasma).

The Group's next opinions will deal with prenatal diagnostics, transgenic animals and the labelling of new foodstuffs.

For its second term of office, the role of the Group has been strengthened, as provided for in the White Paper's recommendations. Mrs Noëlle Lenoir, a lawyer and Chairwoman of the UNESCO International Committee on Bioethics, was elected to the Chair.

The other eight leading personalities making up the Group are: Dr Anne McLaren (GB, biologist), Dr Margareta Mikkelsen (DA, geneticist), Professor Luis Archer (P, geneticist), Professor Gilbert Hottois (B, philosopher), Professor Dietmar Mieth (D, philosopher/theologian), Mr Octavi Quintana-Trias (E, doctor of medicine), Professor Stefano Rodota (I, lawyer) and Professor Egbert Schroten (NL, philosopher/theologian).

For the first time, the Group will present one of its opinions in public at a press conference on 13 December. This particular opinion is concerned with gene therapy. The new policy of openness reflects the desire for dialogue and the perceived need to move closer to the concerns of the people of Europe.

Gene therapy can be seen as the introduction of one or more genes within an organism by way of a vector, e.g. a virus, with a view to treating or preventing a disease linked to a genetic anomaly. This new therapeutic tool is based on progress made in the course of broadly-based research programmes within major international networks, e.g. the Community research programme on Human Genome Analysis.

Gene therapy is dubbed "somatic" where it is concerned with differentiated cells of the foetus, the child or the adult (e.g. cells of the liver, blood or other organs), and is referred to as "germinal" where it is concerned with non-differentiated cells (e.g. gametes or the fertile egg). In the latter case, the genetic modification will be transmitted to the individual's offspring.

The future of gene therapy concerns a number of Community policy sectors, more particularly public health (Article 129 of the Maastricht Treaty) and research, under the fourth Framework Programme.

Biotechnological experimentation is raising enormous hopes for the treatment of genetic diseases such as haemophilia, and acquired diseases, such as cancer or cardiovascular disease or even AIDS. Medicines developed via gene therapy and which have reached the industrial stage will be submitted for testing by the European Agency for the Evaluation of Medicinal Products.

Resources are undoubtedly needed if we are to live up to these expectations, but we also have to be responsive to the risks which are inherent in testing and even in the possible abuse of gene therapy practices.

In its work, the Group of Advisers on the Ethical Implications of Biotechnology apply the following principal criteria: protection of patient's rights and respect for human dignity; enhanced evaluation of risks and results; transparency of practices; surveillance of medical indications; equal access to new forms of treatment in terms of distributive justice; public information and education on democratic constraints.

5. Communiqué de presse de la Commission européenne présentant l'avis sur la thérapie génique.

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IP/94/1185

Bruxelles, le 12 décembre 1994

LE GROUPE DE CONSEILLERS POUR L'ETHIQUE DE LA BIOTECHNOLOGIE REND PUBLIC SON AVIS A LA COMMISSION EUROPEENNE SUR LA THERAPIE GENIQUE

Les remarquables avancées de la recherche scientifique et médicale de la seconde moitié de ce siècle ont ouvert la voie au développement des biotechnologies. Ces dernières couvrent un large éventail de procédés dont les applications, dans des domaines allant de l'agriculture à l'industrie, de l'environnement à la santé, intéressent les divers secteurs de compétence de la Communauté européenne.

C'est la raison pour laquelle, en décembre 1993, le Livre Blanc sur le thème "Croissance, compétitivité et emploi" range le développement des biotechnologies parmi les priorités de l'Europe.

Si ces technologies suscitent des attentes, voire de l'enthousiasme, elles font parfois aussi naître des craintes. Maîtriser ces progrès en vue d'améliorer la qualité et le niveau de vie des citoyens de l'Europe, et de leur assurer le niveau le plus élevé de santé dans le respect des valeurs de notre société, tel est le défi à relever.

La Commission est directement concernée par cet important débat. La création du **Groupe de Conseillers pour l'Ethique de la Biotechnologie** en novembre 1991, suivant les voeux du président Jacques Delors, se situe dans le droit fil de ces préoccupations. Se prononçant en toute indépendance, ce Groupe formule des avis qui contribuent à orienter les actions de la Commission, y compris dans le domaine législatif.

Lors de son premier mandat (1991-1993), le Groupe a statué, soit de sa propre initiative (autosaisine sur la brevetabilité des inventions biotechnologiques), soit sur saisine de la Commission (concernant la commercialisation éventuelle de la somatotropine bovine et l'application de la directive sur les produits dérivés du sang ou du plasma humains).

Les prochains avis du Groupe traiteront du diagnostic prénatal, des animaux transgéniques, et de l'étiquetage des nouveaux aliments.

Le deuxième mandat a vu le renforcement du rôle du Groupe, conformément aux recommandations du Livre Blanc. Mme Noëlle Lenoir, juriste et présidente du Comité International de Bioéthique de l'UNESCO en a été élue présidente.

Le Groupe est en outre, composé de huit personnalités éminentes: Dr Anne McLaren (GB, biologiste), Dr Margareta Mikkelsen (DA, généticienne), Prof. Luis Archer (P, généticien), Prof. Gilbert Hottois (B, philosophe), Prof. Dietmar Mieth (D, philosophe théologien), M. Octavi Quintana-Trias (E, médecin), Prof. Stefano Rodota (I, juriste), et Prof. Egbert Schroten (NL, philosophe théologien).

Pour la première fois, le Groupe rendra public lors d'une conférence de presse le 13 décembre un avis: celui sur la **thérapie génique**. Cette nouvelle démarche traduit une volonté de dialogue et de rapprochement vers les préoccupations du citoyen de l'Europe.

La thérapie génique peut se définir comme l'introduction d'un ou plusieurs gènes à l'intérieur d'un organisme au moyen d'un vecteur, un virus par exemple, pour traiter ou prévenir une maladie liée à une anomalie génétique. Ce nouvel outil thérapeutique résulte des progrès accomplis dans le cadre de vastes programmes de recherche au sein de réseaux internationaux importants, comme par exemple celui du programme de recherche Communautaire sur l'Analyse du Génome Humain.

La thérapie génique est appelée "somatique" quand elle vise des cellules différentiées du foetus, de l'enfant ou de l'adulte (cellules du foie, du sang ou d'autres organes). Elle est dite "germinale" lorsqu'elle concerne des cellules indifférenciées (gamètes ou oeuf fécondé). Dans ce cas, la modification génétique se transmettra à la descendance de l'individu.

L'avenir de la thérapie génique concerne divers champs de compétence communautaires, notamment en matière de santé publique (Article 129 du Traité de Maastricht) et de recherche dans la ligne du quatrième programme-cadre.

Cette pratique expérimentale soulève d'immenses espoirs dans le traitement de maladies génétiques, telles la muscoviscidose ou l'hémophilie, mais aussi de maladies acquises, comme le cancer ou les maladies cardio-vasculaires, voir même le SIDA. Les médicaments issus de la thérapie génique qui auront atteint le stade industriel, seront par ailleurs soumis à la procédure de l'Agence Européenne des Médicaments.

Des moyens sont nécessaires pour permettre de concrétiser les espoirs ainsi soulevés. Mais des réponses doivent aussi être apportées compte tenu des risques inhérents aux essais thérapeutiques ou même à d'éventuelles utilisations abusives des pratiques.

Pour mener sa réflexion, le **Groupe de Conseillers pour l'Ethique de la Biotechnologie** se fonde notamment sur les critères suivants: la protection des droits des patients concernés et le respect de la dignité humaine; l'amélioration de l'évaluation des risques et des résultats; la transparence des pratiques; le contrôle des indications médicales; l'égalité d'accès aux nouveaux traitements dans le cadre de la justice distributive; l'information et l'éducation du public au regard des nécessités démocratiques.