BELGIAN ADVISORY COMMITTEE ON Bioethics

Opinion no 33 of 7 November 2005 concerning somatic and germinal line gene modification with a therapeutic and/or enhancement purpose

Request for an opinion of. 11 May 2001
from A. De Decker, Chairperson of the Senate
concerning the ethical and legal aspects of different questions relating to research into embryos in vitro and the protection of these embryos

Content of the opinion

Questions put to the Committee

The Senate puts the following question.
"[…] In view of various legislative proposals pending in the Senate concerning research into embryos and the protection of embryos in vitro;
In view of the important social and ethical challenges for political decision making with respect to scientific research, the potential uses of modern biotechnology and the implications of this on the protection of the embryo;
In view of article 18 of the Treaty of the Council of Europe relating to human rights and biology and medicine; […]

The undersigned request the Belgian Advisory Committee on Bioethics to, within the period determined in the aforementioned Agreement of Cooperation, present its recommendations in the light of the abovementioned legislative proposals concerning:

- *the concepts "embryo" and "pre-embryo";*
- *the concept "research" in the sense of article 18 of the aforementioned Treaty;*
- *the concept of "adequate protection" of the embryo and pre-embryo;*
- *the implications and risks of the uses of modern biotechnology with respect to the human embryo;*
- *the implications and modalities of scientific research on the human embryo;*

More particularly:

1. *the acceptability of scientific research with respect to somatic gene therapy and germinal gene therapy;*
2. *the distinction between corrective germinal gene therapy and enhancement germinal gene therapy;*
3. *the concept of "treatments with a eugenic nature" and "treatments with a real eugenic purpose": the distinction between pathological and non-pathological genetic characteristics;*
4. *the question of the necessity and acceptability of the creation of embryos for research purposes;*
5. *the question of the necessity and acceptability of the use of embryonic stem cells with therapeutic objectives (therapeutic cloning) and alternatives for the use of embryonic stem cells;*
6. *the implications of Belgian legislation;*

and this in the field of biology, medicine and health care, and in particular with respect to the ethical, social and legal aspects, more specifically concerning the observance of human rights.".

The plenary meeting of the Committee considered the issue on 9 July 2001. This question already gave rise to report no. 18 of 16 September 2002 concerning research into the human embryo *in vitro* and report no. 24 of 13 October 2003 concerning human stem cells and therapeutic cloning. **The current report therefore covers the still pending questions, namely gene therapies in the broad sense.**

Foreword

The present opinion concerns gene therapies *in the broad sense* of the term, being all genetic activities irrespective of whether they relate to the soma or the germ line, and irrespective of whether they have a therapeutic or optimising/enhancement purpose. In the hypotheses of activities *'with therapeutic purpose'* the Committee will use both the terms *'modification'* and *'therapies'*, but in the case of genetic activities *'with optimising/enhancement purpose'*, the Committee will only use the term '*modification*'.
The Committee consequently proposes the following title:
"Somatic and germinal line gene modification with therapeutic and/or enhancement purpose".

CHAPTER I. GENE THERAPIES: STATUS QUAESTIONIS

Genetics is a field that is constantly evolving, so a good understanding of the concept of gene therapy requires an assessment of the current situation.
The term 'gene' was a key term in the 20th century. Initially it was used with regard to the transfer of hereditary characteristics from generation to generation. However, a generally accepted definition of the term 'gene' and the associated concepts have never existed. The gene concept has evolved in the light of experimental discoveries, theoretical developments and epistemological categories.
In our analysis of the status quaestionis we will distinguish three main phases in the development of genetics which cast a light on the perspectives of gene therapy: the conceptual phase, the genomic phase and the postgenomic phase. For a good understanding of the content of the advisory report this chapter also contains a glossary.

I. 1. Glossary

- **DNA:** deoxyribonucleic acid. Long molecular chains consisting of a sugar (deoxyribose), the nitrogen bases (adenine, thymine, cytosine, guanine) and phosphorus. The DNA is the carrier of the genetic information.
- **Nuclear DNA:** DNA present in the chromosomes of the nucleus or cell nucleus.
- **Mitochondrial DNA:** DNA from the chromosome present in each mitochondrium of the cell.
- **Alleles:** different forms of a same gene resulting in different phenotypes.
- **RNA:** ribonucleic acid. Molecular chains consisting of a sugar (ribose), the nitrogen bases (adenine, uracil, cytosine, guanine) and phosphorus. RNA has various functions in cells (see the different kinds of RNA below).

  - **Precursor messenger RNA (pre-mRNA):** RNA that results from the transcription of a coding DNA sequence.

  - **Messenger RNA (mRNA):** RNA that results from the splicing of a pmRNA. mRNA is used by the ribosomes as translation model with the synthesis of proteins.

  - **Antisense RNA:** RNA of which the sequences are complementary to the messenger RNA sequences.

  - **Interfering RNA:** small RNA coded by the genomic DNA with a regulatory function by attaching to complementary mRNA (inhibiting its translation) or to DNA sequences (of which the structure and the possibility of transcription changes).

  - **Micro RNA:** small RNA coded by the genomic DNA that after various modifications attaches to the mRNA (inhibiting its translation) and to the genomic DNA (inhibiting transcription). Some micro RNA finds its origin in the introns resulting from the splicing of pmRNA to mRNA.
- **Editing:** mechanism where uracil molecules in messenger RNA are introduced with the

modification of its message.

- **Enzyme:** molecule with catalysing property, usually a protein or ribonucleic acid.
- **Epigenesis - Epigenetic:** describes the differentiated expression of the genes under the influence of factors within or outside the organism.
- **Splicing:** process where precursor messenger RNA is transformed to messenger RNA by cutting away certain areas.
- **Eugenics:** see item II.2.
- **Gene:** DNA sequence (RNA sequence with certain viruses) that carries molecular information determined by the nucleotide sequences. Falls under the understanding of 'hereditary factor'. The gene functions as a matrix model with the synthesis of premessenger RNA.
- **Genome:** complete set of genes of an organism, an individual or a species. A distinction is made between the nuclear genome (DNA of the nucleus or cell nucleus) and the mitochondrial genome (DNA of the mitochondria).
- **Genotype - phenotype**: the *genotype* forms the whole of genetic characteristics of an individual ensuing from the composition of its DNA (RNA with some viruses). The *phenotype* is the whole of observable characteristics (anatomical, morphological, physiological and biochemical characteristics) of an individual.
- **Heteroplasmy:** hybrid cytoplasm that results from the fusion of the cytoplasm of two different organisms
- **Germ line:** whole of the reproductive cells of an individual that ensure the transfer of the hereditary properties of that individual to its offspring.
- **Locus:** place on a chromosome according to a specific gene.
- **Metabolom:** system of all products of biochemical reactions taking place within an organism.
- **Mitochondrion:** organelle of the cytoplasm specialised in energy conversion functions and that contains a DNA that is a carrier of genetic information.
- **PGD:** pre-implantation genetic diagnosis of an embryo at the stage when the embryo is still made up of but a few cells to trace a hereditary illness before inserting the embryo *in utero* .
- **Proteome:** system of all proteins of an organism that results from the translation of messenger RNA and of post-translational modification
- **Regulation:** process that modulates the expression of a DNA sequence as a cascade. Some of the sequences, the so-called coding sequences, are transcribed in pre-messenger-RNA, that after splicing become messenger-RNA and that play a part in the synthesis of the proteins. Other sequences are transcribed in small regulating RNA (interfering RNA and Micro RNA).
- **Soma:** all non-germinal cells that form the tissue and organs of an individual.
- **Gene therapy:** introduction into a genome with a defective gene of a normal copy of that gene to correct the consequences of the defect.
- **Transcription:** synthesis of RNA sequences on the basis of a DNA model.
- **Transcriptom:** system of all RNA molecules that result from the transcription of the DNA of an organism.
- **Transgen:** gene of an organism that is transferred to the genome of another organism
- **Transgenesis:** process of transferring the gene of an organism into the genome of another organism
- **Translation:** synthesis of protein-creating amino acid polymers from an mRNA model that is used by the ribosomes as example.

I. 2. Gene – genotype - genetics[1]

I.2.1. Traditional conceptual genetics (1865-1945)

We can have this phase symbolically start with the work of Mendel (1865) on the hereditariness of characteristics. Weismann (1892) distinguishes the hereditary substance he calls the germ line ("*germen" in german*), and the non-hereditary substance he called *soma*.
In 1901 the botanist Correns identified the *germ plasma* that contains all hereditary elements. Johanssen described the elements as *genes,* which all together form the *genotype* . The characteristics resulting from the expression of the genotype determine the *phenotype.*
In 1906 Bateson announced to the scientific world that he was working on hereditariness, or *genetics.*
The nature of hereditary entities remained unclear for a long time. Morgan, who won the Nobel Prize in 1933, declared that it was unimportant as to whether the gene was considered a hypothetical unit or a material particle. What counted for him was that a modification in a gene changes a property of the phenotype. Müller (1927) observed genetic modification (mutations) induced by X-rays that passed from generation to generation, of which the phenotypical expression depended on the mutation on the chromosomes.
Kühn (1941) showed that a characteristic (red eye of an insect) is induced by an enzyme that catalyses a cascade of metabolic reactions resulting in the phenotype. That is the first step towards the concept '*a gene - an enzyme'* (protein).

I.2.2. Molecular or genomic genetics (1944 -2000)

In 1944 Avery and his colleagues observed that the transfer of DNA from a virulent bacterium to a non-virulent bacterium made the latter virulent. This discovery passed generally unnoticed.
In 1953 Watson and Crick clarified the DNA structure and the mechanism of DNA replication.
It was then shown that the information contained in the DNA was expressed through the actions of messenger-RNA (complement of DNA), leading to the synthesis of a protein by the placement of amino acids in the sequences in the order specified by the initial DNA.
The 'DNA -> RNA -> protein -> phenotype' sequence was regarded as irreversible and forms the "central dogma" of the molecular biology of Francis Crick.
That 'dogma', actually a postulate, is a translation at molecular level of the Darwinian principle according to which acquired properties are not heritable. It is based on the unidirectional transmission of the information 'DNA -> RNA -> protein'. Since then it has nevertheless been observed that the 'RNA to DNA' transmission was achieved in some cases (retrovirus). The essence of the postulate, namely the non-transmission of the information of the proteins to the DNA, nevertheless remains current.
In this context the genotype, or the collection of genes materialised in the DNA (RNA with certain viruses), forms a genetic program. In the sixties Jacob and Monod established two classes of genes (structural genes and regulatory genes) that match signal sequences not translated into proteins.
At a very early stage some authors saw that the genetic program interacted with its products. Only these products can interpret the programme, and the organism ultimately manages the working of the structural genes by activating or inhibiting the regulatory genes.
Numerous interaction systems between genotype and phenotype have come to light.
Today a protein product is no longer considered as the pure collinear reflection of the DNA sequences. The same DNA sequence can generate diverse messenger-RNA that induce various proteins with different phenotypical characteristics. This is because the messenger-RNA and the proteins of which messenger-RNA induces the synthesis undergo different modification (RNA-splicing, RNA-editing, methylation, glycosylation, etc).
Sequences of separate messenger-RNA can join to cause the form a given protein.
Interaction takes place at different levels:

[1] Stanford Encyclopedia of Philosophy (2004)

- gene products which mutually interact;
- nuclear genes that interact with mitochondrial genes (hence the divergence of the expression of the precursor gene of the protein amyloid that deposits in the brain with the Alzheimer illness, depending on the information contained in the mitochondrial genome)[2] ;
- the question of from which parent a gene comes can have an effect.

A decisive role in that respect is played by regulating factors, consisting of RNA, proteins or molecules with a low molecular weight (which work as cofactors or inhibitors).

1.2.3. Post-genomic genetics (2000 - …)

Paradoxically enough the decoding of the human genome (2001) has reinforced a paradigm change in the field of genetics. Except in a few cases in which the gene has an omnipotent effect, the relationship between genes and phenotypes follows a complicated determinism.

The phenotype is regarded as tributary to the genome, the transcriptome, the proteome, the metabolom and ambient factors.
Over a period of 50 years molecular genetics, that started from the reductionist dogma 'DNA -> RNA -> protein -> phenotype', has made clear that hereditariness and reproduction cannot be reduced to static genetics, but are evolutionary development processes. Genomics has taken a flexible and dynamic form, with a considerable capacity for molecular and structural evolution. Final integration takes place at the expense of the "reformatting" of the information in all steps that lead to the achievement of the phenotype.

In the case of genetic modification induced by experiments using transgenesis (the case with gene therapy) current information shows that phenotypes resulting from the expression of a new gene or from the inactivation of an existing gene are unpredictable. This concerns the uncertainties about the molecular vectors, about the integration/inhibition mechanism and about the disturbances induced in the regulating systems of the organism concerned (micro RNA, interfering RNA).
In 2005 the genome appears as something that functions in networks of multifunctional genes which express themselves differently depending on the development stages and the tissue. The networks are redundant and their working is buffered by internal and external regulating mechanisms of the epigenetic type.

I. 3. Gene therapy

An example of transgenesis is gene therapy, that has the purpose of correcting a genetic illness by integrating a new gene.
The successful applications of transgenesis on a large scale concern micro-organisms and some plant and animal species. This concerns *in this case* organisms of which the populations underwent transgenesis by the incorporation of new genes, and then were subjected to thorough selection, whereby numerous individuals were eliminated until only one or a few individuals remained displaying the sought phenotype. The technique is successfully applied to have organisms produce medically useful molecules (insulin, growth hormone, etc.).
As regards the application of the technique on people, in principle two kinds of gene therapy can be considered: *somatic* gene therapy, where the genome of the cells of the soma is changed, and *germinal* gene therapy that concerns the germ line. The second type of gene therapy will therefore also have consequences on the offspring of the treated individual.
A distinction can be made between gene therapies and enhancement gene modification. The latter has no therapeutic purpose, but is aimed at modifying the genome to increase individual performance at phenotypical level.

In the simplest case gene therapy consists of from a therapeutic perspective the introducing in a genome of a DNA fragment that codes for a protein, being the compensation of a congenital deficiency or making a deficient gene non-active.
Transgenesis can take place whereby DNA that produces antisense-RNA (anti-messenger-RNA)

[2] Busciglio, J., et. al. (2002) "Altered metabolism of the amyloid beta precursor protein is associated with mitochondrial dysfunction in Down's syndrome", Neuron 33, P. 677-688.

or interfering RNA is inserted to inhibit the expression of a gene, and in so doing impede the production of its protein product.
To achieve the therapeutic transgenesis a 'normal' gene is isolated that is connected to a vector, so a recombinant DNA is formed, which the whole must be correctly inserted in the host genome to produce the sought substance.

Another form of gene therapy concerns **mitochondrial DNA.**
Each mitochondrion contains a DNA molecule that contains approximately 40 genes in constant dialogue with the nuclear DNA. Medical observations appear to demonstrate a connection between certain neurological disorders and mitochondrial defects.
One believes that the interactions between nuclear DNA and mitochondrial DNA should be analysed for the purposes of future therapeutic programmes.

Finally, we will discuss **assisted reproduction by cytoplasm transfer,** even if the technique does not really fall under gene therapy.
Experiments have taken place with oocyte heteroplasmy to treat the syndrome of the moderate development of the human embryo. The transport of cytoplasm from a normal donor egg cell to a deficient receiving egg cell led in an experimental series to 13 births out of 30 implanted embryos. Two of the 13 children had chromosomal defects, and one appeared at 18 months to have the disorder "Pervasive Development Disorder".
Oocyte heteroplasmy, that since 1997 has resulted in some thirty births, could therefore be suitable to stimulate the reproductive capacity of deficient egg cells. Children born using this technique, however, all show signs of mitochondrial heteroplasmy, and little is still known about the effects of this. Epigenetic modification could also occur.
At present we do not yet know which the factors work positively or negatively with oocyte heteroplasmy. The Food and Drug Administration has prohibited the continuation of testing in this field.[3]

I.4. Current legal framework in Belgium

The term 'eugenic purpose' is mentioned in the law of 11 May 2003 concerning research into embryos in vitro. In article 5, 4° the law takes a clear standpoint against eugenics: "It is forbidden to carry out research or treatments with a eugenic purpose, this means aimed at the selection or the improvement of *non-pathological* genetic properties of the human species."

This provision must be considered in relation to article 3 of the same law in which, under the conditions which must be met before research into embryos may start, it must be determined that this research has a *therapeutic purpose*.

From the preparatory activities (statements from the legislative proposal concerning research into embryos in vitro, submitted by Messrs Monfils and Mahoux - Doc. Senate 2000-2001-2-695) it appeared clear that as regards *intervention with the human genome* the legislator wanted to make a distinction between germ track therapy aimed at improving the human species (and that must be prohibited) and therapeutic germ track therapy aimed at combating a number of diseases such as chorea of Huntington, mucoviscidosis, haemophilia and various neurodegenerative illnesses.

In that same perspective article 5, 5° of the abovementioned law does not allow research or treatments to be carried out for sex selection, with the exception of selection to prevent gender-bound diseases.

Article 13 of the Convention of the Council of Europe on human rights and Biomedicine forbids

[3] E. Scott Stills, Takumi Takeuchi, Michaels Tucker, Gianpero D Palermo, "Genetic and epigenetic modifications associated with human ooplasm donation and mitochondrial heteroplasmy considerations for interpreting studies of heritability and reproductive outcome" *in* Medical Hypotheses (2004), 62,612-617, Elsevier; Rachel Levy, Kay Elder and Yves Ménézo, "Cytoplamic transfer in oocytes: biochemical aspects" *in* Human Reproduction Update (2004), 10, 241-250; Susan M. Haves, Carmen Spazienza and Keith E. Latham, "Ooplamic donation in humans. The potential for epigenic modifications. Debate" *in* Human Reproduction (2002), 17, 850-852; Brenner CA, Barritt JA, Willadsen S and Cohen J, "Mitochondrial DNA Heteroplasmy after human ooplasmic transplantation" in Fertilil Steril.(2000), 74, 573-578.

any research relating to germinal gene therapy. The Belgian legislator, on the other hand, has left open the possibility that germinal gene therapy techniques that work on a line of gametes of a living being can conquer diseases for the being itself and for its offspring.
This accordingly concerns a therapeutic purpose in the sense of article 3.

To avoid any lapses the law provides for a procedure with a deontological framework (requirement of positive opinion (without possibility of appeal from the local ethical committee of the hospital where the research will take place, and control by the federal commission for medical and scientific research on embryos *in vitro*).

CHAPTER II. EUGENICS

II.1. Historical context

As already stated the term "eugenics" is global, and covers different connotations one can identify in the constantly changing marginal areas of politics, biology, sociology and ideology.

Eugenics is a social movement started up by the English statistician Francis Galton in the middle of the 1860's. He introduced the term in 1883. Galton appeared to be very influenced by reading "*On the origin of species*" by his cousin Charles Darwin. Darwin's work was published in 1859. In 1904 Galton started a national course in eugenics at the university of London. During the same period centres of learning for eugenics were set up in different countries including Germany and the United States.
The basic idea consisted of very many human characteristics - both physical and mental - being heritable, and that one must take measures to optimise/enhance the genetic ("related to the genesis/reproduction") quality of the population.

From the start one made a distinction between *negative eugenics* where one discouraged people with "characteristics" considered as undesirable from reproducing, and *positive* eugenics where one encouraged the reproduction of people with properties one considered desirable.

Techniques where one selects plants and animals *at reproduction level* form an important discovery in applied biology. The progressive improvement of plant varieties and domesticated animal species using these techniques lies at the basis of considerable progress since the Neolithic period.

Following his observations during his journey on the *Beagle* and based on his knowledge of *artificial* selection Darwin drew up his theory of *natural selection*. On the basis of the variability in the characteristics of a certain species, he showed that the individuals of each generation possessing the most suitable characteristics adapted to the environment would reproduce better. Thanks to the coincidental introduction of new variations, this process causes continuous change and therefore the origin of new species.
From the time one realised that the *human species* had also naturally evolved by interaction between the variability of genetic characteristics and the natural and social environment, the idea soon emerged that people would be able to control their own evolution for a better future, because *artificial selection apparently worked in both animals and plants.*

We can ask ourselves how a number of well-intentioned researchers and politicians came to consider the eugenistic movement as a contribution to public welfare, not only from the standpoint of the individual, but also as a whole of measures that must be encouraged by the State. To explain their attitude we must take account of the fact that the understanding of *Public Health* at the end of the 19th century had achieved an incontrovertible status. Facilities arrived such as collective provisions for waste disposal and sewer water, a drinking water supply, the halting of epidemics by vaccination and even *compelling* measures such as quarantines. This all created a mentality positive to collective activities that suggested a better future for society and even for what one called "the human race". A double distinction must be made here: firstly a distinction between wthat science seemed to promise and the absence of a sound basis for these 'scientific' conceptions, and secondly a distinction between the perfectly worthy ethical ambition of those who wanted to improve the destiny of future humanity, and

the inclination of others to favour certain population classes or races. The growing influence of the second term of that double distinction explains the tragic lapses subsequently attributed to the eugenistic movement as a whole.

Although Galton was the first to develop this vision, Darwin himself was not against it. In "*The Descent of Man*" he says: "The two sexes should refrain from marriage if they are in any marked degree inferior in body or mind. But such hopes will never be even partially realised until the laws of inheritance are thoroughly known."[4]. One may remark that Darwin supported individual choice and refrained from promoting actual measures as long as the scientific knowledge required for this was absent. Very many people thought to have been inspired by him appeared not to act with such caution.

II.2. Definitions

Since the origin of the concept of eugenics there has always been much confusion, and all sorts of terms have been thrown together, particularly as regards terminology. As a result, opinions and standpoints concerning this concept have been falsified. The Committee therefore proposes introducing the following distinctions.

It is true that the term *eugenics* originally referred to a general 'improvement' of the human species (the human 'race') with the purpose of spreading 'desirable' genetic characteristics by suppressing the number of 'undesired' properties of the species. Since the Second World War all measures with the purpose of the 'improvement' of a whole population or the human species have generally been put to question, or even regarded as unacceptable. On the other hand, developments in human genetics have given individuals and families the resources to avoid the birth of genetically disabled individuals, to accordingly improve individual and family welfare. To help clarify the discussion it seems sensible to continue using the term **'*eugenics*'** subject to the introduction of ***appropriate distinctions.***

Individual eugenics or *micro-eugenics, private eugenics* and even *liberal eugenics.*

This involves a selection phenomenon at an individual level. We would mention the decision of a couple regarding the conception, implantation or birth of a child who is a carrier of a genetic disorder that leads to a physical or mental disability. Another example is research (currently with few promising results) into sperm or embryos of "superior quality" (for example as regards IQ) or possible future attempts to create genetically "*optimised/enhanced"* embryos. One can also add to this: the example of the informing of future spouses about being the carrier of the same harmful, recessive gene, to allow them to avoid an offspring affected by thalassemia, or pre-implantation or prenatal diagnosis during a pregnancy with a such a couple. Finally, there is the prenatal diagnosis of a pregnant woman from a certain age.

Social eugenics or macro-eugenics or even *collective eugenics.*

This is aimed at the introduction of measures with the purpose or consequence of reducing the number of genetic defects or increasing the number of advantageous characteristics in a specific population or within the whole human species. One can distinguish two kinds.

- *Non-compelling macro-eugenics* meaning at the level of society information is made available about genetics, and one encourages and supports people taking eugenistic decisions without actually compelling them. In the current situation this can concern making tracing methods available for damaged genes, *genetic counselling,* the reducing of resistance to the termination of the pregnancy after pre-implantation diagnosis (PGD) or after the termination of the pregnancy after prenatal diagnosis (PD), etc.

- *Compelling macro-eugenics*, *sometimes called state eugenics.*
This involves the introduction of imperative measures at state level. Here the freedom of the individual or the couple is affected. One can interpret the prohibition of marriages between blood relations *for genetic reasons* as a form of this type of macro-eugenics.

[4] *The Descent of Man*, General Summary, Publisher The Great Books, p. 596

The example of the policy of compulsory vaccinations indicates that the introduction of imperative measures within the context of public health and imperative measures by the state is therefore not always regarded as unacceptable. However, *negative state eugenics* was responsible for misuse in the sterilisation and elimination of the mentally ill in the XX century.

Each type of *eugenics* can have a negative form: elimination or reduction of undesired characteristics or a positive form: the promoting of characteristics regarded as desirable.

This terminological approach entails no value judgement, but can serve as a starting point for discussions about scientific results and ethical and political standpoints.

II.3. Negative eugenics by the selection of embryos and/or foetus

II.3.1. Historical summary – Medical status questionis

A new medical discipline has developed since the end of the 60's: clinical genetics. Its importance has greatly increased due to scientific progress and reinforced cooperation with gynaecology and obstetrics departments. Pregnant women with an increased risk of a child with a genetic illness can increasingly make use of *choriocentesis*. [5](11th week) or of an *amniocentesis* [6] (16th week). These methods can be used to examine if the unborn child is affected by one of the sought abnormalities. Other methods for prenatal diagnosis, including echography, ensure that one can identify abnormalities in a later stage of the pregnancy. Tracing an illness or deformity always confronts the future parents with the decision of whether or not to terminate the pregnancy (VPT, voluntary pregnancy termination).[7]

Resorting to VPT can be avoided in a number of cases by a new form of prenatal diagnosis: *pre-implantation genetic diagnostics (PGD).* This form of diagnosis assumes the use of in-vitro fertilisation (IVF was introduced in 1978) because this form of identification takes place on embryos fertilised in vitro. Couples of which the unborn child has a major risk of being affected by a hereditary illness (mucoviscidosis, Duchenne's disease, etc.) can resort to PGD. While the embryo is at a development stage of just a few cells (usually 8), the physicians take one or two cells and analyse the DNA or the karyotype (number and form of the chromosomes). In-vitro fertilisation leads to the formation of a number of embryos, and thanks to the test one can identify embryos carrying the abnormality. Embryos without the disorder can then again be implanted.
This technique dates from the start of the 90's. In 1992 the team of Alan Handyside (Hammersmith Hospital, London) could therefore ensure the birth of a healthy child for a couple who previously had a child suffering from mucoviscidosis[8]. Without this technique the parents would have a theoretical risk of 25% of having a child with this disorder.

Most centres proposing PGD accept the following categories of couples:

- couples with a high risk of a child that would suffer from an illness or deformity of genetic origin and who have a sterility problem (i.e. already candidates for IVF);
- couples with a high genetic risk who have already undergone “traditional” prenatal, diagnostic testing and who have already resorted a number of times to VPT after the detection of an

[5] Chorionic villus sampling.
[6] Taking of amniotic fluid (fluid from around the fœtus).
[7] For this and other information we refer we to: Hans Galjaard, *Rapport du CIB sur le diagnostic génétique pré-implantatoire et les interventions sur la lignée germinale*, Comité International de Bioéthique de L’Unesco (CIB), Actes, November 2002.
[8] In 1989 the first PGD by Handyside was already involved with gender-bound diseases; it was from a technical perspective easier than molecular diagnosis; see: Handyside AH, Kontogianni EH, Hardy K, Winston RM, « Pregnancies from biopsied human preimplantation embryos sexed by Y-specific DNA amplification », Nature, 1990 Apr 19;344(6268):768-70; Handyside AH, Pattinson JK, Penketh RJ, Delhanty JD, Winston RM, Tuddenham EG, « Biopsy of human preimplantation embryos and sexing by DNA amplification », Lancet, 1989 Feb 18;1(8634):347-9. Handyside, A.H. et al., Birth of a normal girl after in vitro fertilization and preimplantation diagnostic testing for cystic fibrosis, The New England Journal of Medicine, 1992, 327, p.905-909.

affected foetus;
- couples with a risk of a child affected by a genetic illness or deformity and who are against VPT.

At international level PGD is increasingly applied for the screening of aneuploidy and for sex selection for non-medical reasons[9].

A recent extension of PGD indications is *HLA blastomer profiling*, a process wrongly labelled "designer baby" by the media[10].

Preimplantation diagnosis including the variant HLA blastomer profiling raises ethical questions for which opinion will have to be drawn up.

II.3.2. Private negative eugenics: current situation

Private eugenics is a form of eugenics connected to the use of prenatal identification techniques and pre-implantation diagnosis. As a result, one can avoid couples having children carrying a hereditary illness or disability[11].

Current biological and medical events (medically assisted reproduction, prenatal and pre-implantation diagnostics, genetic treatment attempts, programme for the mapping of and sequence-determining of the human genome) again brought the question of eugenics to the foreground. The idea of "eugenics" itself is again raising concern among some.

But eugenics related to progress achieved in genetics and in new techniques of medically assisted reproduction is not of the same nature as state eugenics as developed in pre-war Germany and in the United States, and that is still currently being applied in China. We may therefore not use the same terminology for practices with such a totally different context and purposes. State eugenics has the purpose of *enforcing "the enhancement of the human species"*.[12], and that is not the case with private eugenics. Because of the emotional charge of the term "eugenics", some think that one can better not use this terminology in a situation that concerns the freedom and autonomy of the parents. Other people believe that instead of avoiding the term eugenics, one must rather draw attention to the fundamental distinction between "state eugenics" and its derivatives on the one hand, and on the other hand contemporary techniques for diagnosis and medically assisted reproduction, that one can call*private eugenics*. These are indeed terms concerning radically different circumstances and purposes

Today biotechnology is developing in the context of respect for the autonomy of the individual. The techniques used in negative eugenics do not change the human species. They are simply the orientation of the future of a number of individuals. "New eugenics" is related to technical scientific advances in genetics and medically assisted reproduction. It respects the individual, the free choice of the parents who by resorting to these techniques want children and wish to keep the risk of disabilities with the birth as minimal as possible. Genetic counselling – preferably before the pregnancy - consists of determining the risk of having a child with a specific illness, and informing the parents about the possibility of prenatal diagnosis (PD) or

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[9] Sermon, K., Moutou, C., Harper, J. et al. (2004), "ESHRE PGD Consortium data collection IV: May - December 2001" *in* Human Reproduction 20 (1): 19-34.

[10] For this technique: see G. Pennings, R. Schots and I. Liebaers, Ethical considerations on preimplantation genetic diagnosis for HLA typing to match a future child as a donor of haematopoietic stem cells to a sibling *in* Human Reproduction, Vol.17, nr. 3, 534-538, 2002.

[11] Carol, Anne, « Histoire de l'eugénisme en France », Parijs, Seuil, 1995; Duster, T., « Retour à l'eugénisme », (traduit de l'anglais par Colette Estin), Paris, Kimé, 1992 ; Missa, J.-N. et Susanne, C., « De l'eugénisme d'Etat à l'eugénisme privé », De Boeck, 1999 ; Taguieff, P.-A., « Retour sur l'eugénisme, question de définition » in Esprit, n° 200, Paris, Mars-Avril 1994 ; Testart, J., « Le désir du gène », Editions François Bourin, 1992 ; Thomas, J.-P., « Les fondements de l'eugénisme », Presses Universitaires de France, Parijs, 1995.

[12] "L'individu n'est rien, l'espèce est tout "wrote eugenist, Nobel Prize winner and physiologist Charles Richet in 1922. This idea was later adopted in a racist form in the motto of the Nazis: "*du bist nichts, dein Volk ist alles*" "you are nothing, your people is everything".

pre-implantation genetic diagnosis (PGD), and the implications of these diagnoses. If no therapeutic solution exists for the abnormality diagnosed during the pregnancy, and if the parents and professionals consider this a serious abnormality, the result will usually be voluntary pregnancy termination. Abortion can be applied with chromosomal aberrations (mongolism, etc.) or with serious metabolic disorders (Tay-Sachs Disease, etc.). The technique of prenatal diagnosis leads to the practice of negative eugenics, so one prevents children being born who suffer from serious abnormalities. Parallel to this the right to abortion is given legal support in very many countries: Great Britain (1967), United States (1973), France (1975), the Netherlands (1981), Belgium (1990), etc.

II.3.3. Ethical considerations

II.3.3.1.
Certain groups in society are completely against any form of eugenics, collective and private.

- The essential argument is based on the consideration of the embryo to be a human person from fertilisation (standpoint mentioned by the Committee in opinion no. 18 of 16 September 2002, chapter IV, item 4.2.1.) or that it has sufficient personality characteristics so the termination of its further development should be completely forbidden. This implies that VPT is not acceptable, even in the case of illness or serious deformations.
These people deem PGD unacceptable because this implies that selection has occurred, and that this has the inevitable effect of certain embryos being eliminated.
- They also put forward the idea that the acceptance of private eugenics deviously puts pressure on women who refuse these techniques. This would lead to imperative collective eugenics that, due to economic or cultural pressure, would be similar to state eugenics.
- Finally, they suggest that the importance attached to the avoidance of the birth of a child with an abnormality would have a negative influence on our attitude to disabled children already born, and the care they receive.[13]

Some members have the following remarks.
The first argument is based on an extreme standpoint about the status of the embryo and the foetus.
The second argument refers to an unavoidable phenomenon. From the time of a value being accepted by the majority of the people, one perceives a tendency to follow the movement. The evaluation of this process depends on the value one attaches to one of the standpoints taken. For a number of years, some Dutch, strongly protestants villages did not accept vaccinations against poliomyelitis. After having seen the baleful consequences of their non-acceptance with their own eyes they moved behind the majority standpoint. It cannot be ruled out that a similar movement may form with respect to VPT, for example with trisomy 21. This involves an evolution in social attitudes, an evolution not seen as negative by everyone.
The third argument can be rebutted by remembering the distinction between a human person (born living and viable) and an embryo, and the imperative obligation to guarantee the welfare of all persons and more specifically the least privileged.

II.3.3.2.
Among the population and specialists in genetics and medically assisted reproduction, there exists a certain consensus about the fact that one considers PD (followed by VPT) and PGD ethically acceptable in “severe” or “serious” cases.

Some members of the Committee indeed consider that the status of the embryo and the foetus has no part in the status of the person, and that embryos and foetuses only gradually obtain the qualities of a human being according to intra-uterine development.
Starting from this consideration, they consider that the distinctive weight assigned on the one hand to an embryo, and on the other hand to the possible or probable suffering of the unborn child arriving in the world with a serious disability, as well as the welfare and the health of future parents, justify resorting to this action.

[13] These attitudes are defended, for example, by the *Fondation Jérôme Lejeune*. See the intervention in the French Senate of President Jean-Marie Le Mené: ‘Y a-t-il un eugénisme “clean”?’ on the site: www.généthique.org/doss_theme/dossiers/eugénisme/eugénisme_jmlm.htm

II.3.3.3.
Agreement has not, however, been reached about the ethical question of what a *"severe" or "serious"* disorder or deformity is. Professional associations involving clinical geneticists, reproductive technology and bio-ethical advisers have still not yet agreed about the drawing up of a list of disorders which are accepted as serious enough to justify a PGD or PD. There are indeed more than 5,000 monogenetic disorders, and nearly all of these disorders show signs of variable severity and clinical evolution (see H. Galjaard, a.c.).

It appears normal that specialists hesitate in stating their personal opinion about the question of the severity or gene disease or abnormality. It is indeed the future parents who must bare the responsibility for the child disorder. The estimation of the severity of this disorder is determined by the cultural and social environment (the geographic factor - such as e.g. in the Third World - or financial resources), by their family history (other disabled children), by their religious convictions and by their conviction about what a valuable life is for themselves and for their unborn child.

If one takes account of the fact that in very many legal systems VPT is allowed for psychosocial reasons (which are difficult to define), it would be somewhat paradoxical that disorders, abnormalities or malformations originating from the medical domain would not be accepted as a justification for VPT or PGD.

Certain members of the Committee therefore believe that the decision about the justification of the use of these techniques in essence must first be taken by the parents concerned (or by the mother), after of course they have received correct and complete information beforehand about the disorder, including the consequences in the medium and longer term.

II.3.3.4.
But even if one accepts to follow the decision of the parents as regards actions of a negative private eugenistic nature with disorders or malformations that are medically acknowledged as pathology, problems still exist.
If on the one hand some disorders occur at birth or straight afterwards, there are on the other hand also disorders which only develop at 40, 60 or 80 years of age. And here there are disorders that everyone sees as very serious (Huntington's), serious (certain forms of Alzheimer's) or more acceptable (predisposition to hypertension or obesity).
As regards these disorders occurring later in life, some members of the Committee believe that the decision to apply VPT or PGD is in essence the responsibility of the parents, to the extent this concerns disorders caused by only one gene or a very small number of genes. In other cases PGD cannot be carried out because one must possess a very large number of embryos to be able to make a selection. From the concern to arrive at a reasonable decision, however, is it important that the democratic debate about this problem is deepened, so parents do not have to make such a fundamental decision without ethical support.

II.3.3.5.
A difficult problem in another area is due to physical or psychological characteristics that form a continuum, where certain serious forms occur that can be regarded as pathological, while the majority are considered more or less "normal" (for example different kinds of intelligence, characters, behaviour or affectivity of which serious forms are called neuroses or psychoses).
If one establishes that the interaction of a number of genes corresponds to a more or less greater predisposition to different phenotypes, it is obvious that the "pathological/not pathological" dichotomy is difficult to maintain. For as long as it concerns a clearly described, deficient gene we remain in the medical domain and the actions are then private, corrective eugenics. On the other hand, from a certain point in the continuum between "damaged" and "optimal" gene we no longer have "correction" but "enhancement". But we must honestly admit that it is very difficult or even impossible to reach a consensus about this dividing point. It then also follows that the line between therapeutic genetic modification and enhancement genetic modification is blurred. Consequently *the following alternative* arises: *either* a prohibition of all activities on genes that have an influence on characteristics, *or* admitting that sooner or later the Rubicon forming the line between therapeutic and optimising/enhancement activities will be crossed.

II.3.3.6.
When multifactor genetic characteristics are concerned, it seems hardly likely that one can achieve "enhancement" by negative eugenics. In this case it is indeed so that one must possess a too large number of embryos for the selection of embryos with the beneficial genes.

II.3.3.7.
These technical problems add to the far-reaching changes in mentality as regards ethical questions, and this ensures that even suggestions of a negative state eugenics programme would now no longer be accepted in democratic societies (See the definitions: item II, 2).
One can, however, defend the desirability that the number of hereditary diseases or malformations within the population is kept as low as possible. But it is unthinkable that a person can force a person to a VPT or even a PGD.
However, according to certain members of the Committee, responsible ethics do not rule out promoting the necessary caution and respect, the recognition of the good basis of a eugenetic attitude if this concerns cases regarded as serious by everyone. Such a change in mentality can lead to non-compelling collective negative eugenics.
As regards the "enhancement" of characteristics, this is only possible if *positive eugenics* i.e. the application of genetic techniques on the human germ cell line, ever develops. As far as we know this technique has not yet been applied to people, and is this indeed prohibited by a great many bodies.
This does not mean, however, that this ethical problem will not arise one day (see chapter IV*).*

II. 4. Positive eugenics by active intervention in the human germ cell line

This subject is covered in chapter IV.

CHAPTER III. SOMATIC GENE MODIFICATION

Somatic gene therapy concentrates on somatic cells and has, in principle and according to our current knowledge, no consequences for the offspring. The damaged gene is corrected by using a DNA fragment as a 'medicine' or 'gene prosthesis'. By placing this type of gene in the cells to be corrected one hopes to cure patients suffering from a genetic disorder.

III.1. Historical summary - Medical status quaestionis

It was soon very clear that one of the determining factors for the success of gene therapy would be the efficiency with which the corrective gene would penetrate the cells to be treated. Since 1977 retroviruses have been uses as vectors. These vectors contain a short genome that codes for proteins of which only a part is responsible for their virulence. In the vectors derived from these viruses the virulence genes are suppressed and replaced by a corrective DNA fragment. Because of the problems incontred with these vectors (see below), other transport systems such as synthetic lipids called liposomes (for respiratory disorders), other viruses (adenoviruses, AAV, etc.) or "plasmids" (circular DNA that autonomously replicates in bacteria and is often transferable to other cells) were used.

After very many tests on cells in culture and on laboratory animals the first tests for the introduction of a gene *in a live* human took place in May 1989. It was carried out in the United States by Stuart Rosenberg's team. It concerned patients in a terminal stage for whom no "therapeutic" effect was expected. The gene introduced coded for a protein that induced resistance to antibiotics. The purpose of this study was to examine whether this gene was functional and if a protein would be made by this gene.

Gene therapy became a real experimental therapy from the 90's. In September 1990 the American NIH (National Institutes or Health) gave the team led by W.F. Anderson and M.B. Blaese (Bethesda, US) permission for the first tests relating to somatic gene therapy among people, in other words for the first, direct curative intervention on the human genome. With this intervention one aimed to cure a girl or at least alleviate her suffering. The girl suffered from a serious immunodeficiency as a result of a genetic abnormality. This was a deficiency of adenosine deaminase (ADA), so the person affected had practically no resistance to the pathogens to which she was exposed [14].
- In January 1991, with the permission of the *Recombinant DNA Advisory Committee* of the NIH, the team of S. Rosenberg (Bethesda, VSA) used gene therapy to cure two patients who were suffering from a malignant melanoma in a terminal stage [15].
The test had no positive result, but cancer became a preferential target for gene therapy.

A first therapeutic success was recorded in 1993 in the US with a woman with serious family hypercholesterolaemia.

In the course of the nineties numerous somatic gene therapy tests were conducted worldwide (in an experimental way) but the really prominent successes were recorded by the French team of Alain Fischer and Marina Cavazzana-Calvo. [16], from 1999. For the first time in the world the team successfully treated "bébés-bulle" (babies growing up in a sterile space) who were

[14] The therapy of Anderson and Blaese consisted mainly in the changing of the genetic instructions of the T lymphocytes of the patient, to then restore normal production of the ADA enzyme and in turn have the immune functions again work satisfactorily. A clinical improvement was established as a result of this treatment.

[15] In this therapeutic test protocol the gene that codes for the "tumour necrosis factor" – a substance with a powerful antitumoral effect – was introduced in a special class of lymphocytes, the "Tumour infiltrating lymphocytes" (TIL).

[16] Fischer, A., Hacein-Bey, S and Cavazzana-Calvo, M 2002, "Gene therapy of severe combined immunodeficiencies", Nat. Rev. Immunol. 2,615-21.
Hacein-Bey-Abina, S., Le Deist, F., Carlier, F., Bouneaud, C., Hue, C., De Villartay, J.P., Thrasier, A.J., Wulfraat, N., Sorensen, R., Dupuis-Girod, S., Fischer A. and Cavazzana-Calvo, M. 2002, "Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy", N. Engl. J. Med. 346, 1185-93.

suffering from a genetic immunodeficiency (serious combined immunodeficiency, abbreviation SCID), characterised by a complete absence of the development of T and B lymphocytes. Eight of the ten patients treated by A. Fischer between 1999 and 2002 are now leading a normal life.

In Great Britain 4 identical cases were fully successfully treated. It is obviously too early to predict the long term effects of these treatments. But we may also not forget that apart from gene therapy the only possible treatment consists of a bone marrow transplant. And that is statistically impossible in 25 % of cases, meaning certain death for the sufferers.

III.2. Therapeutic indications and difficulties

At present numerous protocols relating to somatic gene therapy are being tested in the United States, Europe and Asia to treat different diseases.
The chosen domain of gene therapies is made up of monogenic hereditary diseases which can be continuously better understood thanks to the development of genome analyses.

Other potential domains are also being envisaged, representing an important scientific and medical challenge of our time. This concerns:

- cancer (by the reinforcement of the immune system or destruction of the cancer cells, etc.);
- neurodegenerative diseases (e.g. Parkinson's disease Alzheimer's);
- heart and vascular diseases;
- autoimmune diseases;
- infectious diseases;
- other disorders for which medical treatments are not yet satisfactory.

All somatic cells of the organism should be able to be treated in a specific way with genetic treatments, and this depending on the disorder. Accordingly, muscle cells should be able to be corrected for patients with muscular dystrophy, the epithelium of the airways among patients suffering from mucoviscidosis, as well as stem cells of different cancers.

Gene therapy could potentially be applied to all disorders. But with the current level of knowledge and practice these are still distant perspectives.

Specific difficulties occur for each treated pathology, for each transferred gene sequence and for each vector type.

1. *The choice of the gene to be transferred*. This approach is simpler for monogenic diseases, but much more problematic for other, multigene and multifactor diseases (e.g. cancer).

2. *The targeting* of the sick cells which must receive the gene. The targeting of white blood corpuscles goes relatively smoothly, for example; but targeting adult stem cells of the epithelium of the pulmonary system for the purposes of treatment of mucoviscidosis is still a long way from reality.

3. *Control of gene expression*, this means obtaining the protein in the correct quantity and for the required duration. For example the treatment of diabetes type 1 with insulin of which production must be modulated by the sugar level in the blood. One should, among other things, prevent the therapeutic effect from being blocked by different mechanisms such as rejection or inhibition of the production of the protein.

4. *The avoidance of side-effects*. The most important side-effects observed so far:

- *unsuitable immune response*
  Such a case occurred during an experimental gene therapy test treatment in the US, where the introduction of a vector originating from an adenovirus led to an inflammation from which the patient died.
- « *Mutagenesis by insertion* » in other words the integration of the therapeutic gene in the sick cell at a certain place in the chromosome, with the deregulation of the

introduced gene or an adjacent gene as a consequence [17].
The ideal option would consist of one preventing this risk by substituting the deficient gene by the healthy gene that one introduces by "genetic cibling", or using "homologous recombination". Up until the present one has still not been able to correctly introduce a transgene in the genome of a person, but this is being widely experimented.

5. A scientific key question for the success of gene therapies concerns the mechanism to supply the gene in the sick cell, in other words the vector. The most effective vectors are viruses, but they have their disadvantages as we have mentioned earlier. Research is taking place into other transport mechanisms (for example liposomes).

To sum up

After 30 years of research and 14 years of clinical applications the successes of somatic gene therapy still remains limited, but expectations remain high.
We are still not far enough to properly assess somatic gene therapies. These techniques are still applied on a low scale, and their future development requires a rigorous scientific and clinical approach. To this end, just as in all medical research, rules of good practice must be observed to ensure the safety and effectiveness of the clinical applications. In particular, the relationship between benefit and risk to the patient must be meticulously explored, and great caution must be exercised in this domain that intervenes in the core of life itself, with an influence on the identity of the person him/herself.
Analysis of the clinical trials of A. Fischer at the Necker hospital do, however, seem to demonstrate that the analysis of benefit and risk to the patient amply warrant the continuation of work relating to somatic gene therapies.
It is indeed because this analysis remains positive that the Agence française de sécurité sanitaire des produits de santé (AFSSAPS) (that had suspended all abovementioned testing in October 2002 because of the side-effects) has allowed the team of Dr Alain Fischer and Marina Cabazzana-Calvo to resume the studies after modifications were applied to the study protocol as regards the administered doses and age of the treated patients [18]. On the request of the team of Dr. A. Fischer the new attempt was suspended because a third complication arose; the team wishes to change the vector prior to starting testing again[19].

III.3. Ethical discussion about somatic gene modification

III.3.1. General considerations

Somatic gene therapy is situated in the same area as the issue of experiments on people, implying that it must comply with the same ethical expectations, attitudes and requirements.
In its opinion no. 13 of 9 July 2001 concerning experiments on people, the Advisory Committee on Bioethics evaluated the then current normative framework, in particular the conditions of "Good Clinical Practice", the deontological rules supporting them, as well as the ethical operations on which they must be based.
The members of the Committee are of the opinion that the ethical assessments developed in this opinion no. 13, are applicable to the present opinion.

Somatic gene therapy also belongs in a double context of fundamental and applied research.
At the current stage this still concerns experimental research with a therapeutic purpose.

In this area the transition from the laboratory to the human individual requires particularly strict ethical rules. They form the basis of scientific working in an innovative sector where the applications are aimed at the human genome. Debates about this matter are not neutral

[17] Professor Fischer's team came up against the latter complication in two cases and suspended clinical applications to analyse the causes of it.
Hacein-Bey-Abina, S., Von Kalle, C., Schmidt, M., Le Deist, F., Wulfraat, N.,Mcintyre, E., Radford, I., Villeval, J.L., Fraser, C.C., Cavazza-Calvo, M. and Fischer, A., 2003, "A serious adverse event after successful gene therapy for C-linked severe combined immunodeficiency ", N. Engl. J. Med. 348, 255-6.
[18] Decision of 9 June 2004 of the AFSSAPS
[19] Information of Dr. A. Fischer of 12 September 2005

because they take place in the field of scientific and medical performance and are sometimes associated with conflicts of interest.

Furthermore, there is the difficulty relating to the transition of the research into clinical application in a context in which the industry takes no initiatives. The industry no longer has interest in the subject because, as for the majority of rare diseases, technical development is too expensive proportionate to profits that very often remain hypothetical. Subsidisation therefore remains mainly public or charitable, and research remains in essence academic. Whether research into this domain takes place with public or private funds, it has the purpose of contributing to general welfare by the accumulation of new knowledge with the objective of alleviating human suffering. It therefore concerns sharing the benefits by granting access to all results, both positive and negative (see opinion no. 24 of 13 October 2003 of the Advisory Committee on Bioethics concerning human stem cells and therapeutic cloning, Chapter III., item 6).

Finally gene therapy, in the light of certain failures inherent to any new domain, has resulted in unfounded statements by the media, companies and the scientists themselves.
The role of the researcher in this domain is therefore fundamental. Nowadays she/he must accordingly continue her/his work according to rules of context and caution inherent to medical scientific research. He must supply objective and transparent information about the results achieved, and inform the public about both the *probable risk* and the *proven risk*. These understandings must be clearly distinguished because of the danger that this will lead to the blocking of any research and technological progress.

III.3.2. Specific ethical problems

Apart from formal requirements particular to all experiments on humans, one can question wether somatic gene therapy raises specific ethical problems.

III.3.2.1.
As regards actual gene therapy (i.e. therapeutic, so corrective) this does not appear to be the case. When we indeed assume that this concerns a clinical practice aimed at the curing or correcting of a poorly working organ or of certain aspects of an organ in a specific individual, one can compare this with an organ transplant (for example the correcting of a bone marrow gene versus the transplantation of bone marrow). The difference entails the lack of the problem for the donor.

III.3.2.2.
One has encountered reticence, however, for the following reasons.
To certain authors this therapy is dangerous because the line with germinal gene therapy appears blurred. One indeed considers the possibility that a gene introduced by this technique can be communicated to the germ cells, that in turn would have an influence on the whole germ cell line. But as we have already stated, specialists consider this hypothesis extremely improbable.
An objection is also raised that one encounters with very many new techniques: the *slippery slope* argument. The development of this technique of transferring genes could lead to more easily proceeding with the germ track technique that is considered unacceptable. One may respond to this assertion by stating that the use of a technique that can alleviate human suffering should not be prohibited because of hypothetical dangers that one could keep under control, should they actually arise.

III.3.2.3.
When in the near future one is able to manage this technique on a large scale, one will in any case not be able to evade the question of establishing the area of application.
Even with a sympathetic attitude with respect to use of the technique for generally accepted diseases in medicine - therapy aimed at the correcting of defective genes - it will not be simply accepted that this technique may be used for the enhancement of the function of specific organs.
For example, we will assume that one has developed a somatic gene therapy that changes the composition of the blood (so one can cure some forms of anaemia). The idea would quickly materialise that one will start using this technique to change the composition of the blood of

certain athletes. Once the new gene had been introduced we would have a new form of “natural” doping.

It goes without saying that such applications would contravene all ethical and medical arguments concerning doping in sport. This is not only due to reasons of fair play, but particularly because of the risks associated with imbalances that can originate in the body, and because of life-threatening situations that could be a consequence.
Furthermore, one cannot rule out similar problems occurring in other fields. An example here may be a technique that can cure Alzheimer's disease, and that could possibly be used to optimise the memory or the intelligence of people suffering from no illnesses at all.[20]. Such applications raise similar ethical problems to those mentioned above.

Conclusion

A social debate is therefore desirable on the subject of somatic gene modification to take account of the vague nature of the frontier between *pathological and non-pathological* characteristics, and therefore the possible acceptability of genetic modification for improvement compared to therapeutic gene therapy. This problem also arises in the domain of germinal gene therapy that will be covered in the next chapter.
Somatic gene therapy does not differ fundamentally from other therapeutic inventions and scientific approaches in the medical field.
The ethical arguments involved with research in the field of cell therapy were explained in our opinion no. 24 of 13 October 2003 concerning research into human stem cells and therapeutic cloning.

[20] Apart from Alzheimer's, many older people suffer (not all to the same extent!) from memory problems. It this a ‘natural’ process (aging) or a more or less pathological process? If this is a natural process, the intervention will have to be described as optimising (somatic gene therapy); if it is a pathological process this then concerns a therapeutic intervention.

CHAPTER IV. GERMINAL GENE MODIFICATION

Germinal gene therapy concentrates on the cells of the germ line (or reproductive cells) which transfer the hereditary characteristics of an individual to its offspring. Germinal gene therapy consists of the correction or modification of a gene of the reproductive cells or of the embryo cells in the initial development stage.

IV. 1. Historical summary

Since the start of the seventies attention has been devoted to the ethical aspects of the biotechnological revolution that related to the genetic recombination of the human genome. This debate particularly raged in the United States. In Asilomar already, not all scientists gathered to discuss the risks of DNA recombination (particularly with respect to micro-organisms) agreed about the idea of the regulation of the research. During the assembly of February 1975 researchers such as Stanley Cohen (Stanford), Joshua Lederberg (Stanford) and James Watson (Cold Spring Harbor) set themselves against the development of *Guidelines* that could impeded research freedom. To defend their point of view, these researchers particularly put the emphasis on the extraordinary advantages one could expect for public health. Other scientists such as Robert Sinsheimer (Caltech), Erwin Chargaff and George Wald did, however, argue for shopping research into recombinant DNA. They did this not only because of the risk of the spreading of pathogens, but particularly because of the fear that one would not be able to control the techniques with which people could change their own nature: "*Can we really forecast the consequence for mankind, for human society, of any major change in the human gene pool? The more I have reflected on this the more I have come to doubt it. I do not refer here to the alleviation of individual genetic defects but more broadly to the genetic redefinition of man* [21] *".*

Up to now one still only uses genetic therapy on body somatic cells . But in the future one may not fully exclude the possibility of genetic therapy being applied on germ cells. The intention is to accordingly treat certain monogenetic disorders.

Nevertheless, most ethical bodies have declared themselves in favour of a prohibition of germ cell therapy.[22]. We should, however, draw attention to the differences in the approach to this prohibition. In a number of texts of committees for bio-ethics and in a number of legislative texts, this prohibition is set as definitive, and the act is represented as intrinsically unacceptable. In other texts one avoids bombastic declarations about ethics and "human dignity", and the emphasis is particularly placed on the fact that our current knowledge is still insufficient to be able to take account of the potential effects of these experiments. Based on such an attitude one can now already start the discussion about the basic problems arising from the possible developments of this recombinant biotechnology.

Indeed, thanks to improvement of recombinant DNA techniques (homologous recombination, artificial chromosomes, etc.), one day it may be possible to make transgenic people using the application of changes to the germ cells (or in embryonic cells at the initial stage of their development). One should then be particularly alert to the possible crossing of specific lines in the direction of achieving an artificial human person. It cannot be excluded that one will gradually increasingly be involved with the weakening of taboos based on the recombination of the DNA of human germ cells, with the lines being gradually shifted. As a result, the natural person would disappear unnoticed to be replaced by the genetically modified person. The possible non-therapeutic applications of recombinant DNA techniques could form an example of the progressive blurring of the limits between treating medicine (*correction*) and *enhancement* medicine. In the contemporary biomedical sciences, the technological and scientific knowledge at the basis of these new therapies will almost inevitably lead to techniques aimed at the optimisation of certain bodily functions or cognitive functions of an individual. The members of the American committee for bio-ethics — *The President's Council on*

[21] Sinsheimer, R., Troubled down for genetic engineering, *New scientist,* 68, 1975, p.55.

[22] Here we refer to article 24 of the "Universal Declaration on the Human Genome and Human Rights" (General Conference of the United Nations, 9/12/1998) that "condemns practices that could detract from human dignity, such as activities on the germ cell line"; article 13 of the "Convention on human rights and biomedicine" of the Council of Europe also agreed with this standpoint.

Bioethics — found this theme sufficiently important to compile a remarkably documented report with the title *Beyond therapy: Biotechnology and the Pursuit of Happiness*[23]. In recent years a great deal of literature has been published on this subject, particularly in the Anglo-Saxon countries. It represents both extremes of the contemporary biopolitical spectrum. On the one hand there are the 'bioconservatives' who want to forbid all recombination of the human genome in the name of "human dignity", out of respect for the "naturally given" or the sacred nature of human nature. Then there are the 'bioprogressives' who are open to the cautious change of the biological given that the person is, including his genome. [24] [25] But even if people will shortly have the possibility of remodelling their own nature, one can ask oneself if this evolution is indeed desirable. The question remains open and the answers are mixed. Should one consider a person as a plastic animal that one can change by technological and scientific means? Or must one hold firm to the idea of an unchangeable human nature, so it would be sacrilege to change this? It is useful to position this debate in its current biopolitical context by raising the arguments of the bioconservatives and bioprogressives.

IV.1.1. Arguments of the 'bioprogressives' with respect to the modification of the human genome

Since the eighties Anglo-American philosophers were concerned with themselves with the question of the modification of the human genome. In 1984 the British philosopher Jonathan Glover published a book about the subject with the title *What sort of people should there be?*. The application of recombinant–DNA techniques on humans is the most important theme: "*Perhaps one day we shall be able to choose people's genetic characteristics*", writes Glover. "*How should we decide what sort of people there should be ? Or are there reasons for refusing to make such decisions?* [26]". Very many people react with shock when one discusses the ability to change human nature. But this feeling of repugnance is not always paired with valid, rational objections. "May one change human nature?" is the central question in Glover's book. It is his intention to analyse and refute the arguments of those who are in principle opposed to changing human nature by means of genetic modification.

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[23] See the report of the American committee for bio-ethics *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, The President's Council on bioethics, Washington D.C., October 2003. This document is available on the committee's website: www.bioethics.gov. The report has also been published on paper: *Beyond Therapy: Biotechnology and the Pursuit of Happiness, A report by the President's Council on Bioethics,* Regan Books, New York, 2003.

[24] See for example the following works:

1.President's Council on Bioethics (2003) Beyond therapy: Biotechnology and the pursuit of happiness. New York: Dana Press. 400 p.

2.McKibben W (2003) Enough: Staying human in an engineered age. New York: Times Books. 271 p.

3.Callahan D (2003) What price better health? Hazards of the research imperative. Berkeley: University of California Press. 329 p.

4.Elliott C (2003) Better than well: American medicine meets the American dream. New York: W. W. Norton. 357 p.

5.Fukuyama F (2003) Our posthuman future: Consequences of the biotechnology revolution. New York: Picador. 272 p.

6.Rothman S, Rothman D (2003) The pursuit of perfection: The promise and perils of medical enhancement. New York: Pantheon Books. 292 p.

7.Kass LR (2002) Life, liberty, and the defense of dignity: The challenge for bioethics. San Francisco: Encounter Books. 313 p.

8.Kristol W, Cohen E, editors (2002) The future is now: America confronts the new genetics. Lanham (Maryland): Rowman and Littlefield. 357 p.

9.Sandel S (2004 April) The case against perfection. Atlantic Monthly 51–62.

[25]

1. Stock, Gregory, *Redesigning humans*, Houghton Mifflin Company, 2002.

2. Hughes, J., *Citizen Cyborg. Why democratic societies must respond to the redesigned human of the future*, Westview Press, Cambridge (Mass.), 2004

[26] Glover, J., *What sort of people should there be?*, Penguin Books, Harmondsworth, 1984, p. 13.

The strongest objection concerns the risks of genetic recombination among people. Unexpected results are possible, says Glover. If we create people with unanticipated characteristics we will have to take account of this. The possibility of a disastrous, irreversible effect has such dissuasive power that very many people do not want to hear of positive genetic modification. As far as Glover is concerned, the risk of "disasters" means we must take great caution if we proceed along the path of the genetic manipulation of people. Scientists must respect what Glover in 1984 already called the *precautionary principle*. One may only modify the genes in cases where there is little risk, and the advantages are big enough to justify the intervention. Supporting this precautionary principle allows to avoid positive genetic modification being definitively prohibited. This would indeed be both unrealistic and possibly even imprudent[27]".

In his work *The Foundations of Bioethics,* the American philosopher Tristram Engelhardt also suggests that the modification of the human genome is fully in conformity with procedural ethics based on principles of the right to self-determination and charity. The "progressive" story of Engelhardt reads as follows: "When we develop the possibility of working with genetic modification and not only the body cells but also the human germ cell line, we will be able to rearrange human nature according to the purposes the person has decided for him/herself. In the long term this can so radically change human nature that taxonomists in following generations will be able to consider our descendants as a new species. If there is nothing sacred in the human nature (and no secular argument whatsoever can convince us of the sacred character of the person), this means there is no single reason, providing that one proceeds very carefully, for not modifying nature. This critical analysis of our nature helps to better understand the observation of Protagoras: 'The person is the measure of all things'[28]."

The question of the genetic modification of the person also forms the central theme of the book by philosopher and bioethicist John Harris *Clones, Genes and immortality*. In his work Harris asks himself which position should be taken regarding the possibilities that technology offers. According to him genetic modification of the person is inevitable[29]. Harris tries to anticipate the achievements of technology and science in the relatively near future. We now have the ability to introduce new genes in the DNA of germ cells or embryonic cells of the person. We will be able to repair genetic defects, and even better *enhance certain function*. The distinction between treatment and improvement — between "*removing dysfunction*" and "*enhancing function*" — will be crucial in biomedical sciences in the future. Harris is a bioprogressive philosopher and amuses himself by writing '*genetics fiction'*, as did the biologists J.B. Haldane and Herman Müller before the Second World War. [30]. He suggests technological progress that will probably be achieved in the more or less near future. The introduction of new genes would, for example, according to him be able ensure that a recombinated individual is more resistant to infectious diseases, more intelligent or lives longer.

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[27] Glover, J., "This principle of caution is less strong than one ruling out all positive engineering, and allows room for the possibility that the dangers may turn out to be very remote, or that greater risks of a different kind are involved in not using positive engineering. The argument from the risk provides more justification for the principle of caution than for the stronger ban on all positive engineering", *What sort of people should there be?*, Penguin Books, Harmondsworth, 1984, p. 13.

[28] Engelhardt, T..H.. Jr, *The Foundations of Bioethics*, Oxford University Press, 1986, p. 377.

[29] "We are on the brink of a new revolution of quite awesome power. The revolution in molecular and genetics will give us the ability to divert and control human evolution to an unprecedented extent. It will enable us to manufacture new life forms to order, life forms of every sort. The decision before us now is not whether or not to use this power but how and to what extent. It might be tempting to pretend the revolution had not happened and to try to go on as before, but to do so would not only be futile, it might also involve us in causing an immense amount of suffering. There is no safe path. If we fail to make changes to human beings, the result may simply be that we ensure that the future will be much worse for everyone that it need be. If we make the wrong changes the same may be true. What we must try to do is learn to choose responsibly, but there is no sense in which doing nothing is necessarily a more responsible choice than doing something" (Harris, J., *Clones, genes and immortality*, Oxford University Press, 1998, p. 6).

[30] Haldane, J.B.S., *Daedalus or Science and the Future*, London, Kegan Paul, 1925; Muller, H.J., *Hors de la nuit*, traduction française de Jean Rostand, Paris, Gallimard, 1938, p. 118 (original publication: *Out of the Night*, Vangard Press, 1935).

A number of scientists share the standpoints of the bioprogressive philosophers. James Watson, co-discoverer of the double helix structure of DNA, does not mince words in expressing the importance of the recombination of germ cell DNA. "No one has the nerve to say so, but if we could make better people because we know how we can add genes, why shouldn't we do this[31]?". In his book *Redesigning Humans*, Gregory Stock, professor at the *University of California* in Los Angeles, tries to convince his readers of the inevitability of the genetic modification of human germ cells[32]. Stock is convinced that the genetic modification of the person is a logical consequence of progress achieved in the different sectors of the research: in vitro fertilisation, somatic gene therapy, the mapping of the human genome, experiments with the introduction of artificial chromosomes.

Stock mentions a survey performed by Darryl Macer — director of the *Eubios Ethics Institute* in Japan — concerning the perception (about technology for selecting germ cells) of the general public in different countries. If one offers the general public the possibility of correcting genetic defects or enhancing the physical and mental capacities of their children, an important part of the population seems to be in favour of this: 22 % in Israel, 43 % in the United States, 63 % in India and 83 % in Thailand, and these figures would without doubt be even higher in Singapore, Korea or China. These countries have indeed invested enormously in their biotechnology. When a relatively inexpensive technology is made available in thousands of laboratories across the whole world, use will be made of it. Without doubt, the limitations and prohibitory rules originating from national authorities or international 'biopolitical' organisations will not suffice in preventing the genetic modification of the person being applied. Stock assumes that it is preferable for these experiments to take place in all transparency at university laboratories or within research units of large private biotechnological companies, than in the semi-clandestineness of laboratories of religious sects.

The report specified above from the *President's Council on Bioethics* studies the ethical problems relating to enhancement medicine. Thanks to biotechnology we have access to a number of experimental techniques (that indeed have already been tested on animals and some of them also on people) that indicate that in the more or less near future, techniques will be developed that go further than ordinary therapy: selection or the genetic modification of embryos, the enhancement of certain cognitive capacities of children and adults (attention, memory), enabling athletes to perform better (mainly by activities on the genome of the muscle cells), the retarding of aging and the lengthening of the working life, changing of the mood. Even if the clinical application of certain technologies still appears uncertain or distant, the members of the American committee still believe that it is important to today study the potential effects of this performance-related biotechnology on medicine and the community[33].

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[31] Watson, J.D., *DNA, The secret of life,* Knopf, New York, 2003.

[32] Stock, Gregory, *Redesigning humans*, Houghton Mifflin Company, 2002. "We know that Homo sapiens is not the final word in primate evolution, but few have yet grasped that we are on the cusp of profound biological change, poised to transcend our current form and character on a journey of new imagination".
"At first glance, the very notion that we might become more than human seems preposterous. After all, we are still biologically identical in virtually every respect to our cave dwelling ancestors. But this lack of change is deceptive. Never before have we had the power to manipulate human genetics to alter our biology in meaningful, predictable ways. Bioethicists and scientists alike worry about the consequences of coming genetic technologies, but few have thought through the larger implications of the wave of new developments arriving in reproductive biology. "

[33] "This report offers less a list of many things to think about than a picture of one big thing to think about: the dawning age of biotechnology and the greatly augmented power it is providing us, not only for gaining better health but also for improving our natural capacities and pursuing our own happiness. The ambitious project for the mastery of nature, the project first envisioned by Francis Bacon and René Descartes in the early seventeenth century, is finally yielding its promised abilities to relieve man's estate. Though our society will, as a matter of public practice, be required to deal with each of these techniques and possibilities as they arrive, piecemeal and independently of one another, we should, as a matter of public understanding, try to see what they might all add up to, taken together. The Council's experience of considering these disparate subjects under this one big idea — beyond therapy, for the Pursuit of Happiness - and our discovery of overlapping ethical implications would seem to vindicate the starting assumption that led us to undertake this project in the first place: biotechnology beyond therapy deserves to be examined not in fragments, but as a whole" .

The report embraces four subjects: selection and modification of embryos (chapter 2 with as title "*Better children*"), enhancement of athletic performance (chapter 3: "*Superior performance*"), prolonging life (chapter 4: "*Ageless bodies*"), modification of emotive life and cognitive functions (chapter 5: "*Happy souls*").
Even if the conclusions of this document are cautious and invite moderateness, the reading of the reports of the different information sessions (during these sessions the members of the committee could enter into dialogue with scientific experts) prior to the drawing up of the document leaves little doubt about the unavoidable nature of the development of this non-therapeutic medicine[34]".
We note that even if the majority of the scientists interviewed by the American committee are convinced of the inescapable nature of the application of such optimising/enhancement biotechnological action on the person, the conclusions of the members of the committee are more reserved.
The moderateness of the members of the *President's Council on Bioethics* contrasts strongly with the 'technophile' enthusiasm of the supporters of transhumanism, a well-structured movement that originated in the United States and that argues for the biophysical transformation of the person. The transhumanists have the idiosyncrasy that they – sometimes with a certain naivety and simplism -develop a virulent technophile enthusiasm. Their purpose is to exceed the current form of the person. They want to leave the contemporary medical paradigm behind them, that is based on a distinction between therapeutic and non-therapeutic changes to the human body. The most widely argued defence of transhumanism is probably found in the work of the Oxford philosopher Nick Bostrom[35]. The transhumanist objective is the use of biotechnology in a rational way to be able to prolong life without one suffering from certain disorders, and the enhancement of the memory and other intellectual capacities. They also want to refine our emotional experience, make us happier, and in general give us greater control of our own life.[36].

Beyond Therapy: Biotechnology and the Pursuit of Happiness, The President's Council of Bioethics, Washington D.C., October 2003, chapter 6.

[34] Accordingly, Ted Friedman, professor at the University of California in San Diego and chairman of the *Recombinant DNA Advisory Committee*, invited the examination of the possibilities of the genetic improvement of sporting performance. He summed up the elements that caused him to think that such a genetic approach is inevitable. "Why does one think that genetic approaches to athletic enhancement are inevitable? First of all, athletes are risk-takers. They're young healthy athletes who think nothing is ever going to happen to them. And they are known to accept all sorts of risks. Polls have been taken of young athletes asking if it were to guarantee you a gold medal at the next Olympics at the risk of losing 20 years of your life would you do it? And universally, they say yes. They will take that risk for the reward of gold medals. There are enormous financial pressures and national pressures to push athletes to perform and to win. We know that they use a pharmacological approach to enhancement. We know that they're aware of gene transfer technology, and we know that that technology is still immature, but it's advancing rapidly. And we know that many of the studies in gene transfer technology use the genes that are of particular interest to athletes, erythropietin, growth hormones and other relevant genes. (…) Enormous pressures exist in athletics which make this kind of direction very likely, and inevitable". *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, The President's Council on bioethics, Washington D.C. — Fifth Meeting, Thursday, July 11, 2002. Session 4: Enhancement 2: Potential for Genetic Enhancements in Sports — Dr Ted Friedmann.
The words of Victor Conte - who was responsible for the pharmaceutical preparation of the American sprinters Tim Montgomery and Marion Jones - appear to confirm the psychological intuition of Friedman. Conte attributes the following words to Tim Montgomery, world record holder and Olympic champion in the 100 m: " If I can win a golden medal thanks to performance-enhancing drugs it wouldn't matter if I should die of it." (Quoted in the article by Pascal Giberné, Coup de grisou sur les stades, *Le Monde*, 6 December 2004).

[35] See for example Bostrom, Nick, 2001: "Transhumanist Values" http://www.nickbostrom.com.

[36] A good description of the different transhumanist ideas is found in the work of Hughes, J., *Citizen Cyborg. Why democratic societies must respond to the redesigned human of the future*, Westview Press, Cambridge (Mass.), 2004.

IV.1.2. Arguments of the 'bioconservatives' with respect to the modification of the human genome

Obviously not everyone agrees with the conviction of the bioprogressives. A thinker such as Hans Jonas would forbid the person from freely and creatively acting upon oneself - for example using transgenesis or cloning. Such a conviction is based on an essentialistic understanding of the person, a general anthropology that assumes the idea of the sacredness of inalienable human nature, that may not be changed by deliberate human intervention.

But human nature is the fruit of a long evolution. What are the shared aspects of contemporary humans and the *Homo habilis*? The bioconservative movement defends the ontological or theological sacredness of the biological fact of contemporary humans.
Even if he does not support the idea of the sacredness of nature, in a work titled *The Future of Human Nature*, the philosopher Habermas defends bioconservative standpoints tending towards those of Jonas. Habermas argues for the right to a non-genetically manipulated inheritance[37]. The purpose is to arrive at a clarification of the moral feelings created by genetic engineering. He indicates that in scientific literature expressions are used such as "*Playing God*" or "*Partner in evolution*". What according to him is a matter of concern is that the separating line is blurred between who we are and the "organic equipment" we give ourselves. He wants to indicate how biotechnology blurs the normal distinction between what is made (*the made*, the artificial, the soulless machine) and what develops (the natural, the living). The disappearance of the distinction between the natural and the artificial, what will happen in life to the person with a changed genome before birth, can ensure that our ethical understanding can be changed as a member of a species. The self-awareness of the genetically programmed person can also be influenced. As far as Habermas is concerned, human transgenesis is a form of reification of the genetic recombinant individual. When an adolescent learns that an outsider was involved with his genome before his birth and therefore has changed certain characteristics, his perspective of being by natural development can be replaced by the perspective of a synthetically made being. This invasion of the artificial in nature could therefore disturb the psychism of the adolescent, and as a result his choice to live in an individual manner can be limited.
Two authors give a good illustration of bioconservative trends in the United States: Leon Kass and Francis Fukuyama. Fukuyama is a member of the *President's Council on Bioethics* of which Leon Kass was the chairman. Leon Kass is a professor at the university of Chicago, and one of the most important opponents of the cloning of people and the transgenesis of humans in the United States. In his work *Life, Liberty and the Defense of Dignity*, he defends this prohibition in the name of human dignity[38]. Francis Fukuyama, professor at the Johns Hopkins University, defends ideas closely relating to those in his last book *Our posthuman future*[39]. Kass has played a central role in the drawing up of the conclusions of the report *Beyond Therapy: Biotechnology and the Pursuit of Happiness*. This partly explains the distinct reservations expressed with respect to non-therapeutic medicine in this text, despite the cautious, favourable opinion of the different scientific experts heard by the committee. In the conclusions of its report the *President's Council on Bioethics* mentions two reasons for concern with respect to non-therapeutic medicine. First of all there are the traditional reasons for concern, related to the safety of the experiments, to their effects on health, social justice and equal accessibility to these improved biotechnologies. More specifically the risk is emphasised of the occurrence of a "*biotechnologically improved aristocracy*[40]". As a result, the gap between the privileged and the underprivileged within American society could be made still wider. Biotechnological developments could also limit individual freedoms and create social conformism with respect to certain developments made possible by the new medicine[41].

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[37] Habermas, J., *The future of human nature*, Polity Press, Cambridge (UK), 2001.
[38] Kass, L.R., *Life, liberty and the defense of dignity*, Encounter Books, San Francisco, 2001.
[39] Fukuyama, F., *Our posthuman future*, Farrar, Straus and Giroux, New York, 2002.
[40] *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, The President's Council of Bioethics, Washington D.C., October 2003, chapter 5.
[41] "What is freely permitted and widely used may, under certain circumstances, become practically mandatory. If most children are receiving memory enhancement or stimulant drugs, failure to provide

Certain members of the American committee, under the leadership of Leon Kass, are of the opinion that enhancement biotechnology raises more fundamental ethical questions, questions that go to the core of what it means to be human. These essential questions – raised by them possibly in the form of an initial feeling of aversion or rejection with respect to specific biotechnological applications[42] — concern the question of human nature and human dignity. The "natural order" would therefore be threatened by the human *hybris* "playing God". The dignity of human activity would be threatened by "non-natural" means. The preservation of our identity would also be threatened by attempts of self-transformation. Finally, the development of the person would be threatened by conformistic research into the artificial substitution of natural functions. These ontotheological arguments appeal to emotional factors based on an aversion to the person starting to play God while he is not in the possession of the wisdom of God[43].

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them for your child might be seen as a form of child neglect. If all the defensive linemen are on steroids, you risk mayhem if you go against them chemically pure. And, a point subtler still, some critics complain that, as with cosmetic surgery, Botox and breast implants, many of the enhancement technologies of the future will very likely be used in slavish adherence to certain socially defined and merely fashionable notions of 'excellence' or improvement, very likely shallow and conformist. If these fears are realized, such exercises of individual freedom, suitably multiplied, might compromise the freedom to be an individual" (*Beyond Therapy: Biotechnology and the Pursuit of Happiness*, The President's Council of Bioethics, Washington D.C., October 2003, chapter 5).

[42] "The subject being relatively novel, it is difficult to put this worry into words. We are in an area where initial revulsions are hard to translate into sound moral arguments. Many people are probably repelled by the idea of drugs that erase memories or that change personalities, or of interventions that enable seventy-year-olds to bear children or play professional sports, or, to engage in some wilder imaginings, of mechanical implants that would enable men to nurse infants or computer -brain hookups that would enable us to download the Oxford English Dictionary." *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, The President's Council of Bioethics, Washington D.C., October 2003, chapter 5.

[43] "The mere playing at being God, the hubris of acting with insufficient wisdom " *Beyond Therapy: Biotechnology and the Pursuit of Happiness*, The President's Council of Bioethics, Washington D.C., October 2003, chapter 5.

IV. 2. Ethical discussion within the Committee concerning germinal gene modification

IV. 2.1. Standpoint A

Some members of the Advisory Committee on Bioethics are against a principle prohibition of the techniques for recombination of human germinal DNA. They believe that the acceptability of DNA recombination techniques, when they have been fully refined, will have to be judged case by case in the light of the context and the nature of the intended experiment. They argue for an attitude of open and alert monitoring of the technological sciences. They believe it is better to avoid the everything-or-nothing reasoning of those who radically oppose the modification of the germinal genome in the human being. In the talk of the bioconservatives the market, individualism and liberal eugenics are all too often regarded as necessarily poorly or impossible to regulate. The only salutary reaction according to them consists of an absolute, final prohibition of positive eugenics and a list of very strict limitations for negative eugenics. Such non-evolutive and tight regulations will, however, inevitably lead to clandestine research and force the applications onto the black market. A prohibition will not be able to impede the development of highly-desired technologies that require no resources that the State alone can bring together. It would therefore be better to regulate the freedom of research and development, and nevertheless allow experiments for which some want an absolute and definitive prohibition under strict, public and reviewable procedural conditions.[44]

Some members of the Committee think that an adequate answer can be given to the most important objections of the bioconservatives: objections relating to concern about the safety of the experiments, their consequences for health, social justice, equal access to optimising/enhancement biotechnologies, objections with respect to ontotheological concerns about a possible change to "human nature".

The objection that genetic research forms a great danger to future offspring that may be affected by various abnormalities or serious malformations can, according to some members of the Advisory Committee on Bioethics, be answered with the following counter-arguments. There is no reason whatsoever to a priori believe that the genome of people will never be able to be combined with a minimum of risk. The regulation of experiments on people must protect figures from the medical world from too great risks. That is, however, no reason to prohibit experiments which comply with long-established deontological rules that are also respected today on a wide scale.

As regards the objection that the development of reproductive-genetic experiments would have consequences as regards social justice (only the rich would have access to diagnoses and to DNA recombination), according to some members of the Advisory Committee on Bioethics, protection against unjust availability is in place to prevent some exploiting a technique at the deprivation of others. They also believe that gene therapy will in due course be able to help reduce inequalities between individuals. They reject the bioconservative reasoning in which positive eugenistic practices or practices seen as positive eugenistic practices and their consequences are systematically ignored or brought into discredit. They also dispute the idea that individuals with improved physical or cognitive capacities would be morally inferior to "natural people". The modified individuals could, on the contrary, demonstrate a wider awareness, a sharper sense of justice and superior moral virtues. In a future context of the application of genetic recombination of the human being, a child could ask itself one day why it does not have better genes - just as good genes as his friend whose parents did not refuse enhancement intervention (memory, intelligence, health) in the name of respect for human nature and the genetic lottery. Here the wish is to justify the enormous *actual inequalities* of the individuals at genetic level under the pretence that the "natural lottery" is the condition for *equality in law* of people. But even in highly developed societies actual genetic inequalities are

[44] Certain arguments in this paragraph in favour of Standpoint A have been developed further:
- by G. Hottois, « Quel rôle pour les philosophes dans les débats bioéthiques ? », Présentation et discussion de G. Habermas, L'avenir de la nature humaine. Vers un eugénisme libéral ?, article à paraître
- and by J.-N. Missa, « L'homme recombiné : les enjeux éthiques et philosophiques de la modification du génome de l'être humain » *in* J.-Y. Goffi, Regard sur les technosciences, Paris, Vrin, 2006 – sous presse.

not or poorly compensated. If on the contrary we accept that genetic intervention is not by definition a bad thing, the real but very difficult questions arise: those of the vigilant monitoring of eugenistic research and eugenistic development, and particularly that of rightful availability and fair access. It is exactly the *political-philosophical* questions that we must dare to tackle, instead of merely accepting the hypothesis that genetic recombination of the human being can be applied in the more or less near future. The questions of political philosophy are for that matter now already being widely discussed in Anglo-American literature: the genetic possibilities are taken seriously and the conclusions are rarely of the all-or-nothing type. On the contrary, it is attempted to determine balanced conditions and rules without minimising the risks, advantages and disadvantages, particularly based on the prevailing political philosophies (those of J. Rawls and R. Nozick)[45].

As regards the objection that the modification of the genome of a human being would be a threat to natural diversity (if you could design your children à la carte, certain beauty features and intelligence characteristics would be obtaining desirable natural diversity), it can be suggested that the opposite is rather the case. The realm of possibilities increases with DNA recombination. The diversity of tastes and cultures is large enough to ensure people would not all make the same choices. Furthermore, this concerns genetic modification. The weight of the environment and of epigenetic modification, where it is often forgotten that they are just as biological, may not be underestimated. The genes form the structure of the body and the brain. The environment models and changes the neuronal architecture. Nature and culture both have a biological base. The conceptual contrast between genetic conditioning and symbolic (culture-, environment- and education-related) conditioning must therefore be seen as a gradation difference and not as a difference in nature. Symbolic conditioning is not immaterial. It requires a dynamic structural change of the neuronal networks which originate due to education and interaction with the environment. As regards genetic conditioning, this is not necessarily irreversible. It cannot be ruled out that genetic engineering will be able to reverse what it has already done, or develop molecules that can allow the individual to choose to activate certain genes or otherwise. The genes are indeed continuously activated or deactivated by information from the environment. With his/her behaviour the informed individual can work on his/her good and poor genetic dispositions or not.

Then there is the answer to the ontotheological argument that it is sacrilegious and "morally repulsive" to meddle with human nature. This is an emotional argument that often hides behind language that is not logical and rational, such as the bizarre references in this context to "fundamental human rights", a "right to the integrity of the genome", an undefined concept of "human dignity", that forms the ideal mask for bioconservative standpoints.
As the American philosopher Ronald Dworkin emphasised, the power of social resistance against genetic engineering cannot be assessed without understanding the roots of the basic objection.
The resistance results from a distinction between what does not depend on us (our genetic patrimony that God – or nature – has given us) and what does depend on us. This concerns the frontier between destiny and freedom, *chance and choice*. Thanks to or because of genetic engineering, that resulting from destiny will maybe become a matter in our own hands. The shifting of the limits between what does and does not depend on us creates uncertainty and moral unease. This malaise should be rationally considered and not only emotionally. *The excessive appeals from bioconservatives to feelings and emotions (disgust, aversion, horror, etc) in their arguments (e.g. Kass's "yuck factor") can barely hide that they have problems rationally justifying their intuitions* – intuitions considered to justify their pursuit to impose a morality with universal pretence. Well then, not only are these irrational intuitive opinions not universally shared, they can also encourage extremely dangerous discrimination criteria. It appears

[45] See: Glover, J., *What sort of people should there be?*, Penguin Books, Harmondsworth, 1984; Buchanan, A., Brock, D.W., Daniels, N., Wikler, D., From Chance to choice: Genetics & Justice, Cambridge University press, 2000; Hughes, J., *Citizen Cyborg. Why democratic societies must respond to the redesigned human of the future*, Westview Press, Cambridge (Mass.), 2004; Agar, N., *Liberal Eugenics. In Defence of Human Enhancement,* Blackwell, 2004; Bostrom N. , "In Defense of Posthuman Dignity", in *Bioethics,* June 2005, vol.19, no. 3; Allhoff, F. " Germ-Line Genetic Enhancements and Rawlsian Primary Goods ", in *Kennedy Institute of Ethics Journal,* Vol. 15, no. 1, March 2005, p.5

illusionary and hardly relevant to some members of the committee to want to impose a universally conservative or technophobic morality that a priori forbids any change to the human genome. They see it as important to resist any form of paternalism that wants to enforce a general prohibition of recombination techniques which could have a positive impact on the life of people. They therefore argue for the regulated acceptance of genetic engineering, applied to people, regulation that opens the door to new possibilities of technological DNA sciences, to at the same time cause as little suffering as possible and create maximum opportunities for development.
The members therefore agree with the development, in the course of evolution, of human capacity to technically intervene on its given biology.

IV. 2.2. Standpoint B

Other members of the committee do not agree with the idea that the gene pool of the human species is unchangeable; they consequently refute the idea that the human genome is sacrosanct. In the prohibition of any intervention on the genome they see the hard core of a contorted archaic reaction of a religious nature.
It is true that the gene pool in the human species changes under the pressure of circumstances. The distinction between *genotype* (formed by what is recorded in the DNA) and *phenotype* [46] - the physical and health situation of a living being at a given time in his existence, that is the result of the interaction of the genome and external factors - is however useful in considering the relative importance of genes with regard to the influence of the environment.
These members suggest a pragmatic reflection on the – at the same time healing and baleful – consequences of the fact that "life" due to its genotypical aspect (i.e. modification of the human genome) is today a subject of modern technological science.
The members do, however, want to immediately refute the biocatastrophic visions of the risk of the prospect of the total changing of the gene pool of a whole population. They would simply recall that to reduce the frequency of the so-called *poor* genes from one per hundred to one per thousand, twenty-two generations would in reality have to be subjected to more or less imperative sterilisation measures.[47] Furthermore, it is today an absolute fantasy to want to "improve" the human species using a selection and sterilisation policy: to impose such a policy, imperative measures would inevitably be required that would come up against various "obstacles" in the path of the principle of a democratic society. The choice of whether or not to impose such measures would therefore in essence not be a technical-scientific choice but a political one. As far as *germinal gene manipulations are concerned* [48] , it is hardly probably that the gene pool of a population would change more efficiently (faster), unless this would be industrially and directed imperiously organised in a market economy that would feed the new "requirement" of improvement, after it has been elaborated from scratch.

In general, gene therapy as a component of biomedical research and clinical care, is still in the experimental stage, both in its *somatic* and in its *germinal* form. The current debates about this form of therapy, that cover both its ethical and medical aspects, must consequently be seen in the context of uncertainty. At present specialists are simply not succeeding in reaching agreement about the medical-technical feasibility of that type of therapy, more specifically the therapeutic and enhancement genetic changes in the germ line; and just as little agreement is reached on the desirability of en masse allocating the poorly available resources to this research niche. Private finance has for that matter largely turned its back on gene therapy research since the emergence of the new eldorado of regenerative medicine. The ethical discussions on the public forum and in 'civil society' would consequently better concentrate on the one hand on the question of justice as regards access to new therapeutic techniques – a question that befits a democratic society - and on the other hand the uncertainty concerning certain ethical implications of the carrying out of gene therapy in clinical research. Consequently, it appears indispensable to draw up legal and deontological rules to make research into germinal genetic modification and as appropriate its therapeutic application more

[46] Etymology of phenotype: from the Greek *phainomai*, appear, be visible; *typos*, stamp, form
[47] R. Frydman. *Dieu, la médecine et l'embryon*. Odile Jacob, 1999.
[48] The term "*germinal gene manipulations"* camouflages the reality of "*optimising/enhancement gene modification"* which are wrongly called optimising/enhancement gene 'therapies'; wrongly, because they have no therapeutic characteristics, but concern the changing of the human genome in the hope of enhancement.

transparent. At present any success or the ethical implications of the form of therapy appear difficult to determine, so the discussions in this area are inevitably a mixture of pessimism and optimism (*from a medical standpoint*) and of reservation and the will to go forward (*from an ethical standpoint*).
Without portraying the situation without thought and in a gloomy light, the members simply remind of a pragmatic principle of Realpolitik [49]: "We are not on the verge of the danger of the general subjecting of humans to science and technology, but the danger of some people being manipulated by others".[50] [51]

According to the members, the risk that somatic gene therapy moves towards germinal gene therapy is probably smaller than the risk that therapeutic gene therapy moves towards optimising/enhancement gene modification. The latter has no therapeutic purpose, but consists of the application of changes to the human genome from which improvements are hoped for. In a nutshell, if we were to consent to potential therapeutic progress, meaning therapeutic somatic gene modification, would we then inevitably also consent to genetic changes in the germ line?
It is not out of technophobia that contemporary culture and societies increasing seem to realise - or even desire – that medicine expands its traditional role and fits in a medicalised technical-industrial culture, that aims for the measured '*improvement'* of physical and biological welfare in the name of an individualised consumer technology. Consequently, the lines between pure therapeutic or curative medicine and the so-called enhancing modification ('*enhancement technology'*) fade – and that also applies a fortiori to the (still virtual) domain of germinal gene modification. Society in the broad sense – and not only the medical world – is therefore confronted with the question of if it is inevitable (*casu quo* desirable) that medicine exercises such a practice of *optimisation* (of the individual or of the human species), that contrasts with traditional medical 'care' (in which the accent lies on the sick individual or on public health). Some members accordingly ask themselves if it is desirable to tolerate physicians departing from their traditional assignment for the purpose of *improving* life itself? Or whether it is desirable that we allow physicians to penetrate our privacy and make known our organic secrets – and even genetic defects – out of concern for public health? As far as the members are concerned, such questions form the actual starting points for debates about modern eugenics, now knowledge and new technical resources open possibilities of innovative (but not yet validated) germinal activities on "life" - that has become a technical-scientific subject - with the purpose of making life more healthy or "improving" it.
Providing that the conditions for gene modification obtain a deontologic and legal framework that is strict, serene and evolutive, according to the members it must be possible to restrain any lapses and counter the argumentative automatisms in the style of the 'slippery slope' [52]. They are very aware that the impression of a downward slide resonates against the traditional fear of the unknown, that is here accompanied by the modern fear of what we could cause amongst ourselves; so - sometimes unfounded - concern is aroused among public opinion.[53]

The same members also believe (since the present opinion is an answer to an interpellation of the Advisory Committee on Bioethics by the political world) that we cannot pass the question as to what place handicaps of genetic origin have in our society in the light of the new possibilities of genetic modification in the germ line, because an argumentation continuum exists between

[49] In the sense of politics based on actual, practical considerations, rather than on moral or ideological considerations.
[50] D. Bourg, "Bioéthique: faut-il avoir peur?", Esprit, May 1991.
[51] Regarding the "manipulation of some people by others" it is interesting from this perspective to return to the extraordinary, irresponsible lack of caution, not to mention the deliberate intent with which soldiers and the population were exposed to genetic risks during the development of nuclear weapons (and during the first accidents with civil nuclear energy in the fifties). Only in 1955, at the Geneva conference on nuclear energy, did physicians and biologists really make a start on research into the consequences of radiation on the living world and in particular on gene mutations. At the conference it was also – finally – proposed to exactly determine to which level of radiation a person may be exposed without the integrity of the human species being affected. (see. J. Gallini. *Cri d'alarme des généticiens*. Le Monde, 17 August 1955).
[52] If this style of argumentation had been applied to organ transplants, the development of this therapy would have been impeded in the sixties.
[53] We will add a sentence by Paul Valéry here: "Just as Progress was idolised, the cursing of progress was idolised; that resulted in two commonplaces."

the two questions. The members do not see this as a false debate, but propose concisely looking at what happens in reality, and what the pertinent basic questions are as possible assistance in making well-considered decisions as regards genetic changes in the germ line that demonstrate respect for the whole population.
Formerly the "old" eugenics concentrated on stimulating the birth of the strongest at the expense of the weakest. Now things clearly go a step further, thanks to the possibilities that technical genetic science offers to avoid the implantation of an embryo that is regarded as defective or as a carrier of a chromosomal abnormality. But the ability to create new genes and consequently new biological functions takes us yet another step further, that can lead to the modification of the nature of the human species.
A simple question then arises: *To actually improve the human species?*
This is an awesome question, that should be preceded by other questions that according to some are relevant, according to others are iconoclastic, and according to yet others archaic: *Where is the limit between what is pathological and what is normal? What is so-called human normality? Is it wise to contemplate a norm for the human species? Who can assume the right to define the norm? Converting the myth of the zero-defect baby with all the required properties into reality, is that really progress?*
Nevertheless, another more political question arises that automatically results from the last questions and from the answers that may or may not be given. *What is the place of the disabled person in our society and how we can speak of <u>enhancement</u> genetic changes in the germ line without – even subconsciously – detracting from the dignity of disabled persons (and the people in their environment), in other words those who often suffer more due to the way in which they are looked down on by society than their actual disability?* The question refers us to either hyperindividualistic or collective egoism, or to the capacity of compassion in the sense of co-living. This is therefore everything but a false debate without a view of reality. What is wrong is the widespread notion that a "genetic defect" and its phenotypical manifestation are by definition social non-values, a catastrophe for the families and a professional failure by the therapist.

Even if there has not yet been a wide debate about the modern eugenistic risk, general prenatal screening is already a reality. Without wanting to take a step back in this evolution (that is highly beneficial to the health of individuals), we must determine that should matters come so far that PGD [54] and prenatal screening [55] of chromosomal anomalies or otherwise would be systematically proposed and even made compulsory, the nature of the medical action would fundamentally change: medical treatment would then no longer be a curative and preventive individual medical approach, but would de facto come under a more or less imperative public health approach.
And because the concept of public health has evolved, we would remind that the public health approach has in principle two objectives: firstly to make the medical care market more efficient and therefore rationalise its operation, and secondly de facto reduce the risk that an illness occurs and therefore anticipate pathological phenomenon. The – medical and financial – risk and the knowledge of that risk are therefore central to the public health approach, and require epidemiological research and public action to reduce that risk.
There are therefore three reasons to transfer the public health approach from the exclusive medical-scientific arena to the political arena.
Firstly the health approach aims at social change: a return to normal by the elimination of a situation considered undesirable (the illness) thanks to a change in the pathogenic human

[54] We must however add that PGD de facto reduces the need for the application of therapeutic germinal gene therapy.
[55] What is the legal framework for PGD and prenatal screening? PGD enables the avoidance of the birth of a child with a genetic abnormality detected in the embryo in vitro by not implanting an embryo that is the carrier of the identified anomaly, and therefore prevents an abortion. The legitimacy of this practice results a contrario – as necessary – from article 5 of the law of 11 May 2003, that only allows the implantation of people with embryos on which research is conducted provided that that research brings a benefit to the embryo itself.
But the law only concerns embryos in vitro and not embryos in utero. If a genetic illness is detected, prenatal screening enables abortion (voluntary pregnancy termination) to take place when "it is established that the child to be born will be suffering from an extremely serious illness that is recognised as incurable at the time of the diagnosis" (art. 2,4° of the law of 3 April 1990 concerning pregnancy termination).

behaviour.[56]
Secondly the public health approach entails the anticipation of the prevention of an illness where the illness must be defined as a public health problem of which the causes are scientifically and/or technically established. This is, however, with the understanding that the conscience of scientists or technical experts is not equal to the public conscience. At this stage we would like to remind of the terrible responsibility of experts in predictive medicine with its constantly more numerous genetic tests. Prediction is indeed a good aspect if it serves as prevention, but it is dangerous if there is an obligation to release the prediction outside the private domain to map the "biological destiny" of a person to be potentially insured.
Thirdly, an action by the authorities in answer to a public health problem (just like any social policy from an authority) is given shape by a redistribution of goods and services for populations defined by the characteristics of the problem to be solved: "*who gets what and how does this happen?"* And to answer the question, a minimum of scientific orthodoxy must be respected by requiring experimental proof that there is a causal connection between a risk factor and an illness (for example smoking and lung cancer, trisomy 21 and mongolism!). But one must also assess the impact of the health care expenses by the statistical or epidemiological improvement of a series of disorders. Such an evaluation of the goods and services subsequently makes it possible to more fairly redistribute the benefits [57] and share the costs, either (ideally) in an incentive form or in a more or less imperative form.

Willingly or unwillingly, with regard to handicaps of genetic origin we must raise the question of whether the gradual transition of public health to a more imperative approach does not involve the risk that in the name of the public health a new eugenics originates, sometimes called "democratic eugenics". This is "*democratic eugenics"* for which the scientific and the political world will have to assume responsibility because they will both have been at its basis: the scientist by discharging him/herself of the ethical aspect of his activity and discarding the social significance of the activity, and the politician by hiding behind the opinion of the scientific expert in a time of changing and increasingly segmented knowledge [58]. It is exactly for this reason that we deliberately cite the example of the connection between smoking and lung cancer besides the example of the connection between trisomy 21 and mongolism. From the analogy it indeed appears how easily one could arrive at the application of "*hygienically correct"* [59] thinking to two totally different situations [60], in the name of the public health. We must therefore fundamentally dare to raise another question: how long will it be before on the one hand chronic disorders that are the consequence of individual or social irresponsibility, such as alcoholism or smoking, and on the other hand constitutionally determined handicaps of the genetically underprivileged, will be systematically mixed and deliberately thrown on the same heap (because this is economically cost-effective and socially desirable)?
Let us continue with our analysis. The health approach can indeed (in the name of certain progress of technical science which one day may cover the possibilities of therapeutic and optimising/enhancement germinal line gene modification) sometimes stealthily apply a certain amount of force. Since the seventies, thanks to the active association of feminism and liberalism the woman has clearly obtained the right to dispose of her own body. That is irrefutable progress. But what is less obvious is any eugenistic excrescence being avoided by putting the responsibility for abortion for medical reason (for example established trisomy) solely with the woman![61,62] The right of the woman to dispose of her own body and in all

[56] What exactly does *"changing the pathogenic human behaviour in the subject that we are concerned with" mean?* Does pathogenic human behaviour in the case of, for example, trisomy 21 consist of the refusal to have a 45-year-old woman tested for the risk of trisomy, or the fact of her becoming pregnant at that age? The implicit risk of a health approach that would assume a more or less imperative definition of pathogenic human behaviour is quite clear.
[57] The question of fairer redistribution of the limited health care resources raises another question: is the public financing of gene therapies a real priority at present, all the more as private financing is becoming increasingly rare?
[58] The politician calls upon the expert because the politician does not have the knowledge; but he nevertheless remains the one who decides, because he will ultimately make the choice… and must therefore take responsibility.
[59] "*Hygiéniquement correct",* an expression used by Pierre Ronsanvallon in analogy of "*politically correct*" in his book *La Nouvelle question sociale – Repenser L'Etat-Providence*, Seuil, 1995.
[60] Two totally different situations, medical and social, behavioural and chronological and toxicological and genetic.
[61] B. Andrieu. *Médecin de son corps,* PUF, Parijs, 1999.

conscience decide to end her pregnancy may obviously not be a subject for discussion. It is very fortunate that the woman today has the right to decide about the quality of the child to be born, and all surveys confirm that 90% of interviewed women would choose abortion in the case of a trisomic foetus. Here also lies the raison d'être for *real genetic counselling* [63]: determining the risk that a foetus is the carrier an anomaly and informing the parents of this. But in this respect it is important to really allow them the freedom to make a choice in all conscience. Otherwise the progress of prenatal diagnosis would no longer be indisputable.

As for "democratic eugenics" things are very different to abortion for medical reasons, because in the name of individual freedom the State could introduce eugenics not in that name by putting the full weight of the choice – and of any associated guilt – with the individual, so with the woman expecting an "abnormal" child. If the woman actually has legal access to the knowledge without economic discrimination because all tests and diagnostic and therapeutic operations have been reimbursed, she could therefore be the tool of "biotechnological progress". Ideally, abortion for medical reasons has the purpose of avoiding serious disorders, and it is a matter discussed at individual level between the physician and patient within an ambiguous legal framework (could this be otherwise?). But in reality the decision is increasingly less often left to the personal ethics of the patient and/or the physician-obstetric. The freedom of choice of the woman is in reality therefore less obvious than we think because it is determined by influential social models, by possible financial considerations, by the family or the general psychological environment, or by an advisor/client relationship that replaces a physician/patient relationship. The decision is gradually moved from the private domain to the public domain as it is under social and shortly also economic pressure.

The circle is nearly complete. We could soon arrive unnoticed from a fear of eugenic totalitarism at "democratic eugenics"; voluntary and well-considered individual private eugenics that secretively transforms into individual eugenics with a compelling nature as a result of collective pressure (and the fear of subsequent stigmatisation).

According to some, this evolution is all in all progress for public health and the quality of life of parents and baby. According to others, this "progress" is only possible at the expense of a scientific and medical failure: trisomy 21 for example is then not included or treated, but one limits oneself to establishing the existence of trisomy 21 before the birth of the child, and proposing the ending of the pregnancy to the woman concerned. A third group goes yet further: "proposing" is according to this group a euphemism [64], because the woman's society increasingly expects an "approach with a sense of public responsibility" to public health. Such an approach would then consist of bringing an end to her pregnancy and, again, in so doing accept the obligate norm reference concerning what responsible parenthood and a public sense of responsibility means! They add that the evolution will proceed all the faster if one organises the disappearance of pathologies of which one does not know the causes, and society does not make the necessary efforts to offer "persons disabled by the genome" and their nearest real possibilities of integration and development.

The arguments of the respective supporters of the three standpoints about the so-called democratic or undemocratic character of new private eugenics (that must however be distinguished from the gruesome totalitarian state activities of former times) cannot shroud the persuasiveness of the prevailing social and cultural standards in our modern societies. Our personal existence is not merely resolvable to our biological individuality and our genetic patrimony, with ultimately the resulting more or less successful phenotypical development. In fact we also exist outside ourselves by our mutual participation in the sign and symbol world of a human society. And what distinguishes human society from animal society is exactly that is based on language, on feeling, on cultural products and presentations and symbolic forms. Just as for the abovementioned risks of democratic eugenics, it somewhat bears witness to *wishful*

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[62] J.-Y. Nau. "L'éradication programmée du mongolism", in *Le Monde*, 13 March 1999.

[63] The term genetic legal adviser would in itself warrant a long digression, particularly as regards its *neutrality claim.* According to some, the neutral genetic advisor is indeed a fiction, invented to free clinical genetics of a very loaded past, and to discharge the physician of pressing ethical tasks with respect to the couple who must ultimately take responsibility for the decision. The physician would then provide the couple with sterile genetic information and serve in carrying out their decision. To which he inevitably gets the question: "*And you doctor, what would you do if you were in our situation?"* That is the question that humanly brings an end to the inhumanity of ethical neutrality. *Lexique des termes ambigus et controversés sur la famille, la vie et les questions éthiques*. Pierre Téqui éditeur, Parijs 2005, pp.137-146.

[64] In such a context they can barely accept that the term *therapeutic abortion* is simply interchangeable with the term *voluntary pregnancy termination.*

thinking to maintain that the decision about this or gene enhancement germinal gene intervention would exclusively be a matter for the parties involved or their family! *Wishful thinking,* , because deliberately closing the eyes to the weight of (past, current or future) conformism and socio-cultural pressure so some subject themselves to the prevailing models of the time, or worse, cannot withstand the *paternalism of the design of the look* of the time. Because our societies are increasingly controlled by the media, public opinion and social mimicry, we do not have to refer to the other imperative force, that of social models, which relating to modern eugenics can push forward while they all have celebrated in fashion, sport, dietetics or language. We may not lose sight of what powerful "pressure to conform" individuals undergo (and often accept). Should new "valorising" genetic standards or hypothetical care for "improvement" of the human species emerge tomorrow, so-called private modern eugenics [65] could also de facto assume an imperative character in the name of the ideology of the fortune of the day, or in the name of new public health demands.

Conclusion
The message in the standpoint of these members is particularly one of caution and solidarity.

IV. 2.3. Standpoint C

Without identifying with doctrinal standpoints relating to germinal gene modification, other members are advocates of a cautious and gradual approach that is receptive to scientific and social progress.

IV. 2.3.1.
At a *scientific level* they observe the growing complexity of the processes that determine the phenotype of an individual on the basis of his/her genotype. The "human genome project" from the nineties that was based on the progress of molecular genetics and the apotheosis of 20th-century genomics has also put the most important concept in this area up for thorough discussion: the concept of the gene that is expressed merely based on the DNA. In the words of F. Jacob: "In the course of time the gene has been assigned too many properties, too many capacities, too much power, and it appears that the role allocated to the gene must be redistributed between different cellular parties. The gene, and so the genome, bear witnesses to the success of reductionism. But seemingly time has come to reverse the trend. It is no longer possible to merely ascribe to the gene all properties once allocated to it. This does not reduce the weight of genetic determinism to which individuals are subjected…»[66].

Today, functional genomics is gaining the upper hand over structural genomics, and scientists assess the width of the gap between genetic information (the genotype) and the biological functions resulting from its expression and leading to the phenotype.

Accordingly, an increasing number of contemporary biologists are putting the emphasis on molecular "cross-talk" dialogue, "check-points", metabolic, genetic, epigenetic, postgenomic networks.

Account is taken of *the mechanisms responsible for the polyvalence of the genes* [67] (the same gene can play a role with different phenotypes) [68] and with the *interactivity of their products with the expression of the phenotype.* Removal of alleles related to diseases would consequently be able to have unexpected consequences: by remedying certain deficiencies we could induce

[65] Imperative private modern eugenics besides imperative democratic public health eugenics.
[66] Jacob F., *Introduction* in Fox Keller E., "Le siècle du gène", Gallimard, 2004
[67] Roubertoux P.. L., "Existe-t-il des gènes du comportement?", Odile Jacob, 2004
[68] Account is in particular taken of:
- the multiplicity of the alleles of a gene;
- alternative splicing, of which the general occurrence among humans is now acknowledged;
- the interaction between the products of the genes (the epistasy);
- the dialogue between the nuclear genes and the mitochondrial genes. The expression of the coding gene of the protein amyloid that with Alzheimer deposits in the brain then diverges depending on the information contained in the mitochondrial genome;
- the imprinting of the genome: the fact that the expression of a gene differs depending on if it originates from the father or the mother;
- the modulation of the effects of the products of a gene by internal or external ambient factors.

others. The current development of functional genomics requires a greater sense of responsibility when using genetic instruments for curative or enhancement purposes. This can entail the inadequateness of eugenics that is based on germinal line gene modification.

IV. 2.3.2.
As regards private eugenics these members in the first instance consider it necessary to clarify what genetic changes in the germ line could result in. Here two types of changes are considered. The first type concerns the "correction" of monogenic genetic disorders such as mucoviscidosis, myopathy of Duchenne, chorea of Huntington. The second type concerns genetic modification of germ line cells for the purposes of "optimisation".

As far as monogenic genetic illnesses are concerned, information infers that IVF in combination with preimplantation diagnostics (PGD) strongly reduces the risk of the birth of a child with such a hereditary illness in families where the risk is real. The need for gene therapy on cells of the germ line is as a result very limited. Despite the possibilities of PGD, however, a small number of children will still be born with a hereditary illness. A mutation can indeed occur during the production of the cells of the germ line or in the course of the very first development stages. The children should be able to be helped with the therapeutic genetic modification of somatic cells (see chapter III of this opinion).

Enhancement genetic modification in the germ line on its part would, according to literature, be particularly aimed at sporting, intellectual, cognitive, emotional, behaviour-bound and psychological performance (access to happiness). These parameters do not only depend on the genome, but mainly on epigenetic processes that function in extremely complex and particularly plastic networks. This also concerns factors loaded with individual and social values, with a strong cultural component.
Assumptions about controlling physical, spiritual or behavioural performance in humans by gene manipulation in the germ line are currently based on pure conjecture. There is for that matter another transgenerational aspect: genetic modification would be forced upon certain individuals of the offspring whose nuclear and mitochondrial environment and epigenetic cell environment is still unknown, and that would have unpredictable consequences on the resulting phenotype, without account being able to be taken of the requirements and environment with which the offspring will be confronted.

As regards collective eugenics the benefit of enhancement genetic modification in the germ line is yet more strongly disputable, because the consequences of such modification being carried out on an individual scale would be diluted during the consecutive crossings [69].

[69] If, for example, we take a random sample of the Belgian population of 500,000 inhabitants within which a couple has decided have a child who in the initial stage of his/her development (zygote) received a specific gene that is considered to develop a specific ability. All cells of the foetus, both the somatic cells and the germ line cells, will carry the new gene. The child will possess the required property thanks to the activity of the gene that has its expression in the somatic cells. But a quick calculation based on the elementary genetics of Mendel shows that the share of individuals with the optimised phenotype (this means with the new characteristic) in the offspring will reduce in time.
Let us assume that a phenotype is determined by gene a. The non-modified persons have 2 copies of gene a in each cell: one of paternal origin and one of maternal origin; we can say that the persons are a/a.
We will call the gene that determines the desired phenotype gene B. The person receiving gene B has therefore obtained one gene B and one gene a; we can call the person B/a. Because gene B is dominant, the person will possess the required phenotype.
The average number of children per couple in Belgium amounts to 1.2.
Let us assume that the modification results in a selection advantage and that person B/a has 2 children. Because her partner is not modified (and therefore is a/a), each child of that couple has 1 chance in 2 of having received gene B. In other words, the parent with the required phenotype will have passed on the characteristic to half the offspring.
Child B/a will in turn pass gene B to half the offspring.
Grandchild B/a with the required phenotype will still only represent a quarter of the offspring of the progenitor.
Gene B would therefore have to be introduced 5,000 times in generation 0 in order to have 1% of the population possess the required phenotype after 4 generations (5,000 out of 500,000 persons); this would therefore take approximately 100 years, despite the selection advantage of gene B.

According to the members, the modification of germ line cells will only have an impact on society if applied en masse (positive state eugenics), something that is impermissible and unrealistic.

Finally, as regards the relationship between genotype and phenotype, the members emphasise the specific individuality of the human relating to mental epigenesis, which according to them falls under bio-ethics.

Exceptions aside, human individuals , in the infinite diversity of their genomes, as regards their behaviour, are grosso modo tributary to physical and symbolic conditioning at very high level.

Mental development, an important property linked to language, graphic image-forming and virtualised behaviour, is based on epigenetic foundations. These are to a large extent influenced by ambient factors dependent on psychosomatic perception, affective field, education and culture.

In the context of recent advances, the fast and somewhat limitless development of the omnipresent media leads to a modelling of the spirits, bodies and desires through a virtual world of images of which the predominance thoroughly disturbs the perspectives of therapy or improvement.

This does not concern a potential “slippery slope evolution” as mentioned relating to gene therapy, but unreducible flows of which the consequences are baleful because they impede the critical resistance of individuals.

For reasons of pragmatic effectiveness, genetic ethics must accordingly go hand in hand with epigenetic ethics imposed by the technical sciences of communication.

The real bio-ethical debate in its current, pluralistic, multidisciplinary and multisituational complexity, may certainly not escape the modern epigenetic influences that subjugate the mental image world and therefore form a threat to the autonomy of imagination, the freedom of thought, reasoning, belief, criticism and expression.

Ethical reflection finds itself between a real transgenesis based on increasingly more complex developments, and a virtual transgenesis that gives the prospect of notional benefaction.

An open, cautious and gradual approach that takes into account the interaction between thought, science and society, is a simultaneously rational and reasonable approach to the social debate on bio-ethical questions.

Conclusion

The members are not in principle against genetic modification in the germ line with a therapeutic purpose, even if they see this as unrealistic in view of the current development of knowledge. They nevertheless believe that this area does not call for priority in applied research, medicine or specific legislation. Fundamental research in this rapidly changing sector should be continued.

CHAPTER V. CONCLUSIONS AND RECOMMENDATIONS

The Advisory Committee on Bioethics has expanded its considerations on the "gene therapy" concept by discussing all modifications of the genome, with both a curative purpose and enhancing purpose. The Committee wishes to hereby answer the request for opinion from the Senate in which reference is made to pathological and non-pathological genetic characteristics.

As regards eugenics, the members of the Committee are of the opinion that the private selection of eugenics related to the use of prenatal diagnosis (PD) or pre-implantation diagnosis (PGD) is in principle acceptable, providing that one applies certain standards in accordance with the severity of the illness (or abnormality). The informed consent of the parents (or the mother) must also be obtained, and there must be an adequate framework as regards follow-up and the provision of information. The ethical considerations raised by these techniques will be discussed in a separate report.
This report therefore concerns the therapeutic or enhancement/optimising modification of the somatic or germinal genome.

V. 1. Therapeutic somatic gene modification

Therapeutic gene modification has up to the present barely seen successful application. Clinical applications and experience in this matter are insufficient to be able to evaluate its concrete perspectives.
The most important clinical application concerns immune-deficient children in a sterile environment. The treatment was recently suspended for the second time because of side effects, and is currently being further investigated.
The expectations of somatic gene therapy are, however, great, so great that research is being actively continued.

For ethical considerations relating to the clinical application of this technique, the Committee refers to its report no. 13 of 9 July 2001 concerning experiments with persons.
The Committee is of the opinion that its ethical evaluation is also applicable to therapeutic gene therapy.
More specifically, the Committee considers it important to ensure the safety and efficiency of each clinical application by a far-reaching analysis of the advantages on the one hand, and of any risks to the patient on the other.
The principle of caution should be applied with the choice of transport vector and the introduction of the repair gene. One will identify any side-effects of the treatment with care.

Therapeutic, somatic gene modification is not distinguishable from other therapeutic innovations or other scientific research in medicine. The Committee has presented ethical arguments in this respect in its report no. 24 of 13 October 2003 concerning human stem cells and therapeutic cloning.

It is to be noted that cell therapy (stem cells) is enjoying increasing interest beside gene therapy.

V. 2. Enhancement/Optimising somatic gene modification

The Committee observes that enhancement/optimising gene modification for non-pathological properties is at present still only a thing of the future without scientifically proven applications.
One chiefly wants to improve the physical or mental performance of the person. Because the genetic determinism of these characteristics is very complex, applications in the short term are highly improbable.
The general ethical considerations in sub V 1 are also applicable to this situation.
A social debate is desirable to evaluate the feasibility, specificity and opportunities of genetic modification for enhancement. One should also devote great attention to the social and psychological consequences of any applications.

V. 3. Genetic modification of germ cells

In principle the Advisory Committee on Bioethics suggests a global, attendant and open vision in this field, and we invite alertness to the technical sciences and their applications.
The Committee observes that at the current stage of research the possibilities of recombination within the germinal genome are largely speculative, and offer no explicit and controlled clinical applications.
Without in principle being against scientific research on the subject, the Committee has developed three visions on the question of genetic modification of the germ cell line. Here one makes a clear distinction particularly as regards feasibility based on current scientific knowledge, as regards priorities at conceptual and social level, and as regards opportunities in the management of medical research and clinical applications.

Standpoint A

Certain members of the Advisory Committee on Bioethics are against a prohibition of recombinant DNA techniques for the human germ cell line. They are of the opinion that when these techniques have been refined, it must be decided case by case about the acceptability of the recombinant DNA technology, depending on the context and the characteristics of the intended experiments. There is no reason at all to assume in advance that at some time the recombination of the germinal genome among humans will not be able to take place in circumstances with a minimum risk.

These members dispute the idea that individuals provided with improved physical and cognitive capabilities can only be morally inferior to “natural people”. These modified people could on the contrary have a ”broader” conscience, and accordingly show greater sensitivity to rightfulness and higher moral values.

They are also of the opinion that if a reliable and relatively simple genetic modification technique is available, the consequences of not taking action are just as great as taking any action.

These members are of the opinion that gene therapy will be able to contribute to the reduction of certain inequalities between individuals. In the context of the future application of genetic recombination among people, a child may ask him/herself at a certain time why he does not have better genes such as a friend whose parents have not refused optimisation (memory, intelligence, health) in the name of respect for “human nature” and the genetic lottery. These members are certain that one may not underestimate the advantages a person could gain from such experiments.

These members are aware of the fact that the phenotype of a person is the result of interaction between the genome and the internal environment (cellular and somatic) and the external environment (the physical, biological and social-cultural environment) during a person's development. They do emphasise, however, that in an equivalent and stable environment an important part of interindividual variation can be attributed to genetic factors.

These members are of the opinion that any reasoning based on all or nothing must be avoided. This reasoning gives support to people who are radically against the modification of the germinal genome in humans. Regulations that do not evolve and are rigid with an absolute and final prohibition of positive eugenics and a very restrictive list for negative eugenics can only push research to become clandestine and applications to join the black market. A prohibition would indeed not prevent technologies developing when highly desired.
If one on the other hand accepts that genetic modification is not necessarily a bad thing, the real but very difficult questions arise: those concerning alertness with respect to research into the modification of the human genome remain, particularly where this concerns distributive justice and equal access to these possibilities. One must have the courage to tackle these political and philosophical questions, without immediately rejecting the hypothesis that in the nearish future genetic recombination of a person can take place. One would better regulate freedom of research and development, and under strict, public and reviewable procedures, permit experiments that some wish to prohibit in a general, absolute and final manner.

Standpoint B

Other members are of the opinion that the question must again be raised in a context of scientific and operational uncertainty.
For these members the ethical discussions about somatic or germinal gene modification should concentrate on access to new, therapeutic therapies, the transparency of the research and the psychosocial manipulation that may be applicable.
These members also raise the inescapable problem of the place of a genetic disability in our society, and raise the concrete question as to who has the right to define what "a normal person" is. Or as a consequence of this, how one can actually define "improvement" when talking about genetic modification.
They ask themselves about the opportunity to steer medicine in the direction of enhancement/optimising practices for non-pathological disorders, and point out the possible dangers of the interference of certain parties in public health relating to individual genetic profiles.
They are of the opinion that the sector of public health should once again leave the exclusive medical-scientific circuit, and make its entry in the political and social arena. It is indeed naive to deny the possibility of a compelling form of "democratic eugenics" when science forgets its ethical and social significance and the political hides behind scientific expertise that is becoming increasingly segmented.
They point out the risk of disguised eugenics by putting all responsibility for ethical choices at individual level, either in a context of instrumentalising the new social standards, in a context of pressure due to social-cultural conformism, or even in name of new regulations in public health. The human community cannot be reduced to genetic individualism and expression of phenotype. It is also language, feeling, exchange of symbolic presentations and right to differ.

As far as these members are concerned, a simultaneously strict, serene and evolutive, deontological and legal environment for the techniques of genetic modification must enable the impeding of potential derailments. As regards the genetic modification of humans, these members wish to send out a message of caution.

Standpoint C

Other members, without wishing to associate themselves with doctrinal visions in the field of germinal gene modification, advocate cautious and open progressiveness with respect to scientific and social progress, but do acknowledge the risks and advantages involved.
They observe that scientific progress in the field of the structure and functions of biosystems reveals the ever-increasing complexity of the processes which connect the genotype and the phenotype.
At present, the result is that the effects caused by genetic modification and their impact on the different phases of the development of the person cannot be predicted.
These members ask themselves questions concerning the applicability of enhancement genetic modification of which the parameters mainly depend on hypercomplex epigenetic processes that are related to characteristics with an important cultural component.
The assumptions about the controlled and responsible modification of physical, mental or behavioural capacities by the genetic modification of the germ cell line are, as yet, purely hypothetical.
Furthermore, such modifications may interfere with the autonomy of the offspring of treated people.
Finally, these members draw attention to the epigenetic nature of important parts of the person at mental and behavioural level, and the impact of conditioning by the social environment.
Hence, for reasons of pragmatic efficiency, genetic ethics must be accompanied by epigenetic ethical consideration that evolves in a changing context.
They are accordingly of the opinion that as a result, one must take into account the interactions between ideas, science and society, and that this represents both a rational and reasonable approach from the government at bioethical level.
To sum up, to these members germinal genetic modification (in an "improving" aspect) currently seems unreal and forms no priority, not for applied research, medicine or specific legislation. However, science should continue its fundamental research in this sector in rapid evolution.

The opinion was prepared by select commission 2001/1 - 2005 – consisting of *:

Joint chairpersons	Joint reporters	Members	Member of the Bureau
E. Vermeersch	E. Vermeersch	M. Baum	J.-A. Stiennon
L. Michel	L. Michel	E. Eggermont	
	J.-N. Missa	E. Heinen	
		G. Verdonk	
		R. Winkler	

Member of the secretariat
M. Bosson

Experts interviewed (2004)
- Alain Fischer, Supervisor of the paediatric department for immunology and haematology at the Hôpital Necker in Paris, professor at university Paris V, Director of the INSERM department for Research concerning the normal and pathological development of the immune system
- Inge Liebaers, Geneticist, Director of the Centre of Medical Genetics of the AZ-VUB
- Th. Velu, Professor, Doctor, Head Clinician hospital medical oncology, Erasmushospital, ULB

Permanent experts (2005) *:
- L. Cassiers (2005)
- J. Dalcq-Depoorter (2005)

Invited member:
- M.-J. Abramowicz, Deputy Head Clinician of the genetics department, Erasmushospital, ULB

The working documents of the select commission 2001/1-2004 and 2001/1-2005 – the question, personal contributions of the members, minutes of the meetings and documents consulted – are kept on file at the Committee's documentation Centre where they are available to be consulted and copied.

This opinion is available to be consulted at www.health.belgium.be/bioeth

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* The members of the select commission 2001/1-2004 were mentioned in the capacity of members or permanent experts of the select commission 2001/1-2005.