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## **STEERING COMMITTEE ON BIOETHICS (CDBI)**

### **WORKING PARTY ON HUMAN GENETICS (CDBI-CO-GT4)**

Report prepared by Sandrine Sabatier (Doctor of Molecular genetics), at the request of the secretariat of the Steering Committee on Bioethics, to be used as a working document during the exploratory meeting of the Working party on Human Genetics. (The opinions contained in this report are personal and do not necessarily reflect a stance by the Council of Europe).

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# Chapter I

## GENETICS AND BIOMEDICINE

### (Medical applications of genetics)

#### **Introduction:** (Classification of so-called "genetic" diseases)

Before tackling the subjects and principles which might be included in the additional protocol on genetics, it seemed important to us to reiterate the classification of diseases established by medical genetics. It is vital **to identify the types of diseases which are or will be the subject of screening, diagnoses and therapy.**

#### **1. DISEASES LINKED TO CHROMOSOMAL ABNORMALITIES**

These result from the addition or loss (deletion) of entire chromosomes or fragments of chromosomes (anomalies of number or anomalies of structure). Since each chromosome carries tens of thousands of genes, the clinical symptoms associated with chromosomal abnormalities are often impressive (delayed growth, mental backwardness, etc). The loss or addition of entire chromosomes other than sex chromosomes may often be incompatible with life (it is one of the main causes of aborted pregnancies and miscarriages)<sup>1</sup>. The frequency of these chromosomal anomalies, mostly resulting from the failure of the chromosomes to separate during meiosis\*, increases with the age of the mother<sup>2</sup>.

*Some examples: Down's syndrome resulting from trisomy 21 (affects one birth in 800). It is characterised by delayed growth and mental retardation of varying severity. Trisomy 13 affects one birth in 15 000 and is also characterised by mental retardation, together with a failure of the frontal cortex to develop, often proving fatal to babies. In Klinefelter's syndrome, affecting one newborn boy in a thousand, the occurrence of testicular insufficiency is observed. Fragile X syndrome affects one male birth in 2 000 and 0.4 female births in 2000 (it is characterised by severe mental retardation). There are numerous other examples.<sup>3</sup>*

#### **2. MONOGENIC DISEASES**

(Also called Mendelian diseases as they are transmitted in a Mendelian fashion\*). They result from the impairment (mutation) of a single gene. These diseases are transmissible to descendants and may be classified into three sub-groups:

**\*Dominant autosomal diseases.** They result from the impairment of a gene carried by one of the 22 autosomal pairs\*, and produce a clinical phenotype\* visible if only one of the two alleles\* of the same gene is impaired (transmission by one of the two parents). These diseases include various genetic pathologies with symptoms of varying severity.

It should be noted, for a better understanding of the risk of transmission of this type of disease, that there are cases of two apparently healthy parents having affected offspring. This situation can only imply that one of the parents is a carrier and reflects the concept of incomplete penetrance\*. Penetrance is a quantitative factor, defined by the proportion of those people who are necessarily carriers (heterozygous\* in respect of the mutated allele) who manifest symptoms of the disease. For a given disease, the establishment of 80% penetrance means that an individual carrier of the mutated allele has an 80% probability of developing the disease (onset of symptoms specific to the disease). In other words, the risk for parents one of whom is the heterozygous carrier of a mutated gene of having an affected child bound to develop the disease can be calculated according to the laws of Mendelian transmission but also bearing in mind the penetrance of the disease<sup>4</sup>.

Examples: *Familial hypercholesterolaemia, colic polyposis (development of polyps\* in the colon), renal polykystosis, Huntington's chorea (the clinical symptoms of this disease are linked to neuronal degeneration), neurofibromatosis (benign tumours of the soft tissues, often developing along the nervous system), etc.*

**\*Recessive autosomal diseases.** The clinical phenotype of these diseases only appears if both alleles of the gene in question are impaired (homozygous\* individual) (this presupposes that both parents of an affected individual are carriers of the impaired gene).

The incidence of these diseases will, therefore, depend on the frequency of the mutated allele in a given community. The rarer a mutated allele in a community, the lower the probability of a union between two individual carriers of the same mutated allele and the more sporadic the cases of affected individuals. In practice, union between related subjects is more frequently found among the parents of children carrying rare recessive autosomal diseases. There are, however, communities where the frequency of mutated alleles leading to a recessive autosomal disease is particularly high even though the frequency of consanguineous marriages may be no greater than in a normal community. *This is true in the case of mucoviscidosis or cystic fibrosis (the symptoms of which are thick secretions in the pancreas and bronchi) in white populations and of  $\alpha$ -thalassaemia (a cause of severe anaemia) in Cyprus and Sardinia.*

Other examples: *Tays-Sachs disease (a degenerative neurological paediatric disease), drepanocytosis (characterised by chronic anaemia due to the destruction of red blood-cells), etc.*

**\*Diseases linked to the sex chromosomes,** especially the X chromosome (since the Y chromosome carries only a few genes, few diseases are linked to it). These diseases result from the impairment of genes carried by these chromosomes.

One of the special features of heredity linked to the X chromosome is that the male carriers of a mutated gene are invariably affected whereas the same is not true of women who are heterozygous as far as the mutation is concerned (ie with only one chromosome carrying an impaired gene). Among these women, a mutation of a gene situated on the X chromosome does not always have a clinical expression since, during development, one of the two X chromosomes is permanently deactivated at random<sup>5</sup>. These diseases are seldom expressed in heterozygous women; they are known as X-linked recessive diseases.

Examples: *Haemophilia (due to a defect in a factor essential for clotting), Duchenne's muscular dystrophy (characterised by a premature onset of muscular weakness), etc.*

Of the 4 000 phenotypes whose means of transmission is compatible with this Mendelian heredity (monogenic diseases), more than half are dominant autosomal, 36% recessive autosomal and only 10% X-chromosome linked.

### 3. POLYGENIC AND MULTIFACTORIAL DISEASES

Unlike monogenic diseases, polygenic or multifactorial diseases do not follow a simple Mendelian method of transmission since the fact that individuals inherit a so-called "predisposing" gene does not mean that they will necessarily develop the disease. This genetic predisposition brings into play a cumulative effect of genetic variations affecting different genes which individually have only a slight (clinical) effect on the phenotype. We define as "polygenic" those traits or diseases resulting from the impact of numerous genes (each with little impact on the phenotype) and as "multifactorial" the traits resulting from the interaction of numerous environmental factors with several genes.

These diseases are the most frequent and also the least understood. Epidemiological studies carried out for more than 20 years have made it possible to put forward a large number of arguments in favour of the involvement of genetic factors. A genetic tendency threshold has also been established (traced back by family history) above which a certain proportion of individuals will develop the disease especially if they are exposed to environmental triggering factors.

Examples of polygenic diseases: *Diabetes mellitus, high blood pressure, schizophrenia, congenital malformations such as harelip, most forms of heart defects, etc.*

Belonging to this type of multifactorial disease but forming a separate sub-group **are somatic-cell genetic diseases**; unlike the previous three categories, in which the genetic anomaly can be found in the DNA of all of the organism's cells, including the germ cells (spermatozoa and oocytes) and may be transmitted to the following generations, these diseases only occur in specific somatic cells. Although they do not obey the laws of Mendelian transmission, these diseases are genetically influenced. *Most cancers can be classified in this category of disease.*

#### 4. MITOCHONDRIAL DISEASES

In certain human diseases, there are a number of arguments in favour of maternal transmission; this is compatible with anomalies of the mitochondrial genome\*. However, whereas the anomalies in mitochondrial DNA are hereditary, they also often appear spontaneously. The accumulation of these mutations might offer some explanation as to why people born with mitochondrial DNA mutations take so long to develop diseases and, once affected, their condition deteriorates so slowly.

NB The risk of transmission of diseases of the mitochondrial genome is difficult to estimate. Since the distribution of mitochondria occurring when cells divide is haphazard, the different oocytes (germ cells) in female carriers of mutations frequently contain variable proportions of mutated mitochondrial DNA. Children born from the same woman may, therefore, inherit a different number of mutated mitochondria and, consequently, develop symptoms of varying type and severity<sup>6,7</sup>.

Examples: *Alzheimer's disease (the gradual loss of cognitive capacities), Leigh's syndrome (the progressive loss of motor and verbal capacities), Leder's disease (characterised by temporary or permanent blindness), mitochondrial myopathy (deterioration of the muscles), etc.*

#### 5. DISEASES INVOLVING INFECTIOUS AGENTS

Although these diseases are qualified as "non-genetic", we felt it important to mention them since the development of some of them may be influenced by genetic factors. Progress made in genetics (in particular gene mapping) has revealed the genes involved in the resistance or sensitivity of human beings to certain infectious diseases and a number of research teams are currently working on the identification of such genes.

Examples: *In cases of infection by HIV-1 it has recently been demonstrated that people who are homozygous in respect of the mutation of an immune system gene (CCR5 gene coding for a membranous protein) are particularly resistant to infection by the M-tropic HIV-1 layer (layer infecting macrophages and the cause of primary infection in individuals)<sup>8,9</sup>. We could also mention a new form of infectious disease, Creutzfeld-Jakob disease, for which it has been demonstrated that the presence of a polymorphism in the gene coding for the normal Prp prion protein, when observed in the homozygous state, seems to influence the change of a normal Prp protein into the resistant Prp protein conformation which constitutes the infectious form<sup>10</sup>.*

# I. Genetic screening and diagnoses

## I-1. COMMUNITY SCREENING AND GENETICS

### - Genetics of evolution (study of human genetic polymorphism\*)

The aim here is to study genetic variations in given communities and, in particular, the pertinent aspects of the structure of those communities and the geographic variability of DNA sequences. A study is therefore made of the genetic make-up (as opposed to the study of manifestations of genes) of a community under the effect of evolutionary forces characterised by migration, marriages, population drift (random fluctuations linked to the demographic size of communities), etc.

=> These studies on genetic diversity therefore entail taking **samples** (blood, hair, saliva, etc) from a certain number of pre-selected communities.

This screening, focused on the search for polymorphism, is **worthwhile** in that it helps us to understand human history. Although this screening seems to be of greater scientific than medical interest, it should not be ruled out that these studies might help to improve our understanding of diseases with a multifactorial origin (when the communities studied come from different environmental contexts) or offer new data about the existence of genes that are resistant to certain diseases.

### Issues raised by this type of screening:

\***The main problem concerns the choice of communities which are or will be the subject of studies** (as there is a risk that communities might be stigmatised). We can recall the "Human Genome Diversity Project" (HGDP or "HUGO") for which it initially was planned to collect samples in isolated communities. Representatives of indigenous groups were alarmed, fearing that the information collected might strengthen the ostracism of which those groups were already victim<sup>11</sup>. The Mataatua Declaration on the Cultural and Intellectual Property Rights of Indigenous Peoples, adopted in June 1993, included a call to halt the HGDP project.

=> Researchers involved in such programmes should therefore **respect human rights obligations** and show "universal respect for, and observance of, human rights and fundamental freedoms for all without distinction as to race, sex, language or religion" (Article 55(c) of the United Nations Charter).

=> They should also respect the right to self-determination of particular cultural groups, which means that **projects must comply with the standards observed by the culture in which the research is being or is to be carried out.**

=> Ought they not also to be committed to not using any findings likely to be detrimental to the community?



\* This problem, linked to the targeting of particular communities, poses the question of the need for specialised committees entrusted (Chapter III) with authorising screening programmes. It would seem important to ensure:

=> that projects are not aimed at excluding a particular group.

=> that the planned sampling procedures conform to the cultural standards of the community in question.

=> when programmes are being presented, that details should possibly be given about the type of genetic analyses planned (testing for which genes and/or forms of polymorphism).

\* Given the anxiety aroused by these community genetics projects, should **these screening programmes not be conducted as part of a broader approach involving other disciplines?** The study of human diversity in a comprehensive cultural and biological programme (eg the "Expedición humana" project carried out in Colombia) could possibly allay fears of genetic reductionism.

\* There is also the question as to whether the community being screened should enjoy a **right to be informed of the results**. Given that the people do not benefit directly and immediately from these research programmes, we might reply that informing so many people would be a very cumbersome procedure. However, in view of the anxieties aroused, it would seem necessary to treat the communities as working partners and not as merely the study subject. **Should information not therefore be given to the legal representatives of the community in question rather than to individuals?**

\* **The question of the consent of the people being screened** will be raised in Chapter III.

### **Medical genetics (epidemiological studies):**

Mass genetic screening is also carried out on communities during epidemiological studies. It includes:

\* studying the relationship between the genetic and environmental factors involved in triggering genetic diseases. These studies may improve understanding of genetic predisposition and help us to grasp the causes of multifactorial diseases.

\* identifying the genetic factors responsible for resistance or sensitivity to infectious diseases.

\* identifying high-risk communities with a high percentage of mutated alleles for a given gene.

=> Some of this screening has been carried out on anonymous samples kept in blood banks but mostly it uses samples taken from individuals selected among target communities.

This type of screening is **worthwhile** for many reasons:

\*Studying a large sample of individuals will undoubtedly make it possible to find out how the additive or interactive effects of several genes predispose people to certain diseases which only manifest themselves in the presence of specific environmental factors, and will open the way to preventive treatment entailing action to deal with extraneous triggering factors. These treatments should, therefore, be directed as a priority at the most vulnerable subjects.

\*Revealing genes causing resistance or sensitivity to infectious diseases raises high hopes for the treatment of those diseases (by somatic gene therapy). *It is, after all, the comparative analysis of the genotype of more than 2,000 people which revealed the CCR5 gene mutation which seems to protect people from HIV-1 infection<sup>8,9</sup>.*

\*Identifying high-risk communities makes it possible, by studying the means of transmission of the disease (dominant or recessive autosomal etc), to assess the risk of the onset of genetic diseases and start prevention and information programmes designed to reduce the numbers of births of affected children. *It is thanks to such studies that a prevention programme was set up in Cyprus, where the number of healthy individual carriers of  $\alpha$ -thalassaemia posed a genuine public health problem. One Cypriot in 7 was a carrier of the abnormal gene, which suggested that one newborn child in 158 might be homozygous in respect of the gene in question and therefore suffer from the disease<sup>12</sup>. This programme proved effective since the number of births of affected individuals dropped from 53 in 1974 to 0 in 1989<sup>13</sup>.*

### **Questions raised by this screening:**

\*Since most of these screening programmes reveal high-risk individuals and communities, it is important **to ensure that they are not the target of discrimination**. Two main considerations arise.

=> First of all, the particularly frequent occurrence of genetic diseases in certain communities should be ascribed to regional or ecological causes rather than **be seen as an ethnic or racial trait**.

=> Furthermore, it must be pointed out that, at present, the genetic predisposition of certain individuals **is essentially a matter of guess-work** and that individuals are not certain to develop the disease in question.

\*The main question raised by these programmes is that of knowing **what types of screening may be authorised**. To reply, several factors should be taken into consideration:

=> The disease being tested for. **Should a screening programme be authorised essentially in cases where the severity of the disease in question justifies it?** It would seem difficult to offer a general rule in answer to this question. It becomes easier, however, if we consider both the disease AND the target community. The question then becomes: **is it legitimate to test for this disease in that community?**

*(Example: The search for genes resisting infection by the HIV virus has consisted of a testing programme carried out in high-risk communities such as homosexuals and drug addicts. The choice of these communities could be justified since they were particularly affected by the disease. But testing for diseases less frequent in those communities would not have been so easily justified).*

=> The post-screening programme: These types of screening should only be permitted if, when the programme is being implemented, tests exist that make it possible to diagnose the disease in question among individuals identified as high-risk. That also implies that prevention, information or even therapy procedures should be planned to follow up the screening.

**\*Preferably, these broad screening programmes should be brought before an ethical committee,** entrusted with authorising programmes, after determining the aim of the study, the legitimacy of the choice of target community, the planned sampling procedures, etc.(Chapter III)

\*As far as **informing the persons concerned of the result of the screening is concerned,** this becomes necessary once preventive or therapeutic measures can be envisaged. But should it also be a requirement when that is not the case?

*(Example: epidemiologic studies have made it possible to demonstrate that the frequency of individuals with an XYY aneuploidy\* is 1 in 1,000 live births and this anomaly seems to be linked to pathological social behaviour<sup>14</sup>. Should parents therefore be told of the nature of these anomalies since they are as important emotionally as the XYY situation?)*

\*When these programmes are being implemented, it might be expedient **to seek the consent of the individuals being screened** (see Chapter III).

## **I-2. PRENUPTIAL GENETIC DIAGNOSIS**

This type of diagnosis is generally used in communities where a high frequency of mutation for a given gene has been established and in high risk families (frequent occurrence of a genetic disease in previous generations) (example: thalassaemia in Cyprus).

Estimating the risk of having an affected child is of interest in that, when the risk is too high, recourse to prenatal diagnosis or medically-assisted procreation techniques can then be considered. This risk might be effectively estimated in terms of the means of transmission of the disease.

=> This screening consists (using blood samples from both partners) in searching for mutations in the genes known to be responsible for serious diseases.

**Questions raised:**

\* The main question raised by prenatal diagnosis is **knowing whether or not it should be made compulsory**. For the sake of human rights and personal freedom, it would seem improper to make it compulsory.

But what if the disease being tested for is a source of serious public health problems?

\* Furthermore, given the implications of this type of screening, **it should only be authorised for clearly identified monogenic diseases or at least those for which the risk may be calculated with precision.**

**This risk must also be real.** Our current knowledge of multifactorial diseases is still too poor for us to be able seriously to estimate the risk of transmission (we cannot, however, rule out that it might well be possible to do so in the future).

\* This screening should be **recommended in particular for genetic diseases having no effective treatment** that enables affected individuals to live normally. (It might be necessary to consider in addition cases of diseases for which the existing treatment is so costly as to pose serious public expenditure problems, or where the treatment involves heavy constraints for the patient).

Most diagnoses refer to recessive monogenic diseases (ie most of the parents are healthy carriers). **What, on the other hand, should be recommended for serious diseases whose onset is delayed, whose transmission is dominant and for no treatment exists?**

*(If the Huntington's chorea gene is detected in one of the parents, it would effectively demonstrate that the individual is affected!)*

\* **Recourse to this type of diagnosis should not interfere with people's right to procreate**, which presupposes that parents should be allowed freedom of choice, regardless of the screening result.

\* **The consent** of the individuals being screened should be required.

### I-3. PRE-ICSI DIAGNOSIS

Since 1992 one of the techniques in use for remedying certain forms of male sterility consists of an intracytoplasmic sperm injection (ie into the ovocyte) (ICSI). Yet a recent study showed that its use runs the risk - apparently a high one - of transmitting genetic impairments to descendants. Analysis of the karyotype\* of 85 men consulting a doctor with a view to ICSI revealed that 8.8% of them were the carriers of a chromosomal defect, ie ten times the norm<sup>15,16</sup>. We should also point out, however, that this study concerned a limited number of subjects and would therefore require a further-reaching, broader-based analysis.

#### Questions raised:

\*In view of the growing use of this technique (in France, between 1992 and 1995 the number of attempts rose from 59 to more than 7,000) and given the risks of transmitting genetic mutations to descendants (14% of the men studied were the carriers of a mutation of the mucoviscidosis (cystic fibrosis) gene), **genetic screening ought to be proposed to men wishing to benefit from this technique**. This type of screening would enable the couples involved to take their decision in full knowledge of the facts and, if necessary, resort to prenatal screening later on.

\*When it takes place, this pre-ICSI screening should meet the ethical requirements for prenuptial testing referred to earlier (paragraph I-2.). There is, however, a specific issue at stake. In the case of a diagnosis revealing a genetic anomaly for which a treatment is available, **should the technique still be authorised if the parents so desire**, or should they be recommended instead to opt for artificial insemination by donor (AID)?

### I-4. PRE-IMPLANTATION DIAGNOSIS

This is a biological diagnosis carried out on cells taken from the *in vitro* embryo resulting from medically assisted procreation (*in vitro* fertilisation or IVF). Couples asking to be screened usually do so in the knowledge that they are the carriers of a serious genetic disease.

#### Ethical questions:

\*To avoid any attempt at unwarranted selection of individuals, performance of this diagnosis should be authorised exceptionally under certain conditions:

- This diagnosis should only be allowed **if both parents are positively identified as carriers of a genetic defect which may lead to a disease** if it is transmitted by one or both parents.
- **It should be possible to estimate the risk of transmission** of the mutated gene accurately, **and it must be real**.

- The sampling technique enabling the testing to be carried out **must not put the embryo at risk** (cf protocol on protection of the embryo and human foetus).

\*Concerning **embryo sexing** or selection on the grounds of sex, it should only be authorised if the parents are the carriers of a so-called "sex chromosome linked" disease. This means that **it should be carried out only for therapeutic reasons linked to the child's health**.

## I-5. PRENATAL DIAGNOSIS<sup>17</sup>

Prenatal diagnosis enables future parents with a high risk of having a child affected with a given disease to make sure that their child is not the carrier of the genetic defect responsible for the disease in question. Whereas the above-mentioned diagnoses (prenuptial and pre-ICSI) make it possible to calculate genetic risks, this diagnosis makes it possible to convert a probability of a given disease into a certainty. It should however be specified that this examination can only diagnose the genetic diseases being tested for. In other words, recourse to this type of diagnosis by no means offers an assurance of having a "normal" child.

=> Three main techniques are used for carrying out this type of diagnosis. They involve the removal of embryonal cells which, when cultured, make a genetic trial possible.

- Amniocentesis, the oldest technique, involves removing a small quantity of the amniotic fluid surrounding the foetus and containing cells detached from the foetal skin. It is performed between the sixteenth and eighteenth weeks of pregnancy and presents a very slight risk for the foetus since only around 0.5% (0.5-1%) of terminated pregnancies are linked to this examination. NB In the case of twin pregnancies the risk goes up to 3.2%. The test results take a fairly long time to come through, ie three to four weeks.

- Sampling chorial villousities consists in taking small samples of the villous chorion (the tissue which will form the placenta). It is carried out between the tenth and twelfth weeks of gestation and the risk of abortion associated with it is approximately equivalent to that observed in the case of the amniocentesis. However, it offers the advantage of a quicker test result (between 48 hours and three weeks).

- Foetal blood sampling is carried out after 17 weeks of gestation, by puncture of the umbilical cord. The percentage of foetal deaths attributable to this type of examination lies between 0.6 and 1.7% according to the statistics. As to the results, they are obtained very rapidly (between 48 hours and seven days).

- Other technique: In order to facilitate prenatal diagnosis, studies are being carried out to improve existing techniques and also to find others (*For example, we might quote the technique of examining the few foetal cells which may be present in the mother's blood*).

**Questions raised:**

\*One of the main questions raised by prenatal testing is that of **determining whether this examination may be imposed** or whether it should be practised exclusively in cases of high-risk pregnancies.

Given the risk, albeit low, of an aborted pregnancy associated with the different techniques used for this type of diagnosis, **it ought not to be made compulsory**. Even in the case of high-risk pregnancies, it should only be proposed. **Since freedom of choice should be left entirely to the parents**, the doctor's duty should, therefore, be to inform them of the risks incurred and strongly advise diagnosis. However, so that the choice whether or not to make the diagnosis is genuinely free, no pressure should be brought to bear by social security bodies (insurance or benefits). The fact that parents have an affected child after refusing prenatal diagnosis should not in any way restrict their social rights, or the child's.

\*As far as **parental responsibility** is concerned, should or should not legislation be framed concerning the right for affected children to take action against their parents for having refused testing ? (*In the United States and in the United Kingdom, for example, the principle of damage to life has been allowed in some instances.*)

\*When parents accept diagnosis because of a particular risk, should the doctors diagnose only that particular disease or **can they carry out a more comprehensive diagnosis?** Although this question is currently settled by budgetary considerations (diagnosis costs are high), it still has to be dealt with. In such a case, the decision should be left to the parents.

\*When the examination is carried out and the result is positive, especially in cases of diagnosis of an incurable disease in the foetus, the question then raised is **whether the mother retains the right to go through with the pregnancy** when the unborn child would be a burden on society. On this score, it should be stated that decisions by women wishing to conceive or already pregnant are a matter for their own moral responsibility. Out of respect for their moral or religious convictions, **any women having conceived a child should be free, without fear of legal proceedings, to keep the child** and give birth to it, whether or not the child is in good health.

\*The question of **the doctor's responsibility** is also raised by this screening. There have been reports of cases of children being born with diseases for which they were diagnosed as non-carriers. Molecular biology techniques are very difficult to implement so **should the doctor be held responsible only in cases where an error has been made?** (incompetence, inexperience, operational errors, etc). Should parents receive compensation for the psychological and financial burden placed upon them by having a sick child?

\*Another major question raised by this type of diagnosis is that of knowing **which genetic "defects" may be detected** by this diagnosis. As is stated in Principle 2 of Recommendation R(90)13, "prenatal genetic screening undertaken for the purpose of

identifying a risk to the health of an unborn child **should be aimed only at detecting serious risk to the health of the child**". That would, therefore, mean **excluding from this screening the detection of any characteristics unconnected with the genetic impairments which may trigger a disease**.

Only incurable diseases or those for which treatment might be started very early on, even *in utero*, should be the subject of these tests (ie including diseases that develop later).

Once existing techniques have been mastered or new simpler techniques have been developed, the use of this diagnosis will probably become increasingly frequent in the future. In those conditions, it may become difficult to prevent the diagnosis of genetic diseases for which an effective treatment exists. Consequently, should there be an attempt at least **to limit this examination to the genetic diseases which might be regarded as serious because the existing treatment will involve heavy constraints to the person?**

#### **I-6. NEONATAL DIAGNOSIS**

The screening of newborn children is **frequently carried out to detect diseases which may be treated and/or prevented**. *The best example is the Guthrie test for detecting phenylketonuria, a recessive autosomal disease with a frequency in northern Europe of around 1 in 10,000 to 1 in 15,000 live births. Treatment of the disease, if begun early enough, ie in early childhood, may prevent mental retardation.*

#### **Ethical questions:**

\*When this screening takes place, there may be an ethical problem concerning the use of blood samples taken for the tests routinely carried out, ie to detect diseases for which there is a therapeutic or preventive treatment. These samples may constitute a precious source of genetic material that can be used in epidemiological research. **Should parents therefore be asked to authorise screening?** (This question also concerns the CDBI-CO-GT2 - Working Party on Medical Research).

## **II. Access to screening and diagnosis results**

Although the question of access to the various results of screening and diagnosis has already been raised (paragraph I), the general principles should be reiterated here.

\*In the case of screening carried out for community genetics purposes, the communities ought to be informed of the general result observed or obtained in order to establish a co-operation based relationship. However, **information should be passed on to individuals whenever the person concerned might benefit directly in terms of their well-being and health** (example: by means of diagnosis, prevention and treatment).



\*As far as the various genetic diagnoses are concerned, access to the results should be possible if the persons concerned demand the right to be informed.

### III. Therapies

Paradoxically, the treatment of genetic diseases usually entails environmental rather than genetic manipulation.

#### III-1. THERAPIES NOT MODIFYING THE GENOME

The prevention of genetic diseases by screening, diagnosis and early intervention are all part of the treatment. This entails the application of three combined factors: restriction, substitution and suppression.

=> Restriction or diminution of exposure to potentially toxic agents (example: *reduced protein intake to treat children with urea cycle anomalies*).

=> Substitution of deficient products may have a therapeutic or even curative effect (example: *in the case of haemophilia A, substitutive treatment with factor VIII proves very effective*).

=> Suppression of toxic substances or even of an organ likely to be affected has also been used successfully (example: *in Wilson's disease, characterised by hepatic and neurological lesions due to a build-up of copper, treatment by penicillin is very effective*).

The fact that there are various ways of treating genetic diseases ought to be emphasised since, where treatment is possible by means of somatic gene therapy, **patients should always have the chance to decide how they wish to be treated.**

#### III-2. SOMATIC GENE THERAPY

If gene therapy can be defined as the deliberate modification of the genetic material of living cells in order to prevent disease or cure affected persons, **somatic gene therapy may be defined as a modification of the DNA of the differentiated cells in the body**, ie the cells not involved in the transmission of genetic material to descendants.

NB. The modifications envisaged and conceivable today do not consist in repairing defective genes but merely make it possible to place within the genome a functional gene whose expression will replace that of the mutated endogenous gene. It is not impossible, however, that in the distant future it might be possible actually to replace the mutated gene with a functional one.

#### Questions raised:

\*As indicated by the generally accepted definition, **gene therapy must not be used in order to modify genetic characters not related to a disease.**

\*Like any new medical therapy, it must be **carefully evaluated in terms of risk and benefit**. Consequently, although the prospects for treatment by gene therapy of the overwhelming majority of genetic diseases remain fairly remote, **recourse to this type of treatment, when it is possible, should be reserved for cases where there is no simpler therapy of equal effectiveness available**. Somatic gene therapy should, therefore, be rejected in favour of treatments not involving modification of the genome (that, however, remains debatable when the treatment in question imposes heavy constraints on patients.) *Example: progress made in the production of purified human proteins (coagulation factors) may render somatic gene therapy useless.*

\*In the long term, the risk would be that **the technique of gene therapy will be used to treat any and every disease** (once the genes involved have been identified, of course). This idea seems difficult to accept in ethical terms since not all diseases justify this treatment. Compared with organ transplants - regarded, however, as genetically more disruptive than gene therapy and limited in their application by the number of donors - once the techniques have been perfected, gene therapy will be unlimited since there will be an everlasting source of cloned "medicine" genes.

\*This problem is, however, not yet upon us since **numerous scientific obstacles must yet be overcome before serious use of gene therapy can be contemplated:**

=> First of all, we must have the right gene available. This seems simple for monogenic diseases but the same is not true for multifactorial diseases.

=> Once the gene has been identified, it must then be ascertained that its degree of effectiveness is sufficient to obtain a therapeutic result.

=> The gene must also be expressed in the right tissue.

=> The main problem - the object of numerous efforts - consists in finding the right vehicle enabling the "medicine" gene to penetrate in sufficient quantities the cells to be modified. The ethical question raised stems from the fact that the current vehicles being studied are deactivated viruses. All of them currently present major disadvantages. Adenoviruses present the disadvantage of residual immunogenicity and low long-term effectiveness, which would partly explain the disappointing results of clinical trials for the treatment of mucoviscidosis (cystic fibrosis)<sup>18</sup>. The major concern with retrovirus vehicles, still the basic tool for obtaining the transfer and stable expression of a transgene, is their random insertion in chromosomal DNA. This means that their use *in vivo* presents major risks since random insertion may lead to the deactivation of another major gene or even deregulate an oncogene\*. It is the apparent difficulty in the *in vivo* use of viruses that has led research teams to try using non-viral vehicles

constituted from lipids (also used for treating mucoviscidosis or cystic fibrosis<sup>19</sup>), but once again a good deal of progress remains to be made.

=> Even if the issues of optimal, safe and efficient gene construction were to be resolved, there remains the difficult problem of how it is to be administered (*in the case of myopathies, for example, direct administration seems implausible when all muscles are affected*).

This brief summary of the various obstacles to be overcome before all gene therapies may be applied effectively poses the vital problem of **the need for a committee entrusted with authorising test protocols**. These committees (such as the "Commission d'étude de la dissémination des produits du génie bio-moléculaire" - the French committee for the study of the dissemination of biomolecular engineering products) are all the more necessary since this application of molecular biology has sometimes led to media and commercial pressures and clinical trials regarded by some as rather premature<sup>20</sup>. The most urgent aspect of gene therapy is, therefore, to **ensure that protocols are safe in order to guarantee the well-being and integrity of the people being treated**.

\*When the practice of somatic gene therapy is considered in the future, the question then will be **which modifications may be made?** So far it has usually been accepted that the aim is to re-establish a normal expression of a mutated gene. However, it would not be idealistic to imagine that, later on, the aim might be to make the expression of a gene abnormal (*example: The mutation of the CCR5 gene which seems to make the macrophages of individuals homozygous for deletion resistant to HIV-1 infection is linked to no abnormal phenotype nor any pathology. Some people are already thinking of mutating this gene in order to fight infection<sup>21</sup>*), **Could modifications be authorised if they are aimed at voluntarily mutating genes?**

\*Furthermore, although somatic gene therapy carried out *ex vivo* presents no risk for the germ line, the same is not true if it is performed *in vivo*. If the germ line were accidentally modified, should that call into question the authorisation to practice somatic therapy? Or should this modification be considered as one of the symptoms, since the aim was not to modify the germ line - the subject of Article 13 of the convention?

\*When the technique of somatic gene therapy is applied, there are two requirements:

=> **Bringing together medical and scientific knowledge in one place.** *Ex vivo* modifications made to cellular lines and the construction of vehicles in general call for state-of-the-art molecular biology techniques, while their administration in patients calls for medical expertise.

=> **The long-term monitoring of treated patients.** This is all the more necessary since most of the protocols of experimental somatic gene therapy in use today propose treatments which do not maintain the genetically modified cells in the body indefinitely (old cells die and new ones are manufactured). Only the treatment of stem cells with the ability

to divide can give rise to lasting modifications and therefore life-long treatment (**eg: the haematopoietic stem cells found in bone-marrow which produce red blood cells => treatment of haemoglobinopathies\***).

### III-3. GERMINAL GENE THERAPY

\*Defined as the genetic modification of germ line cells, **this use of the technique of gene therapy is prohibited** by Article 13 of the Convention on Human Rights and Biomedicine which states that "**an intervention seeking to modify the human genome may only be undertaken if its aim is not to introduce any modification in the genome of any descendants**".

\*In respect of medical research aimed at introducing **genetic modifications in germ cells not destined for fertilisation**, it is only admissible if it is carried out in vitro and with the approval of an ethical committee (cf explanatory memorandum to the convention).

\* An additional fact should be mentioned here. Recent experiments suggest that it will be possible in the near future to prevent genetic mitochondrial diseases transmission, using the nucleus of one oocyte and cytoplasm (which contains normal mitochondrial elements) of the other<sup>22</sup>.

Does this new fact concern the prohibition stated in article 13 of the Convention? or do we consider that modifications of the mitochondrial genome (which encode only a few genes) distinct from modifications of the nucleus genome ?

## IV. Access to therapies and genetic tests

### IV-1. GENETIC TESTING

\***Access to diagnostic testing should be possible** for anyone desiring to have recourse to it, **without discrimination** and without financial considerations (Recommendation R(92)3).

\*Should tests for diagnosing genetic diseases or a predisposition for such diseases ever be on sale, **such sales should only be authorised under strict and exceptional conditions** (R(92)3). Given the implication of carrying out these tests which, as we shall see in paragraph V, must be accompanied by genetic counselling, it is not recommended that their use should be free and without medical supervision.

### IV-2. GENE THERAPIES

\***Access to gene therapies** should be open to anyone requiring access to that technique, without discrimination.

\*If more than one type of treatment is available and is of similar effectiveness, **anyone requiring treatment should be given a choice** of therapy.

## V. Genetic counselling

### V-1. CONDITIONS OF ACCESS TO COUNSELLING

\*Recourse to genetic counselling should be compulsory before and after any screening and diagnoses and before and after any recourse to genetic therapy.

\*Since genetic counselling is a requirement, states should facilitate access to it, in particular by reimbursing consultations in the same way as all medical consultations. Counselling should, therefore, be integrated into mainstream medical practice.

\*Counselling should also be open to anyone willing to have access to it and should, in particular, be recommended to families with a history of diseases (*eg: cancer*), and communities identified as high risk because of geographical and/or environmental factors, age, etc. In the latter case, as we have already mentioned, anyone shown by screening to be at definite risk of contracting or transmitting a disease should be monitored.

\*If it is felt that no genetic testing should be compulsory, what of genetic consultation? **Should it be made compulsory for certain high-risk categories?** (*eg: for women aged over 38 years wishing to conceive*). Since these consultations are not at all binding on the persons concerned, they would at least enable them to be aware of the risks incurred.

### V-2. AIMS OF GENETIC COUNSELLING

Given the complexity of genetic data, liable to distance patients from doctors, the main aim of genetic counselling should be to inform patients in as clear a language as possible, in order to help them take the necessary decisions.

#### In the case of genetic testing:

**\*It should inform people of the probability of contracting or transmitting a genetic disease.** For that purpose it will often be necessary to retrace the family history.

An initial problem therefore concerns access to a family's genetic information. **Is the authorisation of the members of the family concerned a requirement for the analysis of family antecedents needed to evaluate risk?** This question becomes even more complex when the information is not available, ie when the disease has not yet appeared in certain members of the family (*eg: Huntington's chorea*). In cases where risk calculation would entail

sampling members of the family, it is quite conceivable and should be accepted that certain members might oppose it.

**\*Patients should also be informed about the consequences of the pathology in question.**

\*Furthermore, when the risk of transmitting or contracting a genetic disease is high, it is for the counsellor to **propose the appropriate diagnosis**.

- In the case of pre-nuptial or pre-ICSI diagnosis, that implies proposing alternative solutions (IVF, AID) when the risk is unacceptable.

- In cases of pre-implantation diagnosis, the counsellor should ensure that the risk of transmission of a genetic disease by the parents is sufficiently great to justify the diagnosis.

- As for ongoing counselling before prenatal diagnosis, it consists in informing patients of the various possibilities of diagnosis, and informing them of the risks (even if they are low) of abortion linked to the techniques. In this type of diagnosis, in addition to counselling, the doctor-counsellor should help the parents, cope with the stress caused by the often very long delays in obtaining results. Furthermore, in the case of a pessimistic finding, he or she should also assist the parents in taking their decision, for example concerning a therapeutic termination of pregnancy. Counselling is all the more necessary at such times since decisions are often taken under pressure and parents are ill-prepared.

\*For all the available diagnoses, **the counsellor should inform the persons involved of the potential risks of diagnostic error**. He should also explain to the patients that diagnoses cannot detect everything but only test for a particular complaint.

\*Given the large number of possible diagnoses, the counsellor may sometimes run the risk of facing the problem of **knowing what type of diagnosis to propose**. In the case of a couple with a definite risk of transmitting a genetic disease, should the counsellor preferably propose recourse to medically assisted procreation followed by a pre-implantation diagnosis, or a prenatal diagnosis? (That raises a difficult question of knowing whether it is morally preferable to select and implant recently fertilised healthy embryos rather than abort a several month-old foetus.)

In the case of therapies:

\*When diagnoses have established the presence of a genetic mutation liable to be the cause of a disease, **the genetic counsellor should inform the patient of the possibilities of prevention and treatment**.

\*As far as prevention is concerned, that might include advising regular recourse to diagnosis in order to detect the clinical disease as early as possible (*eg: frequent mammographies to detect breast cancer*).

**\*The counsellor should describe the various possible treatments** (if they exist) and their implications (including the of risks linked to intervention). When choices are proposed, the well-being of the person concerned should be borne in mind. **The counsellor's role, in other words, is to assist the patient in the choice of the appropriate treatment.**

When gene therapy is being considered, very full information should be supplied to patients. Given the anxieties aroused by this technique, it is obviously important to explain to patients what the treatment involves, its aim, the risks, post-intervention follow-up, etc.

\*Another of the counsellor's duties is to **refer patients to the specialists** who need to be consulted.

### V-3. THE PRACTICE OF GENETIC COUNSELLING

#### Who does the counselling?

\*Where counselling exists, it differs from one country to another. Genetic counselling may be performed by specialists, by general practitioners with some knowledge of medical genetics or by professional genetics counsellors.

Given the complexity of the genetic information to be conveyed, the ethical implications and the psychological ramifications which may go beyond the experience of a general practitioner, **the task of counselling should rest with specialists**, and in particular **geneticists** rather than scientific genetics experts. The former are in a better position to respond to patients' questions, given their professional experience. Should we not go so far as to contemplate training special professional counsellors? (*as is the case in the United States*). Given the family and emotional implications, it is obviously important for geneticists to be assisted by psychologists or trained to deal with the psychological anxieties resulting from the often momentous decisions to be taken. (*For example, in France most geneticists acting as counsellors prefer to work in conjunction with psychologists.*)

\*Since the decisions to be taken by people involved in genetic consultations often have major consequences, the right of patients to a second medical opinion should be extended to **the right to a second consultation with another specialist physician.**

#### How is the counselling to be carried out?

One of the main questions concerning the arrangements for genetic counselling is knowing whether or not it should be **directive**. Recommendation R(92)3 of the Committee of Ministers insists in Article 3 on the need for non-directive counselling. It is true that **presenting the information in a non-directive fashion enables the patient's autonomy to be respected**, as it allows patients to reach a decision of their own free will.

In practice, however, it seems that it is difficult to apply this rule strictly. As a survey carried out by UNESCO revealed, some people interpret non-directive counselling as a lack of interest in their problem. In certain situations where the most efficient treatment must be carried out as quickly as possible, it seems difficult to present the situation in a totally non-directive way, all the more so since, in certain emergencies, patients are often in a fragile psychological state and need the counsellor to help them make up their minds to a specific course of action. It is true, on the other hand, that in non-emergencies - especially in situations calling for serious moral decisions (eg the decision to opt for medically assisted procreation or abortion, etc) - counselling should in no case be directive since the patient must bear the responsibility for any decision to be taken.

Bearing these facts in mind, non-directive genetic counselling should rather be defined as a consultation in which specialists refrain from imposing their personal moral, religious or ethical convictions. Only the patient's convictions concerned should prevail when decisions are being taken.

## VI. Genetic research

Although the practices of research are covered by the additional protocol on biomedical research, nonetheless the specific problems of genetic research should be raised here.

\*One of the main tasks of current genetic research consists in identifying the gene mutations which are responsible for genetic diseases. To this end, we must first identify families in which a large number of members develop the disease which is the object of the study. Once identified, the families will be subjected to blood sampling for the purposes of genetic trials.

**The main feature of this type of research is the need to draw up a complete family tree for each family being studied.** This "intrusion" into the privacy of a whole family over several generations, together with the fact that the susceptibility of the individuals concerned is already aroused by the symptoms of the disease, means that genetic counselling should automatically be arranged in order to explain clearly the need for the research.

**Another special feature of genetic research stems from the fact that it is very difficult to predict all the types of analysis which may be necessary during the experiments.** Given the possibility of unexpected discoveries (in the wake, for example, of paternity tests) only the information liable to have an impact on the health of the persons concerned should be divulged. Nonetheless that raises the problem of consent, which should allow for a broad range of possible uses of the genetic material.



**\*An ethical problem is raised by community genetics of communities** where the establishment of cellular lines, originating from the targeted community, has often been carried out in order to make the genetic material necessary for the different genetic studies more widely available. Although the establishment of these lines poses no problems per se, as long as ethical standards are respected (consent and anonymity), the patentability of these lines may on the other hand discredit these research programmes whose main concern should be making progress in the knowledge of the genome and not making a profit. In order to allay the anxieties aroused by these community genetics programmes, it might be important to establish rules concerning the purposes to which collected material may be put. On this score, we might refer to Article 21 of the Convention on Human Rights and Biomedicine, **which enshrines the principle of prohibiting financial gain in the use of any part of the human body.**

## Chapter II

### GENETICS AND SOCIETY (Social applications of genetics)

#### I. Use of genetic tests for recruitment

The revelation by diagnosis of disease-causing genetic impairments (Chapter I) raises anxiety as to the use of such tests for social (ie non-medical) purposes. One of the main fears is their possible use by employers before recruitment to exclude certain workers who may be likely to develop a given disease<sup>23</sup>.

\* While a general medical checkup on recruitment may be warranted in some instances, particularly where the job requires special standards of physical fitness, on the other hand there is no possible justification for genetic tests. If used, they would make it possible to detect genes of predisposition or genetic mutations responsible for diseases whose onset is delayed. It would of course be morally reprehensible to reject anyone on the ground of their propensity to develop such a disease in the future. As for discrimination against persons with a predisposition, this should not be permitted in any circumstances because, as emphasised above, genetic predisposition does not mean that the disease in question will actually develop.

Pre-recruitment use of genetic tests is all the more disturbing in an age when people's occupational integration guarantees their social integration. Discriminating against "genetically vulnerable" persons would therefore be tantamount to excluding certain categories of persons from society, which is inadmissible. **The use of diagnoses thus ought to be prohibited; as long as no illness is certified, there is no unfitness for work.**

\* Epidemiological studies like the one commenced in May this year by the French research agency for prevention of occupational diseases (INRS) are sometimes carried out to **monitor workers' proneness to occupational hazards**<sup>24</sup>. The intent of these studies is apparently to ensure better medical surveillance of employees exposed to certain risks in order to find them a more suitable post. These studies nonetheless cause deep anxiety for the trade unions of employees because of fear that they may make way for a "genetic file" and result in selection of persons according to "genetic risk".

As will be explained in Chapter III, and as already mentioned in Chapter I in connection with genetic screening of communities, **anonymity in epidemiological studies would be advisable in order to prevent any resultant discrimination against "predisposed" individuals.** However, one must acknowledge the usefulness of such programmes as affording greater future insight into the development of what are called occupational diseases.

\* Assuming these epidemiological studies demonstrate that genetic predisposition, working conditions and onset of disease are correlated, **arguably the medical profession should be authorised to prescribe a genetic diagnosis for the persons concerned in order to make them aware of the potential hazard.** In that case, and in so far as medical information comes within the private sphere, the employee should not be required to disclose genetic tests results to the employer. Indeed, **the employee should no doubt be reserved the right to decide as to the measures necessary in the event of risk.**

\* **Nor should employees aware of a "genetic risk" before recruitment be required to inform the employer** - unless, perhaps, the presence of clinical symptoms already foreshadows impending unfitness for work.

## II. Use of genetic tests by private insurers

Use of genetic diagnoses by private insurance companies poses a problem of major proportions. As has already happened in the United States, it is to be feared that insurers may use genetic information to select policyholders representing a "good risk" because the likelihood of their developing a genetically determined disease is minimal.

\*To avert such discrimination between individuals, Article 12 of the Convention on Human Rights and Biomedicine stipulates that **"tests which are predictive of genetic diseases ... may be performed only for health purposes"** (or for medical research purposes), which implies that an insurer is not entitled to ask for a predictive genetic test to be carried out as a precondition for concluding a contract.

\*If it is accordingly established that there must never be an obligation to undergo tests in order to take out insurance, **what about the results of the insured persons' previous diagnoses? Must they inform the insurer of the risks (if any)?**

This question is truly problematic considering that the insurance law of many countries would seem to require insured persons to inform the insurer of all relevant facts known to them. Insurers furthermore consider it impossible to draw up a fair insurance contract unless the parties are equally provided with information. Unequal information moreover constitutes the main cause of apprehension for insurers, according to whom the danger is that free access to genetic tests may prompt people to insure themselves heavily against a risk known only to themselves (and not to the insurer).

*Pending research, the French Federation of Insurance Companies in 1994 declared a 5 year moratorium enjoining the various insurance companies not to resort to genetic testing.*

Genetic tests undeniably pose a difficult problem in that they transform into predictable risk the uncertainty which used to be the foundation for the concept of risk governing insurance. In the light of this new circumstance, it may be necessary to ask **who loses more by the transformation, the insurer or the insured?** Without too much demur, it might be argued

that this awareness of risk chiefly endangers individual freedom of contract. **Therefore, should we hold that intending policyholders must not be under an obligation to disclose the results of previous genetic testing?**

If the insured are granted the right not to inform insurance companies of genetic test results, **neither should they be required to disclose their family antecedents** whose analysis, as pointed out in Chapter I, also helps assess the likelihood of a person's developing a genetic disease.

\*In the light of the foregoing, and having regard to the anxieties of insurers, would it not be advisable to envisage more flexible legislation? Certain studies on this subject have proposed that above a certain subscribed level of insurance, it should be possible to ask policyholders to undergo further medical examinations. Other studies were more in favour of establishing a level of insurance above which only the results of previous genetic tests should be disclosed to the insurer. But if such a possibility is contemplated, it may well be appropriate to set the level so high that the arrangement in question - if it existed - would be used only in exceptional cases.

If it is intended to grant insurers this right to demand the results of genetic tests where the insurance exceeds a certain value, two questions arise:

- **Should a distinction be drawn between monogenic and multifactorial disease?** A diagnosis revealing a gene mutation responsible for a monogenic disease might indeed justify disclosure of the information, since the disease is certain to develop. Conversely, any information relating to the detection of a predisposition should not be communicated, since the risk is very difficult or impossible to assess.

- **Would this form of two-tier contractualisation be justifiable for all classes of insurance?** In the case of group insurance, for example, subscribed by a corporation on behalf of its employees, clients or members (constituting a guarantee of benefit), **should the insured also let the insurer know the results of genetic tests?** Here the question has different connotations than in the case of personal insurance, because the staff's affiliation under a group insurance contract is usually compulsory or routine. In the case of personal insurance, this measure should no doubt be restricted to certain types (*eg life insurance, supplementary health insurance*).

Furthermore, so that people's freedom to take out high-value insurance is safeguarded, **insurers should not be able to withhold a policy from risk-prone applicants.** All they should be allowed to do is adjust the premium to the risk.

Yet another problem arises, however, with reference to this "two-tier" legislation": how to deal with the case where a person wishes to take out high-value insurance when aware of a genetic risk, not through a diagnosis but in the light of family antecedents.

### **III. Genetic tests and access to education**

This third area of application of genetic tests is not yet a major subject of debate but needs to be considered. On the basis of a study involving monozygotic twins, it has been calculated that intelligence (measured by IQ) is about 50% genetically determined. What is more, admittedly controversial research programmes to identify "intelligence genes" are already contemplated<sup>25</sup>.

Should such genes be identified in the future it would be advisable, having regard to the risks inherent in this discovery, to stipulate that **the right of access to education should be secured without discrimination based on individual genetic endowment. Educational establishments (at whatever level) should not be permitted to request or to use genetic test results as a precondition for enrolment.**

Use of genetic diagnoses for this purpose would be even less justifiable in that "genes of intelligence", if discovered, would only be capable of demonstrating a predisposition and would in no way reflect the real abilities of individuals, because abilities develop by way of dynamic interaction between the genome and social, cultural and other environmental factors.

## **IV. Judicial use of genetic tests**

### **IV-1. IN CIVIL PROCEEDINGS**

Human genetic fingerprints (or DNA profiles) are now commonly used by the judicial system, eg in civil litigation to establish descent; genetic tests allow paternity to be attributed or refuted with over 99% reliability.

\*Regarding certification of descent, the question thus arises how unrestrictedly genetic tests can be made available for use by the public: **whether to allow permissive use of these tests or whether to emphasise the non-disposability of civil status records and accordingly stipulate that biological evidence may be brought solely in the course of action at law.** France, for instance, has opted for non-disposability; since 1994, genetic testing to establish descent has been possible only in pursuance of an investigative measure ordered by a court.

The child's interests would no doubt be more effectively safeguarded if the use of these tests for establishing descent could be genuinely controlled through the agency of the judicial system.

\*In the event of litigation prompting the judicial authorities to call for genetic testing, it would be appropriate to obtain the consent of those concerned (Chapter III). **However, can the test be made compulsory on the ground that it allows the true facts to be established in a contentious situation?**

## IV-2. IN CRIMINAL PROCEEDINGS

The criminal justice system is where genetic tests (or genetic fingerprinting) have their widest judicial use; they are routinely carried out in rape and murder trials as well as for identifying corpses.

Genetic testing was already a standard practice with identified suspects but is now becoming more extensive, as has been observed in France where in August 1997 the Rennes court of appeal ordered all male residents of Pleine-Fougère aged 15 to 35 to undergo genetic tests. This measure, taken to identify the murderer of an English girl, was particularly unusual in that it involved a large group of individuals within which there were no designated suspects (it was further intended to ask the local male population in the 35-55 age group to undergo the tests that November).

\*The first issue is therefore to specify **the cases in which genetic tests can be employed**. Recommendation (92) 1 of the Committee of Ministers on the use of analysis of DNA within the framework of the criminal justice system has laid down that "recourse to DNA analysis should be permissible in all appropriate cases, irrespective of the degree of seriousness of the offence". Yet considering recent uses of genetic tests which, we have seen, can involve a large number of people or an entire community, **it would endanger individual freedom if their use were not restricted to the gravest offences**. If tests which may rely on large-scale screening are authorised, it would in fact seem inconceivable to authorise them in respect of ordinary offences.

\*The second issue, then, concerns who should undergo the tests. **Should it be permitted to carry out tests on persons not identified as suspects** (as has happened in France) or should their application be confined to suspects alone?

\*As to the conditions under which the tests are performed, people not regarded as suspect should be left at liberty to accept or refuse genetic examinations, **on condition of explicit consent in case of acceptance**.

What line should be taken with suspects and convicted persons? **Should they be given the right to refuse tests?** Respect for human dignity and personal privacy would dictate that this right be secured, but need it be secured in all cases (eg when identifying a criminal)?

**\*Samples of genetic material should be used strictly in keeping with the purposes for which they were collected.**

\*When testing is carried out in practice, **is it really capable of identifying the culprit?** Genetic fingerprints, commonly applied in private or public forensic science laboratories, are in fact ever more frequently held up before the courts as incriminating evidence. It should be observed, however, that the method is far from infallible; while it can completely clear suspects, it cannot incriminate them with the same certitude.

- **The technique does indeed demand faultless expertise and exactitude.** The greatest difficulty is making sure that the DNA analysed positively belongs to the criminal. PCR (polymerase chain reaction) is an *in vitro* DNA amplification technique which, in a very short time-span, yields a vast number of reproductions of the DNA to be analysed. It nevertheless has the disadvantage that the slightest molecule of extraneous DNA is liable to be amplified and to distort the results.

- **Furthermore, the increasing sensitivity of the methods used counsels caution.** By way of illustration, let us mention a technique now being studied in Australia for making genetic fingerprints of ordinary fingerprints<sup>26</sup>. Investigators, aware that the human hand desquamates naturally, looked for traces of the identity of the person who had held various objects by recovering a few cells and analysing the DNA. The strength, but also the weakness, of this technique is that DNA of diverse origins is deposited after an object has passed through various hands. What is more, the technique appears so sensitive that an object can be found to carry the DNA of someone who never touched it (scales of skin can be exchanged by a handshake).

The above-mentioned technical innovations demonstrate that **in these ever more efficient genetic examinations, allowance for the risk of error is crucial**, especially considering that the results have weighty implications in criminal proceedings.

\* Storage of genetic samples and data will be discussed in Chapter III (data protection).

## Chapter III

# COMMENTS RELATING TO APPLICATION OF GENETIC TESTS AND THERAPIES

## I. Consent of subjects

### I-1. PERSONS WITH LEGAL CAPACITY

#### Genetic tests

\*All forms of genetic screening and diagnosis conducted for medical purposes should require the **explicit and informed consent of the subjects** (ie the persons on whom a genetic analysis is performed).

- With regard to diagnoses carried out on embryos (pre- implantation), **should the consent of the mother only, or of both parents, be obtained?** The *in vitro* fertilisation technique often requires the explicit agreement of both parents, and thus might also be advisable for pre-implantation diagnosis subsequent to IVF.

- With regard to genetic tests carried out as part of screening for medical research purposes (also a concern of the Working Group on Medical Research CDBI-CO-GT2), **it would be expedient in addition to obtain the consent of the persons involved in the programme at the earliest possible stage.** This may not always be easy, however, especially with anonymous sources of material (*eg from blood banks*). **Should donors therefore be asked to consent in advance to possible genetic tests on the material donated?**

Furthermore, where these screening programmes involve the whole of a given community, it would no doubt be appropriate to obtain, as well as individual consent, the **collective consent** of the groups, peoples or communities concerned via their legal representatives.

\*When genetic tests are conducted for purposes unrelated to health (or to medical research), it would be expedient in all cases that the persons concerned give their explicit and informed consent.

Genetic fingerprints made from anonymous samples collected at crime scenes during judicial investigations (blood, hair, sperm, etc.) should constitute an exception. **Should the requirement of consent also be waived in certain criminal cases** (*by court order*), especially where there is material evidence of a person's implication in a crime?



## Therapies

Out of respect for human dignity and the human person, **the explicit and informed consent by individuals undergoing or due to undergo gene therapy must be stipulated.** No treatment which entails modification of the genome should be effected without the knowledge of the person concerned (nor should any other treatment).

### **I-2. PERSONS WITHOUT LEGAL CAPACITY**

\*Diagnosis or screening for medical purposes, together with gene therapy, applied to minors or adults without legal capacity, should be permissible after **the consent of the parents, guardians or other authorised representatives is secured.** The person concerned should also be asked for his/her opinion or consent if capable of giving it.

Recommendation R (92) 3 of the Committee of Ministers on genetic testing and screening for health care purposes provides that "testing of these persons for diagnostic purposes should be permitted only where this is necessary for their own health or where the information is imperatively needed to diagnose the existence of a genetic disease in family members". **Does this preclude genetic tests connected with a medical research project or an epidemiological study?** (More a matter for the working group CDBI-CO-GT2).

## **II. Accreditation**

### **II.1 TECHNIQUES AND PROGRAMMES**

The genetic tests and therapeutic techniques available at present have such significant implications for human dignity, integrity and health that **a supervision system governing their use is imperative.**

\*Accordingly, any new protocol for screening, diagnosis and therapy should be **endorsed by a committee of experts which would bear the responsibility of its application.** The committee would preferably be made up of persons **not involved in establishing the protocols** in order to deliberate with complete impartiality. The committee would verify inter alia:

- That the proposed protocol is of genuine value;
- That it will genuinely achieve the purpose for which it is designed;
- That its application will not undermine the dignity, health and bodily integrity of those concerned;
- That safety standards will be upheld, ie the likely risks will not be disproportionate to the potential benefit for the subjects. The safety concept, as already pointed out, is of major relevance to the certification of gene therapy protocols. Safety standards, one may remark, should be still more

stringent where gene therapy is to be used in treating neurological complaints (*eg Parkinson's disease*). The reason for the scant progress hitherto in prevention of such diseases is that brain cells are highly vulnerable; in adults, every neuron affected is irretrievably lost.

- That it plainly exhibits the requisite standards (where these exist). An example is the decision reached this August by 25 public forensic science laboratories in 16 European countries to harmonise analysis protocols for judicial use<sup>27</sup>.

- That the screening centres and clinics where the protocols are to be applied possess the requisite expertise (cf paragraph II.2 below).

**\*The committees of experts in question should also be mandated to approve the programmes under which the protocols will be used, together with biomedical research programmes.** Inter alia, they should verify:

- The usefulness and soundness of the programmes in terms of therapeutic, preventive or medical research benefits;

- Their compliance with a number of ethical standards as to choice of the target populations (for genetic screening of communities), sample collection procedures, consent of the subjects and information to be provided before and after execution of the programme.

## II-2. GENETIC ANALYSIS CENTRES AND CLINICS

Carrying out diagnoses, genetic fingerprinting and gene therapy involves **molecular genetics techniques requiring faultless expertise and exactitude, failing which the results obtained cannot possibly be reliable**, and any error in this respect may have unfortunate consequences. Exactitude is still more indispensable where the techniques used are highly sensitive as in the case of the preliminary PCR for production of genetic fingerprints.

Certain countries realised the need for quality control of analysis centres some years ago. (*In France for instance, a check carried out in 1990 led to the accreditation of only 5 of the 27 centres inspected*).

**\*It is therefore necessary to stipulate that only those centres accredited in recognition of their expertise and qualification, as certified by quality control, may carry out genetic tests.**

**\*The same should apply, moreover, to the application of gene therapy protocols - necessitating, as already emphasised, a combination of medical and scientific expertise in one place.**

### III. Genetic data protection

Protection of biomedical data will be included in a special section of the Protocol on biomedical research (CDBI-CO-GT2). **The question is therefore whether special provisions on genetic data need to be incorporated into the Protocol on human genetics.**

\*The use of genetic data for research purposes (epidemiological studies, identification of genes, etc.) should not diverge from the provisions made in the Protocol on biomedical research. **That is, the data should be anonymous as far as possible.** Indeed, only the relevant information should emerge, concerning for instance the background, habits and diet of individuals, as personal identity does not necessarily constitute a relevant piece of information.

Also, where given families, ie a limited number of persons, are studied, **the medical practitioner taking samples from the family members should be responsible for ensuring anonymity of the data as soon as possible, where possible.** The doctor in question should in fact simply be bound by professional secrecy and refrain from disclosing the identity of the families on which the study was conducted.

\*The genetic data of persons diagnosed should receive special protection in view of their sensitiveness; they **concern the private sphere not only of the subject but also of the subject's progenitors and descendants.**

As already stated in Chapter I, any person screened should be able to obtain access to the results, **but what of information which may directly relate to descendants and progenitors?** Should the patient still be left at liberty to give or deny family members such information as may concern them? **Indeed, where the information provided by screening is crucial to the health of a family member, should the doctor nonetheless be required to observe professional secrecy?**

\*Another issue raised by the potential use of genetic data concerns compilation of genetic fingerprint files for use by the judicial system. At present such files already exist in the United Kingdom and the Netherlands, and are soon to be introduced in Norway, Sweden and France.

The point is thus to establish which persons may have their prints recorded in these files. **Is it necessary, as in the United Kingdom, to provide that only the genetic fingerprints of convicted criminals can be classified in these files?** (classification of anonymous genetic data collected at the scene of crimes presents no particular ethical problem, precisely because of their anonymity).

In addition, with regard to persons who have been genetically tested and cleared of suspicion, should provision be made as recommended by the Committee of Ministers for **destruction of biological material and deletion of genetic data?**

## GENERAL PRINCIPLES

As we have seen, the advances made in the field of genetics have brought about a major change in our outlook on the human being. Effective recognition of the role of genetic factors in human pathology has thus led to the realisation that people are born with a greater or lesser advantage according to their genetic endowment.

To gain a fuller understanding of this genetic heritage, an integral part of our identity, extensive programmes have been instituted. Programmes to map the human genome (over 6 000 genes registered so far), determine the role of the various genes, reveal genetic dysfunction and even attempt the reconstitution of impaired genes all contribute to the single aim of comprehending and commanding our genome.

Because comprehension and command of our genetic heritage are progressing day by day and could be improperly used, it would seem expedient to lay the foundations for general principles to be set out in the additional protocol on genetics to the Convention on Human Rights and Biomedicine.

The first principle, already embodied in the Convention (Article 11) and deriving from respect for the rights of individuals (Article 14 of the European Convention on Human Rights), stipulates that "**any form of discrimination against a person on grounds of his or her genetic heritage is prohibited**".

Two further elements could possibly give rise to general principles:

- Firstly, **it offends human dignity** to consider that the abilities and characteristics of a person **result essentially from the expression of his/her genome**. Discrimination between persons on the ground of a genetic predisposition (to illness, to intellectual or physical capabilities, etc.) should be prohibited (principle I, Article 11 of the Convention) since personal development is mainly the outcome of dynamic interaction between the genome and the environment of that person.

- It would also be expedient to define "**the right of persons to the integrity of their genetic heritage**". This principle would justify the stipulation that modifications of the genome must not interfere with its functional integrity. Furthermore, the right of persons not to be exposed to mutagens would be grounded in this principle. The term mutagens denotes all chemical, ionising, radioactive or other factors which might alter the genetic heritage. An exception should be made where these substances are used for a curative medical purpose.

## GLOSSARY

- \***Allele:** Alternative form(s) of a gene in a given locus.
- \***Aneuploidia:** Any number of chromosomes which is not an exact multiple of the haploid number (in humans the haploid number is 23, the number of chromosomes in a normal gamete). Aneuploidia usually refers to an additional copy of a single chromosome (*eg: trisomia 21*).
- \***Autosome (autosomal):** Any chromosome apart from sex chromosomes or the mitochondrial chromosome.
- \***Karyotype:** An individual's set of chromosomes. Term also used for the micro-photography of the chromosomes of an individual, arranged in accordance with a standard classification.
- \***Haemoglobinopathies:** Anomalies of the haemoglobin in which mutation leads to a quantitative anomaly.
- \***Heterozygote (heterozygous):** Used to describe individuals possessing two different alleles (of a same gene), in a given locus of a pair of chromosomes (the locus is the position of the gene in question on the chromosome).
- \***Homozygote (homozygous):** Describes an individual possessing a pair of identical alleles in a given locus of a pair of chromosomes.
- \***Meiosis:** Special cellular division occurring in the germ cells of sexual organisms, during which the gametes containing a haploid number of chromosomes are produced from diploid cells. It entails two divisions. The reduction of the number of chromosomes occurs during the first division.
- \***Mitochondrion (mitochondrial) :** Mitochondria are organelles present in the cellular cytoplasm, acting as cells' energy producers. These organelles contain small loops of DNA carrying the necessary genetic information for the production of the 37 molecules which enable energy to be manufactured.
- \***Oncogene:** a gene which can transform a cell into a tumour cell.
- \***Penetrance:** Phenomenon referring to the presence or absence of the visible expression of a mutated gene.
- \***Phenotype:** Observable expression of a gene or particular genes (clinical manifestations). The genotype constitutes all the genes (by analogy with music scores, notes are equivalent to the genotype and melody to the phenotype).
- \***Polyps:** Benign tumours developing on mucosae.
- \***Polymorphism:** Occurs in a community of genetically determined alternative phenotypes. Polymorphism may also refer to variations in the DNA sequence.
- \***Mendelian transmission:** According to Mendel, a mutated character is said to be dominant when it is expressed in a heterozygous individual consequently possessing a single copy of the impaired gene. It is called recessive if it is expressed only in homozygous individuals (possessing two copies of the mutated gene).

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