Opinion and recommandations on"Genetics and medecine : from prediction to prevention". Reports.

N°46 - October 30, 1995

Contents

Opinion and recommendations

Genetics, the science which studies the transmission of hereditary characteristics, was created by Gregor Mendel in 1865 and already has a tumultuous history since it was used as scientific justification for very powerful eugenic currents in various countries during the first half of this century.

This is no doubt because its very object is at the heart of the fundamental interrogation which constitutes the human being : where do I come from, who am I, what shall I bequeath to my offspring, in what way am I both similar to and different from other people. This is why the science of genetics has had and still has more individual, political, and social repercussions than any other. At the present time, progress in human genetics shows promise of a not very distant future when all the human genes - of which there are approximately 100 000 - will have been identified, located on the chromosomes, and when their functions, or at least their implications in genetic diseases will be almost fully understood. The myth of the gene as the stuff of which life itself is programmed, is such that of it is born the illusion that perfect knowledge of the genome of an individual will lead to an understanding of the reality and fate of that individual. Metaphors such as the book of life which would give access to the essential human being if only one could decipher the genetic alphabet and syntax, refer to that notion. Such a concept is scientifically unacceptable and ethically dangerous.

A gene corresponds to a factor for biological determination whose expression and functional significance frequently depend on the influence of other genes and of the environment which in the long term is unpredictable. Even if one were able to understand fully the significance of all genes and of their combined expression, only the biological properties of living cells and organisms would be known; not the psyche and the emotions of the human being. The genetically determined properties whereby the psychic capacities of the human being are accessed are in fact particularly vulnerable to the environment and the influences of a specifically human world external to genetic determinants, a world of culture, knowledge, social mores, values, and of the history of human societies, all of which are in

turn shaped by the specific personality of those who transmit them, by the events, by the emotional experience and by the trials of a lifetime. The genome, component of a body, cannot be made to represent the entire human being. However, even though it is limited to the possibility of predicting more or less accurately and precisely, some facets of the biological fate of human beings such as susceptibility to certain diseases or to other non pathological characteristics, the power conferred by genetics is such that it could have far reaching repercussions on individuals and society, now and in the future.

Progress in human genetics and in the technicalities of methods of diagnosis, particularly in molecular genetics, have supplied new tools which have gradually constituted the basis for predictive medicine which it is hoped will open the way to preventive medicine. A vast range of medical applications, which extends much further afield than the study of hereditary diseases, is opened by the study of genetic characteristics. There will be further extension in the next few years due to research on the human genome. Thus it is now possible to consider broadening preventive policies starting with prevention of handi at birth, and going on to diseases occurring during adolescence and in adults (diabetes, cancers, cardiovascular diseases), and even conditions found in old age (Alzheimer's disease).

The basic principle of predictive medicine is to forecast the appearance of certain diseases before their symptoms are expressed. However, there are grave uncertainties about the value of the predictions and whether it is truly possible to prevent the conditions, and also whether this form of prevention is truly beneficial to individuals and to society.

Prevention aims at avoiding or delaying the onset of diseases and a priori is a very recommendable activity. It has been invaluable in many fields such as the elimination of infectious diseases through immunisation, or perinatal policies which have led to spectacular reductions of infant morbidity and mortality.

Prevention comes in many forms which are not necessarily medical such as, to quote but a few examples, campaigns to inform about the dangers of smoking or of road traffic. It may address the population as a whole, as for vaccination, or groups of people exposed for instance to a particular environmental risk factor such as workers in a specific risk situation because of the nature of their activity, or to individuals and families whose behaviour, environment, biology, or genetic structure are such that they are particularly likely to contract a disease or transmit one to their offspring. In the first two cases, prevention may be described as "collective" and is launched without reference to the particular condition of the subject at which it is aimed. In the third case, it is "individual" and specifically refers to the characteristics of the person concerned. Ethical considerations are not identical in all three cases.

Experience has clearly demonstrated in public health campaigns (smoking, road accidents) how difficult it is to follow preventive advice which attempts to modify socially attractive behaviour, even though suffering and death are predictable. Such problems could become considerable if there were a multiplication of constraints which were associated to the discovery of an ever increasing number of genetically determined factors of susceptibility.

Over and beyond the usual scientific and medical criteria for beneficial and deleterious effects, the evaluation of preventive measures must take into account the social and psychological constraints and resistance which appear when attempts are made at promoting new rules of behaviour. Economic stakes, with competing interests between potential savings in the nation's health expenditure and market objectives for the health industries and the medical profession, also need to be taken into consideration.

The pertinence of any preventive action almost entirely based on genetic considerations raises a further point. Genetic factors are not alone responsible for bringing about many diseases so that preventive measures must also bear on the environmental factors.

There are specific features in testing for genetic characteristics which must be emphasised :

these traits concern the individual as a unique being but also represent elements which link the individual to his family, past, present, and future. Their examination and their revelation bear both on the intimate biological nature of the individual and on his relationship with his family. Ethical considerations must embrace the duality of an individual's relationship with himself and with his family.

The evidencing of a genetic characteristic may be experienced as an anomaly or even discrimination against and stigmatisation of the individual. The ethical responsibility of society is involved.

This raises a difficult question: destiny and freedom in the face of knowledge of genetic risks. On the one hand, ignorance is seldom a freedom promoting factor, and knowledge of susceptibility to avoidable ailments bestows upon an individual the responsibility of drawing the consequences of this knowledge. After all, it is universally accepted that acceptance of one's fate is a key to true exercise of one's freedom since otherwise there is nothing more than wishful thinking. Nonetheless, the significance of the exercise of freedom by a person whose genetic predisposition leaves no choice but a life in the grip of terrible constraints or preventive mutilation or risk of incurable disease, is open to question. Another individual dimension of a genetic fate revealed is that sometimes, in the case of the handing down of a serious disease, it is tantamount to a curse put on the lineage, since the parents may be considered guilty of transmitting a faulty gene to their children who in turn, feel guilt at the possibility of transmitting it to their own descendants.

Other matters pertain to general rules of medical ethics : in predictive and preventive action, before prescribing and carrying out tests on healthy subjects who frequently never asked to be tested at all, one must consider and evaluate the preventive and curative action which can be taken as a result of the information obtained by such tests.

Ethical consideration of preventive action must take into account the evaluation of the benefits, the effects of which must necessarily be far in excess of any deleterious results. Prevention in the first phase means evaluation of a risk. The evaluation may be related to an individual, a family, an ethnic group, or the population as a whole.

A distinction must be made between :

A) a presymptomatic diagnosis which reveals in an individual the existence of a genetic anomaly before any of the clinical signs which may occur are visible. Such a diagnosis pertains to genetic diseases for which there is a very high risk of appearance in carriers of the mutation. It may be made before birth, in the neonatal period, or later in life.

In this respect, there is a significant contrast between cases where previously evaluated prevention is possible and those where there is no possibility of prevention.

For instance, the presymptomatic diagnosis of the mutation causing familial adenomatous polyposis allows the possibility of preventive follow-up and treatment.

The presymptomatic diagnosis of the mutation responsible for the appearance of Huntington's chorea on the other hand can only provide information on the certainty of the disease's onset, but neither prevention nor cure can be offered.

B) A genetic diagnosis is performed to evaluate the risk for the descendants of the individual being tested. Such a diagnosis is carried out either during a familial study or in the more general framework of mass screening. For example, in certain areas of the Mediterranean, the high frequency of beta-thalassemia (Mediterranean anemia) is a reason for suggesting screening at around twenty years of age for heterozygous forms of the mutation so as to be able to inform couples of any risk to their children and of the possibility of prenatal diagnosis.

C) Probabilistic predisposition diagnoses for a serious affection with the aim of evaluating for an individual the risk of appearance of the disease compared to such a risk for the population as a whole. In this case also, a distinction has to be made between conditions with or without any possibility of assessed prevention.

It is clear that in a single gene disease, a mutant gene is the first cause of the trouble, but in a multifactorial disease, the various risk factors, be they genetic or connected to the environment, belong to a sequence, of varying length, of events.

This means that at the end of the sequence, appearance of a disease (or more frequently of an observable phenotype) is likely to be the cumulative effect of the various parts of that chain of events. If preventive measures were possible, they could only play upon external factors whose interaction with genetic factors had been demonstrated.

The prospect of personal and social repercussions very obviously calls for ethical reflection. In fact, in France as elsewhere around the globe, such reflection is resurgent in the last ten years or so concomitantly with the development of molecular genetics. This is expressed in a variety of ways and not just as questions but also directives, guidance, or sometimes law governing knowledge of the genome and its applications. As genetic tests are being rapidly developed at present - and their effectiveness will probably surpass that of the corresponding therapies for some time yet - the results of this ethical reflection need to be collated, up-dated, and precisely defined in particular with a view to incorporation in the legislative framework adopted by France in July 1994.

Recommendations

1) An examination of the genetic characteristics of an individual may, whatever the result, have profound repercussions on the life of the person who submits to it. For his independence to be respected, he must have an understanding as complete as possible of the consequences of his decision to accept the test or not.

Such understanding implies information on the nature of the test, the significance of results, the possible existence of prevention and therapy and consequent constraints. This information must be imparted by a professional person with good knowledge of medical genetics, must be direct and oral so that a dialogue can take place, and must then be put down in written form.

Any determination of the characteristics of the genotype of an individual must only be undertaken for medical purposes by prescription or for scientific purposes and only if the subject has specifically given written consent.

The results of the tests must be communicated in person by a physician whose competence permits a full explanation of the significance of the results. A follow-up of the patient must be provided in order to alleviate possible psychological repercussions because of the results of the test, be they positive or negative.

Certain kinds of information may have potentially harmful effects on the individual. He may therefore refuse to be given the results of the test and his right not to know must always be respected.

2) Medical confidentiality must be observed as regards third parties, including other members of the family. If discovery of a genetic alnormality of a familial nature leads to considering biological sampling of all the members of that family, they must be approached by the requesting individual and not by the physician. If the patient refuses to make known to members of his family the risk revealed by the genetic examination he has submitted to, the physician cannot warn them of the possible risk of developing a disease or of transmitting it to their descendants. The physician must inform the index patient of the responsibility he is incurring and do his best to convince him that he should inform his

relatives. If that procedure fails, the principles of medical confidentiality and of the duty to inform patients and their families of a risk which may be averted by preventive measures, will be in contradiction. The physician will be confronted with a serious ethical conflict on which society must pronounce itself, taking into account the unacceptability of refusal to help endangered persons, particularly if children are involved.

The study of genetic characteristics of children should not be systematic. It must always be related to a specific case and based on an analysis of medical and familial data. Parents and attendant physician must only request a test for a child if the disease associated with his genotype may become manifest before the age of 18 or if preventive therapy before 18 years of age may be of benefit. A child who has been genetically tested and for whom medical follow-up is required, must be informed as soon as he is able to understand the procedures. In cases where the test would lead to an appraisal of a risk for the child's future descendants, his family's duty is to inform the child as soon as procreation becomes a possibility and he is able to understand and decide for himself to submit to testing. Transmission from one generation to the next of genetic information may be necessary. Provision must therefore be made for the conservation of a family's genetic data for at least a generation and also for at-risk individuals to be given this information when it becomes useful to do so.

3) Computer storage of identifiable data relating to persons whose samples have been tested must be carried out in such a way that confidentiality is protected in observance of legal rules and of recommendations issued by the CCNE in its previous Opinions.

Biological samples which may be required at a later date for further testing, for purposes of diagnosis or verification, must be preserved so as to be able to respond to a patient's needs.

Should there be an extension of research to a domain not foreseen at the time of sampling, consent must again be obtained.

When the collection of biological samples is made in the framework of a research programme, the instigators of the research are duty bound to complete such research work with the means available and in the conditions described at the time of consent being given by the individuals who have been sampled.

Non use for a prolonged period of time of such collections by scientists who are making no progress in their research could be harmful to the legitimate expectations of those persons who have consented to use being made of samples of their DNA. It would therefore be necessary to set reasonable deadlines after which access to the collections would be open to other scientists wishing to work on the protocol for which consent was given. In cases where the investigators abandon the research project, they should inform persons concerned of consequent modifications.

4) Use of the results of a study of genetic characteristics for purposes other than medical or scientific, for instance for an insurance contract or for employment, is prohibited even though the tests may have been requested by the persons concerned or with their consent.

Instances of a study of genetic characteristics being useful for preventing work-related diseases are rare indeed in the present state of scientific knowledge. The use of genetic testing in occupational medicine must therefore be exceptional and rigorously restricted to cases on limited list for which the risk for the individual is sufficiently established and cannot be removed by changes to the work environment.

5) Approval procedures by the Drugs Agency (Agence du Médicament) must be set up for the reagents used in genetic testing protocols. Their sale must be regulated and so must approval and supervision of laboratories performing the tests.

When studies are practised on a large number of individuals, precise preliminary work must

be done to evaluate the predictive value of the tests and the usefulness of preventive and curative measures to be recommended to people selected by the tests. This must be done before authorisation is granted for the studies.

Evaluation should not be based solely on medical criteria. It must also take into account the various aspects of quality of life and the way in which it will be modified either when screening is performed or because of constraints due to prevention.

The evaluation of a genetic screening and prevention programme must include the fact that such a programme can only be effective if the protocol is considered acceptable by the target population and by the medical profession.

6) The attitudes of individuals and their families to genetic screening and preventive measures are a consequence of the quality of the medical information given to those concerned. It is essential, therefore, that members of the medical and para-medical professions should attend appropriate medical genetics training courses at universities and that practising physicians be provided with refresher courses.

Pedagogical information imparted during secondary education, in biology or philosophy classes, should make it possible to reduce the risk of discrimination or stigmatisation due to knowledge of genetic characteristics.

Associations representing families with an interest in a genetic disease should be encouraged in their efforts to widen medical and scientific information.

A close watch must be kept on the quality of the media information written for the general public which may lead to false hopes because of a penchant for sensational news. Another possible danger is that the sizeable potential market for genetic screening may lead to vested financial interests which could be detrimental to the truthfulness and independence of information.

7) Genetic tests give information on the identity of persons and emphasise their diversity which contributes to the rich nature of humankind. To use such information for the purpose of selection or of discrimination in social or economic terms, be that in the realm of public health policies, employment, or insurance systems, would be crossing a boundary of the most extreme gravity and would question those principles of equality of rights, dignity and solidarity for all human beings upon which society as we know it is based. The CCNE insists on the necessity of observing those fundamental principles whatever aims may be pursued by genetic testing. Human Rights are at stake.

Scientific report

A. Introduction

Prevention aims at avoiding or delaying the onset of diseases and a priori is a very recommendable activity. It has been invaluable in many fields such as for instance the elimination of infectious diseases through immunisation, or perinatal policies which have led to spectacular decrease of infant morbidity and mortality.

Prevention comes in many forms which are not necessarily medical such as, to quote but a few examples, campaigns to inform about the dangers of tobacco consumption or of road traffic. It may address the population as a whole, as for vaccination, or groups of people exposed for instance to a particular environmental risk factor such as workers in a specific risk situation because of the nature of their activity, or to individuals and families whose behaviour, environment, biology, or genetic structure are such that they are particularly likely to contract a disease or transmit one to their offspring. In the first two cases, prevention may be described as "collective" and is launched without reference to the

particular condition of the subject at which it is aimed. In the third case, it is "individual" and specifically refers to the characteristics of the person concerned. Ethical considerations are not identical in all three cases.

Progress in human genetics and in the technicalities of methods of diagnosis,, particularly in molecular genetics, have supplied new tools which have gradually constituted the basis for predictive medicine which it is hoped will open the way to preventive medicine. A vast range of medical applications, which extends much further afield than the study of hereditary diseases, is opened by the study of genetic characteristics. There will be further extension in the next few years due to the research on the human genome. Thus it is now possible to consider broadening preventive policies through the range of the prevention of handi at birth, diseases occurring during adolescence and in adults (diabetes, cancers, cardiovascular diseases), and even conditions found in old age (Alzheimer's disease).

There is constant evolution in what is known on this subject and here research (discovery and characterisation of a gene for instance) and medical application will frequently overlap, if only so as to give patients the benefit of scientific progress as early as possible. Therefore research and medical application thereof must follow the same ethical rules.

The basic principle of predictive medicine is to forecast the appearance of certain diseases before their symptoms are expressed. In the present context of technical progress and increasing knowledge, it is hardly surprising that a great many questions arise about their medical applications. Grave uncertainties exist about the value of the predictions and whether it is truly possible to prevent these conditions, and also whether this form of prevention is truly beneficial to individuals and to society. Experience has clearly demonstrated in public health campaigns (tobacco, road accidents) how difficult it is to follow preventive advice which attempts to modify socially attractive behaviour, even though suffering and death are predictable. Such problems could become considerable if there were a multiplication of constraints which were associated to the discovery of an ever increasing number of genetically determined factors of vulnerability.

Over and beyond the usual scientific and medical criteria for beneficial and deleterious effects, the evaluation of preventive measures must take into account the social and psychological constraints and resistance which appear when attempts are made at promoting new rules of behaviour. Economic stakes with competing interests between potential savings in the nation's health expenditure and market objectives for the health industries and the medical profession also need to be taken into consideration.

The pertinence of any preventive action almost entirely based on genetics raises a further point for consideration. Genetic factors are not alone responsible for bringing about many diseases so that preventive measures must also bear on the environmental factors.

There are specific features in testing for genetic traits which must be emphasised :

the results given by the tests are constitutional data which identify the individual in biological terms and which, beyond the tested individual, frequently concern his family and future descendants. From that point of view, there is a difference compared to ordinary tests based on biological analyses. Special precautions must be taken when such tests are prescribed and executed and their results make known. In particular, the kind of information given to those concerned is of essential importance.

Making use of genetic testing for preventive purposes entails two phases :

- firstly, an identification of increased risk individuals;

- then, preventive action in favour of identified patients, including either medical follow-up or therapy to prevent or slow down the pathological process.

1. Methods for the selection of increased risk individuals

For the purposes of this report we shall only consider methods of genetic screening.

Genetic screening methods are applied on the basis of the following criteria:

a) the prevalence of the disease for which preventive measures are sought, the condition being characterised by its phenotypic expression.

Must be considered firstly the prevalence of the disease in the population at large, then an evaluation of the risk of appearance of the disease for the tested individual (positive predictive value), in the context of public health policy or of a familial study;

b) an analysis of the value of the genetic test: its sensitivity on the one hand, its specificity on the other.

Sensitivity measures the percentage of individuals for which the test results are positive and who will in fact contract the disease. In genetic screening, the usual evaluation criteria must be used, i.e. the proportion of false positives and of false negatives, but to these must be added the concept of penetrance of a genetically determined characteristic, i.e. the probability that an individual carrying the morbid mutation will produce phenotypic expression.

Specificity measures the percentage of non-affected individuals whose test results were negative. It is obtained when the test always and only detects the mutation of the gene responsible for the disease. But such specificity for the gene does not always coincide with specificity for the disease. This is the case when non-carriers of the morbid mutation run a risk, sometimes a large risk, of developping the disease, either in non-hereditary forms, or forms due to other as yet unknown mutations.

This notion of specificity cannot be retained for susceptibility genes which correspond to constitutional polymorphism (HLA characters for example).

2. Preventions

According to the timing of the preventive method used, two cases arise :

- primary prevention based on action directed specifically at the very cause of the affection. For instance, in single-gene disease, genetic counseling may discourage procreation in at-risk couples, although it should be noted that this would lead to preventing conception of both unaffected and affected children.

- Secondary prevention which consists in acting on the process leading to the expression of the pathology. Such prevention includes a presymptomatic genetic screening of diseases which can be effectively managed before the appearance of any symptoms. Thus, phenylketonuria, in which, if a strict diet is observed almost from birth, mental retardation due to the metabolic defect can be avoided.

A particular form of secondary prevention aims at the following generation by avoiding the birth of affected children. A prenatal diagnosis is made and the pregnancy is aborted (to use the words "secondary prevention" in this case may shock some people, but it is accepted by the international scientific community).

Prevention to begin with is the evaluation of a risk. An individual, a family, an ethnic group, or the population at large may be the subject of evaluation.

B. Scientific data

I. Role of genes in diseases

1. Single gene diseases

These are genetic disorders determined by a single gene which, depending on their mode of transmission, include the following mutations :

autosomal dominant mutations

An autosome is a chromosome which does not determine the sex of the individual. A dominant gene is expressed when it is present on a single chromosome. If this gene bears a mutation, it will be responsible for what is called a dominant disease. The chance of transmission of the mutant gene and thereby of the disease to a child, is 1 in 2.

(For example, renal polycystic disease, 1:1000 births ; Huntington's chorea, 1:15000 births).

autosomal recessive mutations

A recessive mutant gene will have pathological consequences only if both homologous genes, inherited from each parent, bear a mutation. A carrier of the mutant gene on a single chromosome - therefore a heterozygote - is healthy because the normal phenotypic expression is provided by the normal gene on the other chromosome. Disease occurs when a child inherits a mutant chromosome from each heterozygous parent. The chance of an affected child for 2 heterozygous parents is 1 in 4.

(For example : cystic fibrosis, 1: 2500 births.)

x-linked mutations

When genes are on the X chromosome, since girls have two X chromosomes, the presence of the mutant gene is generally of no consequence for them in terms of phenotypic expression, but they are carriers and may transmit the X chromosome with the mutant gene to their sons. A boy has only one X chromosome and will be affected if he has received the mutant chromosome from his mother (one boy in two).

(For example : Duchenne muscular dystrophy, 1:7000 births)

a particular kind of mutation : dynamic mutations

Recently, certain affections have been grouped under a new genetic model, dynamic mutations, the expression of which is an amplification of nucleotide triplets from one generation to the next.

(For example : mental retardation linked to the fragile X chromosome, 1 :1500 births; myotonic dystrophy, 1:5000 births).

mutation polymorphism

In single gene disorders, a single disease due to the modification of the expression of a gene may be caused by various mutations of that gene (for cystic fibrosis, more than 500 mutations have been discovered). For some single gene diseases, each family has its own mutation.

Neomutation has been observed. This is particularly frequent in X-linked diseases. About a third of children affected by Duchenne muscular dystrophy carry a neomutation.

2. Diseases associated with chromosome disorders

The anomaly may lie in the number of entire chromosomes (e.g.trisomies) or an anomaly in the chromosome structure. This may be unbalanced with the loss or gain of a chromosome segment comprising genes responsible for disorders, or balanced in which case there are no consequence for the individual concerned, but a unbalanced form may be passed on to descendants and have serious consequences (sterility, foetal death, malformations.....).

3. Multifactorial diseases

Such affections are not determined by mutations alone ; they are the result of an unfavourable combination of a set of factors, genetically determined or otherwise (environmental factors). In such disorders, the determination of genetic characteristics can only provide a probabilistic evaluation of the risk. These are genes of susceptibility.

In multifactorial diseases, some DNA polymorphism may be associated with a modification of the risk of occurrence of the disease (either increased or decreased).

II. Methods of analysis of genetic characteristics

1. Chromosome analysis

Cytogenetic progress in association with molecular biology techniques (in situ hybridization) make it possible to carry out a fine analysis of chromosome aberrations.

2. Gene analysis

Genes can be analysed through their phenotypic expression or by an examination of the genome.

analysis of the phenotypic expression of a mutant gene

This is done:

- either directly by an analysis of the product of the gene's expression : such is the case for inborn errors of metabolism or for hemoglobinopathies ; this is also true for histocompatibility antigens (HLA antigens)

- or indirectly by analysis of the metabolic modifications specific to the disease : such is the case for phenylketonuria.

In some cases, a direct examination of the protein which new techniques have made possible, provides easier access to information than gene analysis. Such is the case in particular of dystrophin in muscular dystrophy, and also that of the FMRP protein in mental retardation due to the fragile X syndrome.

analysis of the genome

DNA analysis made it possible to localize with precision the affected gene on a segment of the chromosome (genetic map), and then in an increasing number of cases, isolation and characterisation of the gene and identification of the protein (muscular dystrophy, cystic fibrosis).

At present, the more frequent single gene diseases have been mapped and in many cases characterised.

A molecular probe, specific for a gene, makes it possible in some cases to arrive at a direct

diagnosis of the causative mutation (sickle cell anemia, fragile X syndrome, Huntington's disease....). But for the most part, in single gene diseases, the number of possible mutations is vast and their characterisation for each family is not possible in practical terms for the moment.

An indirect diagnosis strategy must therefore be used which has to be adapted to each disease or even to each family. This strategy requires a previous family study to be made. Mapping of the portion of the chromosome carrying the mutant gene makes it possible to achieve an indirect diagnosis because of polymorphism in the DNA. Their location near the gene, flanking or even in the gene, is evidence of the transmission of that gene within a family. Discovery of a large number of DNA polymorphisms (microsatellites) has facilitated this kind of diagnosis.

These polymorphisms have also led to identification through genetic fingerprints. Thus, there have been suggestions that a genetic "identity card" might be established with the help of a few hundred such microsatellites distributed along the genome. Of course, such a card can only, in theory, differentiate one person from all others but does not reveal any genetic characteristics nor, in particular, susceptibility of that person to diseases.

C. Scope of application of genetic characteristics studies

Under this heading we are considering only studies of healthy subjects. A clear distinction must be made between :

- presymptomatic diagnosis of diseases for which the risk of onset in the individual with the genetic trait is very high (100% or close to 100%). Differentiation between conditions where preventive action is possible and those where this is not so must be made.

- genetic diagnosis with the aim of evaluating the risk for the descendants of the index case.

- probabilistic diagnosis of predisposition to a serious disease with a view to evaluating in an individual the risk of occurrence of the condition compared to the risk of occurrence in the general population. There again, the possibility of prevention or otherwise must be considered separately.

I. Presymptomatic diagnosis

Such a diagnosis reveals the existence of a genetic abnormality before there is any clinical evidence of disease. It is made for genetic diseases in which there is a very high risk they will appear in carriers of the mutation. It can be performed out before birth, during the neonatal period, or later in life.

Prenatal diagnosis was the subject of a previous Opinion of the Committee (Opinion n° 5 dated 13th May, 1985 on problems arising from prenatal and perinatal diagnosis).

Use of this diagnosis is regulated by law n° 94-654 of 29th July 1994 concerning the donation and use of elements and products of the human body, medically assisted reproduction, and prenatal diagnosis, and by decrees n° 95-558 and 95-559 of 6th May, 1995.

1. Neonatal diagnosis

Diagnosis of phenylketonuria is very representative. This is done by taking a blood spot sample within a few days of birth. An excellent national programme has made it possible to diagnose all affected children (1:15 000 approximately). Prevention of the consequences of this metabolic disorder by a strict diet beginning in the first few weeks of life and continued for several years makes it possible to avoid about fifty cases a year of mental retardation.

The successful outcome of phenylketonuria screening has led to the possibility of screening neonatally for other presymptomatic conditions using the same blood sample.

If no effective preventive action is available, the essential question is evaluation of a possible benefit in the development of the condition and whether there is any advantage in informing the parents of risk in future pregnancies. It is for this reason that neonatal mass screening of genetic conditions such as cystic fibrosis or Duchenne muscular dystrophy has not generally been undertaken. Mass neonatal screening for sickle cell anemia, however, has been effective for instance in Guadeloupe because it has helped to provide better care for sick children and genetic counseling given to parents about future pregnancies.

2. Presymptomatic diagnosis later in life

presymptomatic diagnosis of dominant diseases

Conditions which only affect carriers of the mutant gene

_ Huntington's disease

This dominant disease becomes symptomatic in adulthood (around the age of 40). It is a degenerative disease of the central nervous system which develops progressively and irreversibly with no known therapy.

In 1983, the gene responsible for the disease was located on the short arm of chromosome 4 and thereafter, in the next ten years, were developed increasingly reliable direct diagnosis techniques as new polymorphism markers were described. In 1993, the discovery of the molecular anomaly concerned (an unstable mutation with lengthening of a nucleotide triplet) made a precise direct diagnosis possible so that an individual diagnosis could be obtained without a family molecular biology study having to be made.

As long as no medical management of Huntington's disease is available, an affected individual who wishes to be informed of his true status must be able to obtain help from a multidisciplinary genetic centre.

_ Polycystic kidney disease

Polycystic kidney disease is a dominant disease at the origin of about 10% of renal deficiencies requiring dialysis.

The disease develops with variability. In about 50% of cases, there is progression to terminal renal failure so that regular dialysis and/or renal transplant become necessary, on average around 50 years of age with an age interval of 35 to 70. Within a single family, mode of progression varies from one affected person to another.

In 1985, the mutant gene was located on chromosome 16. This gene (PKD1) has just been identified. Since then, it was discovered that in about 10% of the families, the disease is not linked to the markers situated on chromosome 16. There is at least one other gene (PKD2) on chromosome 4.

Ultrasonography is generally used to diagnose this renal desease. Between the ages of 20 and 30, sensitivity of the test is at least 80%; beyond that age it is 100%. This goes to show that molecular biology with its own limitations and problems is not decisive for early detection. However, it is useful to reassure healthy individuals in families for which the causative gene has been properly identified.

Diseases which may develop in mutant gene carrying or non-carrying individuals

_ Hereditary cancers . (1)

Molecular biology has contributed fundamental and important information regarding the determination of the oncogenic process. Care must be taken to distinguish between constitutional germinal mutations present in all the cells of the body and therefore easily detected when screening blood samples, and somatic mutations (sometimes identical) which are only to be found in cancer tissue and therefore can only be discovered in a sample at that location or in excreted cells.

Knowledge of these mutations is important for research on the molecular processes of cancers and an analysis of such mutations may be useful for early diagnosis or therapeutic management.

Globally, only a small group of tumours (5 or 10%) represent the hereditary forms of cancer in which the mendelian traits predominate. For sporadic forms, by far the most frequent, causes connected to the environment are singled out (e.g. tobacco for lung cancer or certain kinds of papilloma virus for cervical cancer).

Research on the genetics of familial forms of cancers has been ongoing for several years. It began with the study of retinoblastoma and Wilms' tumour. Knudson's theory on successive mutational events leading to cancerisation was based on his study of retinoblastoma. In the case of familial cancers, a constitutional mutation is the first event. In 1994, a gene was found to be responsible in more than a dozen types of familial cancers and located. The gene has been identified for about ten more cancers. Analysis of these genes has made it possible in some cases to discover the mutation concerned.

Methods of diagnosis are based either on an analysis of co-segregation of polymorphism markers in a family, or on a direct analysis of the mutation. This is the realm of presymptomatic diagnosis. The risk of developing the desease for individuals who have inherited the genetic anomaly is generally extremely high, around 80%, and may be as much as 100%. This is therefore a dominant inheritance with a high degree of penetrance. In some cases, however, phenotypic expression varies for the same mutation producing different locations for the cancer. Data for familial forms of frequent cancers for which genetic tests are available can serve as models.

_ Colorectal cancers

This is the second most frequent cancer and affects both men and women equally. In France 25 000 new cases are diagnosed every year. Dominant inheritance is suspected for 5 to 10% of cases. Familial adenomatous polyposis (FAP) represents 1% of cancers of the large bowel. Hereditary non polypous cancer of the colon and rectum (HNPCC) represents from 3 to 5 % of such cancers. More recent data, however, indicates a hereditary factor in a higher percentage of cancers of the colon, up to 30% according to some authors. These malignancies may appear early in life. The gene for FAP has been identified and numerous mutations characterised. Four genes for HNPCC have been identified recently with numerous individual mutations. It can be difficult to differentiate between a mutation causing the disease and a harmless polymorphism. When the same mutation is found in several affected individuals it is possible to detect in a family young carriers of the mutant gene. They run a 100% risk of cancer of the colon and rectum before the age of 50. For individuals carrying the mutant gene, preventive strategies are considered: repeated colonoscopy and polypectomy, preventive colectomy in FAP and in some cases for HNPCC. However, colectomy, i.e. the removal of the target organ, does not prevent subsequent cancers in other sites.

_ Breast cancer.

Breast cancer is one of the most frequent malignancies affecting women globally. In France, 25 000 new cases a year are detected and one woman in ten is affected. Dominant

inheritance is claimed to be present in 5% of patients. In the last few years, there has been major progress leading to the locating and identification of several genes involved in the carcinogenic process. Mutations of gene BRCA1 are to be found in about half of the familial forms of breast cancer, in particular those associated with cancer of the ovaries. Further genes would seem to be responsible for other familial forms, such as gene BRCA2 which has already been located. Mutations of gene BRCA1 are not found in cancer tissue of sporadic forms. A study of a family by molecular biology could therefore identify the defective gene and find, within that family, the young women who inherited the mutation.

The frequency of women carrying one of the mutations of the familial form of breast cancer has been evaluated at 1:250. If this turned out to be true, it would be one of the more frequent dominant genetic characteristics so that, a priori, mass screening would be justified if effective prevention were available.

This is far from being the case at present; the only possible prevention would be bilateral oophorectomy and mastectomy of women carriers of the mutant gene as is practised in the United States. Supposing the existence of a technique for screening mutations at the root of hereditary forms, the sporadic forms of breast cancer which are far more frequent since they concern approximately 1 woman in 10, will not be detected with this kind of screening technique. In this way, out of 250 women tested to detect 1 woman with a familial form, about twenty women not carrying a mutant gene will subsequently be affected by breast cancer.

Constitutional mutations of other genes may play a role in breast cancers, such as mutations of gene p53 responsible for the Li-Fraumeni syndrome which associates several locations and could be responsible for childhood sarcoma. The prevalence of germinal mutation of p53 is 0.01% in the population at large and 5 to 10% in young patients with multiple neoplasms. However, not all families affected by the Li-Fraumeni syndrome carry the germinal mutation of p53.

Finally, the gene for ataxia telangiectasia, recently identified, could also in the heterozygous state, be an important gene for susceptibility to various cancers, inter alia breast cancers.

presymptomatic diagnosis of recessive diseases

_ Hemochromatosis

Hemochromatosis affects adults and develops slowly. It is a disorder of iron metabolism. Deposition of iron in the tissues provokes several severe clinical conditions : hepatopathy (cirrhosis), diabetes, cardiopathy. Treatment by repeat phlebotomy prevents the appearance of cirrhosis of the liver or diabetes in patients detected by early clinical diagnosis and enables them to enjoy a life expectancy identical to that of the population at large.

It is an autosomal recessive disease. The gene has not been identified. It should be on chromosome 6 since there is a very strong link with the HLA locus and in particular with antigens A3 and B14. Other polymorphisms of DNA can be useful for familial studies.

The first genetic studies were carried out in Brittany, where the frequency of heterozygotes seems to be about 3%. There is a belief that this genetic disease is very frequent but remains largely unknown.

The frequency of the disease and the possibility of preventive action may be sufficient justification for a familial genetic study starting with an index case. However, mass screening using biochemical serum testing for iron overload, would not seem to be justified because if results were abnormal, the diagnosis would need to be confirmed by liver biopsy which is a high risk procedure. Furthermore, no evaluation has been made of prevention by repeat phlebotomy for non-symptomatic patients.

II. Evaluation of genetic risk for descendants

Such evaluation can help to determine primary or secondary prevention.

1. Familial genetic studies

balanced chromosomic abnormalities

This may be the presence in a family of a balanced anomaly in the chromosome structure, translocation for instance. Discovery in a relative reveals a high risk of transmission of the anomaly in an unbalanced form to descendants.

x-linked diseases

In chromosome X-linked diseases such as Duchenne muscular dystrophy or hemophilia, a familial study including a genetic test makes it possible to detect among the women, sisters, aunts, nieces of the affected individual which of them are carriers of the mutant gene. They may be given a prenatal diagnosis if they so wish. The test also serves to give complete reassurance to women who have inherited the normal gene.

diseases due to dynamic mutations

Diseases due to dynamic mutations, which is a new genetic entity, raise more complex diagnosis problems.

_ Fragile X syndrome

The fragility of the X chromosome is the foremost cause of inherited mental retardation (one boy in 1 500, one girl in 2 500). A repetitive sequence of DNA is lengthened and appears first as a pre-mutation of no pathological consequence for men or women. When the premutation is transmitted by a woman, it may become unstable and the children inheriting the mutant X chromosome will be mentally retarded.

In a family, healthy individuals carrying the pre-mutation can be recognised :

- women run the risk of bearing affected children;

- the men transmit their pre-mutant X chromosome to all their daughters who will be normal but run the risk of bearing affected children. This is a novel situation in genetics since a healthy man can be apprised of the risk of affected grandchildren without it being necessary to test genetically his perfectly healthy daughters.

_ Huntington's disease

In affected families, some individuals know that they are carriers of the mutation and that if they transmit it to their child, the child will be affected also.

2. Genetic studies of large high-risk populations

A policy for screening of at-risk couples has been applied in populations where some single gene diseases are particularly frequent (Tay-Sachs disease, hemoglobinopathy). In these cases, genetic examination is based on the analysis of the product of the gene expression implicated in the disease, hemoglobin for instance.

_ Tay-Sachs disease

Among Ashkenazi Jews of the United States, New-York in particular, one individual in 25 or

30 is heterozygous for Tay-Sachs disease (this is a progressive neuro-degenerative disease with a life expectancy of 3 to 5 years). Screening has been extended to Ashkenazi Jews in Israel and has been instrumental in a 90% reduction of births of affected children.

_ Hemoglobinopathies

In Mediterranean countries, beta-thalassemia, or Mediterranean anemia, is the most frequent single gene disease, particularly in Italy and Greece.

In Sardinia in the last fifteen years, the incidence of thalassemia has been reduced from 4:1000 births down to 0.5:1000. Similar results have been obtained in Cyprus, whereas there used to be 60 to 70 births a year of children suffering from thalassemia, since 1985 only one affected child is born a year.

Could similar strategies be considered for screening high-risk couples for other autosomal single gene conditions ? Most of these are rare or even exceptional and it would be utopian to consider any form of mass screening. For cystic fibrosis, however, the problem is different.

_ Cystic fibrosis

In populations of Western Europe or originating from there (North America and Australia), cystic fibrosis is the only severe and frequent autosomal recessive disease. Approximately one individual in 25 is heterozygous. In the face of this epidemiology, screening for heterozygotes and therefore at-risk couples is amply justified.

In cystic fibrosis, protein is not expressed in cells that can be sampled easily (blood cells for instance). A screening strategy must therefore aim at an analysis of the gene itself through a study of the DNA, extracted and amplified using a tiny blood sample, or hair bulb, or cells from the buccal cavity after rinsing. However, cystic fibrosis is the result of a variety of gene mutations. One of them is frequent (AE F508) but there are more than 500 rare mutations. How could screening of heterozygotes for the mutant gene of cystic fibrosis be organised ?

There are a few privileged situations where such screening could be a possibility. By associating the determination of the frequent mutation to between 5 and 8 other fairly frequent mutations for a given population, 90 or even 95% of heterozygotes could be detected.

What are the possibilities for the population of France ? Using the technique of screening for the more frequent mutations, it would be possible to detect about two thirds of the at-risk couples in Northern France and half of those of Southern France. The difference is due to the variable frequency of mutation AE F508.

In some couples, one of the two will be a carrier for a known mutation and the other a non-carrier. In such couples, the risk is very small but the evaluation of the risk, of which they must be informed, is still higher than in the population at large (1:2500).

III. Testing genetic susceptibilty fior severe diseases in adults

A great number of human diseases, in particular some of the most frequent such as cancer, and cardiovascular pathologies, are not determined simply by the mutation of a gene. A whole set of factors, some of which are genetically determined and others not, combine to produce unfavourable results. Each factor, taken separately, is not pathogenic in itself. Furthermore, it can play a protective role in another context. This is so for most of the HLA antigens. For instance, DR2 is a risk factor for multiple sclerosis and even more so for narcolepsy whereas it is a protective factor for insulin-dependent diabetes. It also seems that haplotypes HLA DR13 have a protective effect on cancer of the cervix in women infected by the HPV-16 virus, whereas other haplotypes are associated with an increased

risk of cancer. It is also known that heterozygotes for sickle-cell anemia are protected against malaria.

In terms of biological causality, although it appears clearly that in a single gene disease, a mutant gene is the prime factor, in multifactorial inheritance, the various risk factors be they genetic or environmental, belong to a long or not so long chain of events. Between genes and organisms come many levels of organisation: interaction between molecules within a cell, between cells in a tissue, between tissues within an organ, between organs in a body, not forgetting external influence exerted by environmental factors. These are so many links in a long chain of causality. Therefore, at the macroscopic end of this chain, the possible determination of a disease (or more generally of an observable phenotype) is frequently an indirect effect of the elements of that chain.

What is one to expect then from genetic studies of common diseases from the point of view of preventive action ?

It is likely that results will depend very much on the degree of knowledge about the pathogenic process which in turn will depend on the number, the nature of factors involved and the complexity of their interaction. The joint action of these major groups of factors are to be found in fact in all pathologies. The difference between one disease and another is the respective proportion of each factor. Any disease can be sited on a diagram (fig. 1) where the "genetic G" pole is on the far left and the "environmental E" pole on the right. A disease will be all the nearer to G if the hereditary component is large. Close to G will be found diseases inherited according to mendelian rules. On the extreme right of the diagram will be found the infectious diseases for which hereditary factors have always been considered to be low. However, this is now being questioned for some of these diseases, such as tuberculosis, leprosy, and schistosomiasis.

Also, genetic characters may influence the receptivity to infection by a virus which has an influence on a carcinogenic process (papillomavirus in cancer of the cervix uteri). Midway we find the common diseases.

Tay-Sachs Disease Diabetes Measles

Galactosemia

Spectrum of diseases according to genetic component G and environmental component E.

Supposing it were possible to screen individuals at some risk, any such screening would only be of use if preventive action of any true value could be offered. If such preventive action were possible, it could not be used on the genetic factors and would need to be active on external factors whose interaction with the genetic components would be demonstrated.

Cardiovascular pathologies

In the Western hemisphere, these diseases together with cancer and neuro-degenerative affections, represent one of the major health problems. Two factors - which are not independent - are involved in the genesis of frequent pathologies, atherosclerosis and hypertension, the familial nature of which has been known for a long time. This data has inspired research on the metabolism of lipids and regulating arterial hypertension on the one hand, and on genetic factors with a bearing on both these issues on the other hand. Concurrently, epidemiological studies have demonstrated the essential role of environmental factors by a comparison in particular of myocardial infarcts in various populations around the world. For example, incidence may vary by a factor of 1 to 8 between Toulouse and Belfast. For the metabolism of lipids, after biochemical work based on variations of levels of some lipid components in the blood, research was initiated on an analysis of genes governing lipid metabolism.

A dominant single gene disease, familial hypercholesterolemia, was used as a model. The frequency of carriers of the mutant gene (mutation of the receptor of LDL, *low density lipoprotein,*) is 1:500 in the population at large, but this condition is responsible for only 5% of infarcts before the age of sixty.

A polygenic system for the regulation of lipid metabolism was sought and a great number of likely genes were found. Correlation studies between polymorphisms of such genes, cholesterol levels, or the incidence of infarcts did not reveal, in spite of intense activity, sufficiently discriminating genetic traits for them to become criteria for risk evaluation. At present, research is moving into combinations of various genetic traits, but progress is slow. As for the regulation of arterial blood pressure, there has been research into genes of the renin-angiotensin systems, in particular on polymorphisms in gene ACE (angiotensin-converting enzyme). Several of the alleles predisposing for myorcardial infarcts seem to be "hyper-functional" alleles instead of deficits as in most ordinary genetic conditions. At the present time, a precise evaluation of the multigenic risk is still not feasible for multigenic cardio-vascular disease.

Possibilities in the domain of familial hypercholesterolemia remain to be evaluated, but in practical terms there are difficulties because in fact, on the one hand, the mutations are numerous, almost one specific to each family, (automation of molecular analysis might be a solution to the problem) and, on the other hand, there is a great diversity of phenotypic expression within a single family.

- Diabetes

Type I diabetes, which is insulin-dependent, may appear in adolescence. It is an autoimmune disorder of a familial nature. A link with antigens HLA DR3 and DR4 is demonstrated. Frequency of the disease is 0.2 to 0.3% in the population at large, 5 to 10% in first degree relatives, 15% in siblings of an affected individual when they are identical for HLA, and 40% in an identical twin. A probabilistic diagnosis of the risk of insulin dependent diabetes by genetic testing (determination of HLA antigens and other genes) would be of little use in the population at large or even in families with one diabetic member.

However, early serum markers for the development of autoimmune events are now known. These are various antibodies acting on pancreatic cells and decarboxylase antiglutamate antibodies which may be detected several years before any clinical signs become apparent. Early studies have shown that such tests would be highly specific and of great value in predictive terms (80%), so that in future, a set of serum tests would contribute pre-symptomatic information in a high percentage of cases instead of risk evaluation as in genetic tests. However, preventive measures which could be offered need to be assessed to be certain they are effective and harmless.

Genetic components have been recently described for type II diabetes which might benefit from the observance of a diet by way of preventive measures.

Type II diabetes, non-insulin-dependent adult-onset diabetes, more often than not is highly genetic and sometimes transmits like a single gene with high penetrance disorder (case of MODY due to a mutation of the glucokinase gene).

In spite of the obvious advantage of detecting susceptibility genes in a disorder which can frequently be much improved by simply observing a diet, there is a difficulty in achieving this result because there may be a great many genes involved and so far only a few of them (four as of now) have been identified.

_ Cancers

Genetic traits may play a major role in the onset of breast cancer by increasing sensitivity to environmental carcinogens. Ataxia telangiectasia is a rare genetic disease inherited in the

autosomal recessive mode. In the population as a whole, there are 1 to 2% heterozygotes; these individuals are sensitive to ionising radiation and run a high risk of becoming cancer victims (the risk is multiplied by 100) and of being affected by breast cancer in particular. It is considered that 10% of so-called sporadic forms could be connected to this heterozygous state. No means of diagnosis exist as yet, but the causative gene (AT) has just been identified. Such concepts would need clarifying when considering preventive strategies using repeated X-ray examinations which could lead to an increase of the risk of breast cancer.

Neuro-psychiatric diseases

Progression is generally very slow. Alzheimer's disease, however, might well be the first example of a close association between a constitutional genetic characters and the frequency of appearance of the disease, both in familial and sporadic forms. We have here genetic variants of a group of proteins, apolipoproteins, which play a part in the metabolism of lipoproteins. Various molecular forms could be associated to a risk of diseases due to disturbed metabolism of these lipids, in particular cardio-vascular diseases, but predictive value is low.

In familial forms of Alzheimer's disease, it was found that 40% of heterozygotous carriers of the variant Apo E4 and 90% of homozygotes contract the disease. There is also a clear increase of the risk of onset of the sporadic forms of the disease in Apo E4 heterozygotes and particularly so for homozygotes. But this molecular form is frequent in the population as a whole, since about a quarter of the population is heterozygous and 2 to 3% are homozygotes. What information can be given to such individuals in particular when the test for lipoprotein variants was undertaken for other purposes ?

Furthermore, 3 or 4 susceptibility genes with high penetrance and specific to Alzheimer's disease have been recently identified.

Principal single gene predispositions to the development of dominant inheritance tumours.

Predisposition	Frequency (Estimated)	Main tumour sites	Gene concerned
HNPCC (Lynch Syndrome)	1:500	colon endometrium	MSH2 MLH1
Inherited breast cancer	1:500	breast ovary	BRCA1 BRCA2
Neurofibromatosis type 1 (Recklinghausen)	1:3 500	nervous system multiple site	NF1
Familial polyposis	1:10 000	colon and rectum	APC
Inherited melanoma	1:10 000	skin	MTS1
Bourneville's tuberous sclerosis	1:10 000	nervous system kidney	TSC2
Li-Fraumeni Syndrome	1:30 000	multiple sites	p53
Neurofibromatosis type 2	1:35 000	nervous system	NF2
Inherited retinoblastoma	1:40 000	retina	RB
Multiple endocrine neoplasia type 1, MEN1	1:40 000	pancreas parathyroids adrenals pituitary gland	(MEN1)
Multiple endocrine neoplasia type 2,	1:40 000	thyroid parathyroids	RET

MEN2		**adrenals**	
Hippel's disease	**1:40 000**	**kidney nervous system**	**VHL**
Gorlin's syndrome	**1:60 000**	**kidney nervous system**	**NBC**
Wilms tumour (WAGR, Denys-Drash)	**1:100 000**	**kidney**	**WT1**

These estimated frequencies are given as an indication. They may vary by a factor of 2 or more.

From Gilles Thomas, Médecine Sciences N° 3, vol.11, March 95, p. 345.

Ethics report

Introduction

Genetics, the science which studies the transmission of hereditary characteristics, was created by Gregor Mendel in 1865 and already has a tumultuous history since it was used as scientific justification for very powerful eugenic currents in various countries during the first half of this century.

This is no doubt because its very object is at the heart of the fundamental interrogation which constitutes the human being : where do I come from, who am I, what shall I bequeath to my offspring, in what way am I both similar to and different from other people. This is why the science of genetics has had and still has more individual, political, and social repercussions than any other. At the present time, progress in human genetics shows promise of a not very distant future when all the human genes - of which there are approximately 100 000 - will have been identified, located on the chromosomes, and when their functions, or at least their implications in genetic diseases will be almost fully understood. The myth of the gene as the stuff of which life itself is programmed, is such that of it is born the illusion that perfect knowledge of the genome of an individual will lead to an understanding of the reality and fate of that individual. Metaphors such as the book of life which would give access to the essential human being if only one could decipher the genetic alphabet and syntax, refer to that notion. Such a concept is scientifically unacceptable and ethically dangerous.

A gene corresponds to a factor for biological determination whose expression and functional significance frequently depend on the influence of other genes and of the environment which in the long term is unpredictable. Even if one were able to understand fully the significance of all genes and of their combined expression, only the biological properties of the living cells and organisms would be known; not the psyche and the emotions of the human being. The genetically determined properties whereby the psychic capacities of the human being are accessed are in fact particularly shaped by the environment and the influences of a specifically human world apart from genetic determinants, a world of culture, knowledge, social mores, values, and of the history of human societies, all of which are in turn shaped by the specific personality of those who transmit them, by the events, by the emotional experience and by the trials of a lifetime. The genome, component of a body, cannot be made to represent the entire human being. However, even though it is limited to the possibility of predicting more or less accurately and precisely, some facets of the biological fate of human beings such as susceptibility to certain diseases or to other non pathological characteristics, the power conferred by genetics is such that it could have far reaching repercussions on individuals and society, now and in the future.

The prospect of personal and social repercussions very obviously calls for ethical reflection.

In fact, in France as elsewhere around the globe, such reflection is resurgent in the last ten years or so concomitantly with the development of molecular genetics. This is expressed in a variety of ways and not just as questions but also directives, guidelines, or sometimes law governing knowledge of the genome and its applications. As genetic tests are being rapidly developed at present - and their effectiveness will probably surpass that of the corresponding therapies for some time yet - the results of this ethical reflection need to be collated, up-dated, and precisely defined in particular with a view to incorporation in the legislative framework adopted by France in July 1994.

The present report begins with a brief overview of essential rules expressed on the subject internationally and in France, with references (I).

To classify the multiple ethical considerations applicable to genetic tests, the report sets out three domains :

- the private life of the individual, including personal identity issues and familial relationships (II);

- the individual and society, where matters pertaining to the dignity of the individual are of overriding importance (III);

- public health issues, with their specific considerations, for which the authorities have special responsibility (IV).

In conclusion, it seemed useful to supply in the annex a few examples to illustrate ethical issues associated with genetic screening in a family and in the population at large.

I. Basic rules and references

In medical genetics, some of the ordinary rules of medical ethics also apply. But in view of the specific nature of this domain, it is immediately clear that there are particular demands in its application, for instance as regards conventional rules of beneficial behaviour, autonomy of the patient (consent and confidentiality), and justice (fair distribution of risks and benefits, costs and advantages).

Thus genetic screening raises specific ethical problems for individuals, families, authorities, and for medical and medical research personnel. Solutions may be based on previously established general or special rules, such as the following :

a) Medical deontology *"primum non nocere"* which includes four principles :

- do no harm,
- prevent harmful effects,
- eliminate harmful effects,
- contribute beneficial effects.

b) The general principles of screening strategies for diseases formulated in 1968 by WHO, which can be summed up as follows :

- Screening must be for a serious disease, frequently found in the population being tested, and which can be detected before any symptoms are visible.

- The method of screening must be reliable, efficient, and low-cost.

- An effective preventive strategy must be available.

For genetic diseases, these general principles are extended to screening of healthy carriers of a mutant gene who may be informed of the risk of transmission to their descendants.

c) A set of rules for genetic screening proposed in 1972 by the Hastings Center in the U.S.A., as follows :

- Programme aims to be clearly defined and realistic; genetic screening techniques to be highly reliable.

- Absence of any constraint; free informed consent.

- Access to information and genetic counseling delivered by qualified staff, in easily comprehensible form and with a therapeutical outlook.

- Confidentiality.

d) A report produced in 1983 in the United States by the President's Commission For the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research which states directives for screening and counseling in the field of genetic diseases. The directives are based on the following ethical principles : confidentiality, autonomy, information, well-being, equity.

e) A report on "Genetic screening. Ethical issues." published in the United Kingdom in 1993 by the Nuffield Council on Bioethics.

f) UNESCO's 1995 report by the International Commission on Bioethics.

g) The Académie Nationale de Médecine's 1995 report on genetic diagnosis and gene therapy.

h) Several opinions of CCNE :

- opinion N° 4 dated 6th May 1985 on medical records for epidemiological and prevention studies.

- opinion N° 5 dated 13th May 1985 on problems posed by pre- and perinatal diagnosis.

- opinion N° 17 dated 15th December 1989 on the dissemination of identification by DNA analysis techniques (genetic fingerprint techniques).

- opinion N° 25 dated 24th June 1991 on the application of genetic tests to individual, familial, and population studies. (Problems raised by DNA "banks", cell "banks", and computerised data).

- opinion N° 30 dated 27th January 1992 on ethical issues raised by an obligation to take genetic tests for female participants in the Albertville Winter Olympics.

i) Laws n° 94-548 of 1st July 1994 and N° 94-653 and n° 94-654 of 29th July 1994 on bioethics.

II.Guidelines and ethical rules for the private life of individuals

At least as much and even more than any other medical examination, a genetic test implies entry into the intimacy of an individual, of his body, and the significance he attaches to it in relation to his psychic identity. Furthermore, almost constitutional frailties may be revealed, of an innate and non accidental nature, the interpretation of which for the representation of self and the consequences for present and future life may be of major importance. To give due consideration to such facts implies taking very special precautions when a test is offered, when its results are given, and for the confidentiality of those results. The relational

and familial aspects of genetic facts further amplify the intimate nature of the results : traits inherited from parents can be transmitted to offspring and shared in various ways with siblings and close relatives. Finally, they may also concern the spouse with whom procreation is being considered. Such possible effects on family relationships must motivate extra care being taken regarding the use of genetic testing.

1. Conditions when offering tests.

For the purposes of medical forecasting and prevention, genetic testing is practised on healthy individuals.

The following paragraphs are an updated version of rules previously pronounced by CCNE on attitudes to be adopted vis-à-vis tested subjects and their families :

respect of subjects' autonomy

Must be respected the right of the individual to take an informed decision on the performance of a test which may reveal in his genetic make-up the presence of a mutant or susceptibility gene which, whatever the result, could have a far reaching effect on his life.

For that to be done, three conditions are essential:

- freedom of choice and absence of any form of constraint.

- total understanding of the implications of a decision which implies information on the nature of the test, the significance of the results, and existing prevention and therapy.

- legal capacity to give free and informed consent.

This obligation of autonomy is applicable not only to the individual who first expressed a request in an at-risk family, but also to all other members of that family, be they also potentially at risk or not, and it must span several generations.

When the test requires a biological sampling for the whole family, the question arises of how to inform each one of them, and how to persuade those who may be reluctant. One cannot entertain the notion that for those who may or may not be aware of the object of the genetic study, or even may not be aware of the exact nature of the medical condition affecting one of their relatives, a physician who would be given their names and addresses should get in touch with them directly. The originator of the request must personally contact his own relatives and this may be an operation of some delicacy requiring a great length of time. Furthermore, the request may not meet with success because freedom of choice has to be given to those approached.

consent

To comply with the law, no determination of characteristics in the genotype of an individual can be undertaken unless specific consent has been given by that individual. Should research be extended to characteristics in a domain which is foreign to that for which authorisation was given at the time of sampling, because of possibilities of DNA storage for instance, consent must once again be requested.

Information on the genotype of an individual can only be imparted in the context of shared medical confidentiality, for therapeutical objectives and with formal consent from the individual concerned.

Familial studies may reveal the non marital nature of a filial generation which was unknown or concealed, but knowledge of which in biological terms is essential for the interpretation of results and possibly their use for diagnosis purposes. To prevent such a revelation from

disturbing the life of a family, law N° 94-654 of 29th July 1994 provides that "exceptionally, when such a study is undertaken for medical purposes, the consent of the person may be not requested in order to protect the interests and respect the trust given by that person" (art. 145-15 of the code of public health).

information about the test

Information must always be given person to person orally; supportive written explanations must be given concurrently. The written document, although it may help reflection on the part of the individual concerned, must not be the only means of information. The information must be imparted by a qualified person with training in medical genetics. Training such qualified staff in sufficient numbers is obviously a problem particularly since communication may be time consuming and require several sessions. Furthermore, a period of time should be allowed for thinking over the information before consent to testing is granted.

Prior information on the possible results of the test and their significance is part of the above process.

The information process must continue after testing to explain once more the consequences of the results obtained and to help alleviate any psychological repercussions.

2. Announcing results to the person concerned

right to know and right not to know

Knowledge of the results of a genetic test may limit the moral autonomy of an individual. Such a situation may arise in the case of a familial study or in a research programme. In single gene diseases, knowledge of test results may modify the behaviour of the individual : for instance, in X-linked conditions, a woman who knows she is a carrier of a disease (muscular dystrophy, hemophilia...), or in dominant inheritance, knowledge that one is a carrier of a mutant gene and will be affected at a future time (Huntington's disease). The subject may therefore refuse communication of the results.

Knowledge of negative results may also affect the tested subject. Guilt feelings have been observed in those, in a family, who have not inherited the mutant gene of Huntington's disease.

An even more complex case is knowledge of probability as arises for susceptibility genes. Is a person to whom has been revealed the existence of a gene of susceptibility to a cancer or to a neuro-psychiatric disease, who has no other resort than systematic testing in order to possibly transform a probability into certitude after who knows how long a time, in a position of full autonomy ? There is great uncertainty about whether it is appropriate to communicate results of the traits of a genome which would only be able to provide a probabilistic evaluation of the risk of severe disease without any possibility of offering effective preventive action.

communication of results

Laboratories must have an internal organisation capable of protecting confidentiality and privacy by preventing the dissemination of information about a person who has undergone testing or about his family (e.g. paternity data).

Results must be communicated by a physician whose qualifications enable him to explain their significance.

Marketing of genetic testing through the mail, examples of which exist abroad, may be the cause of serious dysfunction in the transmission of information.

3. Conditions of familial studies

confidentiality and respect of privacy

Medical confidentiality is an obligation as regards communication to third parties, including other members of the family. If a patient refuses to reveal to members of his family the genetic test he has undergone, the physician cannot warn them of a possible risk. The right of each patient to confidentiality may be in contradiction with the interests of collateral relatives who could benefit from preventive action if the results were known to them.

genetic characteristic testing in children

When the existence of a genetic disease within a family is found, examination of genetic characters of the children of that family must not be treated as routine procedure. Specific situations based on an analysis of medical data (nature of the disease, date of onset, possible prevention, ...) and family data must be the basis for further action.

In Opinion n° 25 of 24th June 1991, CCNE underlined ethical problems raised by the examination of children.

"Parents may request analysis of their child's genotype only if the disease connected to that genotype could appear before the age of 18 or could be alleviated by preventive action undertaken before the age of 18".

Such restrictions must be respected, in particular in presymptomatic screening of adults for severe diseases for which exist neither treatment nor prevention, as is the case for Huntington's disease.

If preventive measures do exist and if the chances of success of treatment depends on early implementation, then the child must be tested and, depending on test results, given appropriate follow-up. The child should be informed as soon as he is old enough to understand.

In a few number of cases, testing genetic characters in a child would lead to the evaluation of a risk for his future descendants: detection of a balanced abnormality in the chromosome structure, or of a mutant gene in X-linked conditions. In such cases, there is an obligation on the family to inform the child as soon as he has reached the age at which he can procreate, and is able to understand and take a decision about undergoing tests.

In certain circumstances, knowledge of genetic characters of a child may be essential so that the risk for the descendants of another member of the family can be ascertained. This occurs in X-linked diseases when the affected child is deceased and the genetic traits of a healthy child permit identification of the X chromosome which does not carry the mutant gene.

In any event, prolonged and patient information sessions with the parents are an absolute necessity before considering such tests. The decision cannot be entirely made on the basis of the wish to know of parents or attendant physician.

knowledge of genetic risks for descendants

As a result of family or population studies, an individual may be apprised of a risk to his descendants. The risk may depend only on the passing on a personal genetic trait (X-linked conditions, dominant inheritance diseases) or be the consequence of union with a spouse carrying the same genetic trait (recessive inheritance).

Clear information must be provided about the risk, possibilities of pre-natal diagnosis and difficult decisions the couple may have to take about continuing or terminating a pregnancy.

Transmission from one generation to the next of information about genetic traits may be necessary. Provision must be made for keeping familial genetic data for at least a generation and methods devised for passing on such information to at-risk individuals when it becomes useful.

Problems arising from pre-natal diagnosis have been the subject of CCNE's Opinion n° 5 of 13th May 1985 and of the law dated 29th July 1994.

4. Conservation and utilisation of data

biological samples (dna)

Care must be taken to protect the interests of those individuals from whom a sample has been taken. In particular, any samples which might be of further use at a later date for tests on themselves or members of their family must be kept.

Storage of samples is essential for possible verification.

Use of samples for studies on the onset of certain genetic or infectious diseases (HIV for instance) cannot be allowed to take place if the individuals concerned have not been informed of the nature of the study, the consequences of its results, or without their previous consent.

In neonatal screening, the possibility of needing and keeping for use at a later stage the blood spots on filter paper should be considered . They could be of the utmost importance for instance for retrospective diagnosis of genetic disease which has caused the early death of a new-born infant.

Ethical recommendations stated previously must also be followed when collections of biological samples are made for a research programme.

- Motivation of individuals when participating in a research programme in human genetics is frequently a desire to hasten the progress of knowledge, diagnosis, prevention and management of diseases affecting themselves or members of their families. They may justifiably request that every effort should be made to achieve these aims with the help of samples taken from their DNA or their cells. Consequently, prolonged confiscation of sample collections by research workers who fail to make optimal progress in their efforts would probably not fulfil the expectations of the individuals concerned, or might even be a violation of an implicit commitment to do everything possible to obtain results which are of vital importance to them.

- Initiators of research for which a collection has been put together and for which consent has been given, are under an obligation to carry out that research with the means available and in the stated conditions. They may also avail themselves of a right of priority to use that collection for their own research.

- In the eventuality that initiators of research were to decide not to carry out the research themselves, they should inform the individuals concerned of any modification their decision might entail for the pursuance of the research.

- A reasonable length of time should therefore be set, beyond which access to the collection of samples would be open to other scientific teams besides the initiators for research work according to the initial programme for which consent was given, whether the initiators have already arrived at significant results leading to publication or filing for patents, or have failed in their efforts.

computer storage of personal data

Computer storage of nominative data concerning individuals who have had samples taken must be undertaken in conformity with rules of medical confidentiality and privileged information as set out in law n° 78-17 of 6th January 1978 concerning the use of computers, computer data bases, and individual liberties, as complemented by law n° 94-548 of 1st July 1994 concerning the processing of nominative data with a view to health research.

Recommendations for the establishment and use of automated medical records were defined by CCNE in its Opinion n° 4 of 6th May 1985, and also in Opinion n° 25 of 24th June 1991. The above rules and recommendations can be summed up as follows :

- the right for the individual concerned to oppose automated processing of his personal data or to ask for its deletion from the records, if he has good reason to do so;

- right of access, through a physician of his choice, to recorded information;

- right of rectification;

- right to oppose the transmission of data concerning him;

- obligation to obtain informed and express consent from the person concerned, before any computerisation of data for research purposes, since the nature of this research calls for biological samples to be identifiable;

- forbidding access of any third party, in particular employer or insurance company, to any information contained in a record and furthermore, forbidding third parties from asking the individual concerned to produce any such information;

- the keeping of these records should be authorised only for a small number of officially approved centres providing demonstrable and sufficient guarantees as to their scientific and ethical reliability.

III. Reflections concerning the dignity of the individual in society

Though genetic knowledge helps to define the components which constitute the identity of human beings, it also emphasises the specificity of each individual and offers possibilities of classifying them into groups carrying a common or similar characteristic. The possibility as such is morally neutral and can be used for the common good. However, it enters into conflict with an ethical perspective which is of a formal nature but is at the very centre of the principles of Human Rights : equality in dignity.

François Jacob strongly underlines this concept : "By a strange misconception, efforts are made to confuse two very separate notions : identity and equality. One of them refers to the physical or mental qualities of individuals; the other to their social and legal rights. The first pertains to biology and education, the second to morality and policy. Equality is not a biological concept... The crux of this discussion is of course the social and political aspect, either for the purpose of basing equality on identity, or because of a preference for inequality, for the purpose of justifying it by diversity. Surely equality was specially invented because human beings are not identical.... Diversity is one of the major rules of the biological game... And this diversity, this infinite play of combinations which makes each and everyone of us unique, cannot be overestimated. This very diversity gives rise to the richness of the species and is the source of its potentialities."

The ethical issue of selection and discrimination is therefore at the centre of our society and in so far as genetic testing is concerned, there are two intensifying aspects :

- Negative discrimination (stigmatisation), on the basis of a trait or susceptibility to some disease. Physical handi would be reinforced by social discrimination. Normality and pathology, from their social viewpoints, have to be considered. François Gros underlines : "Care must be taken to prevent insidious progression from hereditary traits with morbid or vital consequences, to hereditary traits which do not comply with the norm".

- Anticipatory or prospective discrimination, practised for the sake of a future that has not and indeed may not happen, but which if announced becomes a threat.

That is why prevention, reasonable and useful in terms of humanity, takes on a very different hue in social terms. The different uses of the forms of words (in the French language) such as "prévention", "préventif/tive", "prévenu" , are significant. As Emmanuel Maheu explains : "Prevention, the word sounds familiar, with an obvious meaning. There is no ambiguity: doing you good is the unequivocal meaning. This is a positive word, one might even say a comforting word. Intentions are obviously beneficial, and clear to all.

To be "prévenu", to be forewarned, is as a popular saying goes, to be forearmed. Who would refuse such reinforcement of ones defences ?

"And yet....," Devos might say. In legal lingo, which is very different from medical parlance, to be "prévenu" is to be accused or indicted for some misdemeanour or crime. On a more personal basis, to have "préventions" about someone, is synonymous with having preconceptions, previous and unfavourable bias about someone. That is surely less gracious. On the other hand, to be "prévenant" is to be thoughtful and considerate in one's dealings with others, in other words warm hearted and friendly. As soon as one explores this family of words, the multiple possibilities of meaning become very striking.

Is this just an exercise in semantics ? It is accepted that words have meaning. Here we easily discover several and find a non-monolithic family of words. We are led to suspect that prevention is a concept that is not easily defined."

One must be all the more careful about any possible discrimination because genetic tests can be used for purposes which are neither medical nor scientific. This is a lesson that history taught our society. Furthermore, some social realities of today raise this question in no uncertain terms : insurance and employment.

1. Reflections on the use of testing of genetic characteristics for medical and scientific purposes

The importance of independence and consent of individuals and the obligation to respect confidentiality of results and protection of personal data, have been emphasised in a section of this report which sets out rules of ethics for the uses to be made of genetic tests for medical and research purposes.

One risk of a trend of disputable ethical merit is worth mentioning : using tests to market inflationary offers taking advantage of human aspirations for total security. Apart from genetic traits for severe pathologies, for everyone to become cognisant of the multiplicity of "defects" which affect them could become an impediment to the freedom of the individual: "How many of us will feel completely healthy once we have been tested for everything" (Lord Kennet, May 1994).

This raises a difficult question: destiny and freedom in the face of knowledge of genetic risks.

On the one hand, ignorance is seldom a freedom promoting factor, and knowledge of susceptibility to avoidable ailments bestows upon an individual the responsibility of drawing the consequences of this knowledge. After all, it is universally accepted that acceptance of

one's fate is a key to true exercise of one's freedom since otherwise there is nothing more than wishful thinking. Nonetheless, the significance of the exercise of freedom by a person whose genetic predisposition leaves no choice but a life in the grip of terrible constraints or preventive mutilation or risk of incurable disease, is open to question. Another individual dimension of a genetic fate revealed is that sometimes, in the case of the handing down of a serious disease, it is tantamount to a curse put on the lineage, since the parents may be considered guilty of transmitting a faulty gene to their children who in turn, feel guilt at the possibility of passing it on to their own descendants.

2. Reflections on the use of studies of genetic characteristics for purposes other than medical or scientific

The use of information obtained by a study of genetic characteristics for purposes other than medical or scientific raises many ethical problems which have been pointed out in various reports both in France and abroad, and also in texts on genetics adopted by the Council of Europe and the European Parliament (2) .

Biological samples could be diverted from their medical purpose and used to seek out other genetic traits, such as the discovery of genetic prints for judicial uses, or to detect traits connected with certain behaviours such as violence, criminality, drug addiction, or again for traits which are particularly frequent in certain ethnic groups and which might be made available to the authorities of totalitarian systems engaged in conflict.

A more immediate risk is that of discrimination based on selection through genetic criteria in the fields of insurance and employment. If genetic characters were put to such uses this would herald a complete overturn of the foundations of our society which are built on principles of equality and solidarity.

CCNE, in its Opinion of 24th June 1991 on applying genetic testing to individual, familial, and population studies, had recommended that any third party, in particular employers or insurance companies, should be prohibited from access to data held in a DNA bank and from requesting the individuals concerned to produce such information. The laws dated 29th July 1994 on bioethics (laws n° 94-653 on respect of the human body and N° 94-654 on the gift and use of elements and products of the human body, medically assisted reproduction, and prenatal diagnosis) reiterate this prohibition. The laws stipulate that "genetic study of the characteristics of a person can only be undertaken for medical purposes or for scientific research" (art. 16-10 of the civil law code (*code civil)* and art. L 145-15 of the code of public health (*code de la santé publique*). "The act of diverting from its medical or scientific research objectives, information obtained about a person through a study of that person's genetic characteristics is punishable with one year's imprisonment and 100 000 Francs fine." (art. 226-26 of the penal law code (*code pénal*)).

Before considering the consequences of such laws on employment and insurance, it should be noted that the law is to be discussed anew after five years and therefore attention must be paid to any decisions on the subject in other countries and in particular member countries of the European Union (3). The possibility of free choice of an insurance company in the European Union may lead French insurers to request that the existing law be made less demanding so that they would not be at a disadvantage because of stricter rules than competition in the rest of Europe.

use of genetic testing in the field of employment

Genetic tests to discover predispositions or pre-symptomatic diseases might be tempting for employers who wish to select applicants for a post or to consider the career prospects of existing employees. By eliminating individuals at risk of developing a disease, they could hope to reduce costs related to absenteeism, lowered productivity, and obtain better profitability from training and sales campaigns. Such tests would be no more than a further means of selection made available to employers. Clearly, using tests in this way would lead

to excluding people from the labour market on the basis of criteria which might well be invalid since they could be due to an erroneous interpretation of test results or bias or misunderstandings or unreliable analyses. But the fact that the usefulness of genetic tests to predict the productivity of employees is doubtful is not sufficient in itself to preclude the risk of their being used by employers who on occasions do use for that purpose even more questionable methods.

However, though there might conceivably be some benefit for employers, there is a contradiction with the fundamental rights of workers to non discrimination for health reasons and those relating to protection of privacy. Such rights which have just been reinforced by the laws on bioethics, are proclaimed in several articles in the labour code (*code du travail)* and the penal code (*code pénal)*.

An employer may not ask an applicant for a post or an existing employee for information unless it is directly connected to and necessary for the post on offer or for an evaluation of vocational abilities (art. L. 126-6 of the labour code). Few genetic tests, if it was allowed to use them for that purpose, would meet such conditions. It should be noted, however, that this condition which was introduced by the law dated 31/12/1992 on "Conditions of recruitment and freedom of the individual" is unlikely to be much of a deterrent since it does not entail any sanction.

Since entry into force of the law dated 12/7/1990 on "discrimination for reasons of health or infirmity," any selection of individuals based on their state of health is an offence (art. 225-1 of the penal code). Such discrimination is punishable by two years of imprisonment and a fine of 200 000 F. , when it arises on the occasion of an offer of employment or if it represents a refusal to employ or is the reason for ceasing to employ an individual (art. 225-2 of the penal code). Furthermore, dismissal motivated by the state of health of an individual is null and void (art. L.122-45 of the labour code).

Prohibition of discrimination for health reasons does not solely concern affected individuals but also those who are at risk of being affected by a disease. This is so because the law of 12/7/1990 was voted to protect Aids patients and also those who are infected by the virus but do not as yet suffer from full-blown Aids. Discrimination based on the results derived from presymptomatic or probabilistic genetic testing would therefore be illicit.

The law does however provide for an exception : there is no infraction when a refusal to employ or a dismissal is based on medically verified inability within the occupational medicine system. To what extent do the laws of 29/7/1994 on bioethics authorise the use of genetic testing to verify such inability ?

There is a general obligation on employers to take all necessary steps to protect the health of workers and guarantee their safety and that of third parties. However, it is not a duty of the employer to seek out on that score, information on the state of health of an applicant or of an employee. He cannot therefore ask them to submit to such tests even though they may be intended for the prevention of diseases and would clearly be medically defensible.

Possible repercussions of genetic predisposition to a condition or of a presymptomatic diagnosis can only be evaluated in the light of medical aptitude for a given employment which is solely the purview of the occupational health physician. But this aptitude, which must be verified by a medical examination before recruitment and by further periodic examinations, must be evaluated at the time of the examination and not as regards future risks.

The use of presymptomatic or probabilistic testing should not normally, therefore,

be allowed. In fact, as long as the disease has not broken out, there is no inaptitude for work and a decision based on such a diagnosis would be of a discriminatory nature.

However in certain cases, when the probability of onset of a disease for reasons connected

both with genetic predisposition and the working environment is particularly great whereas this is not the case for other workers, and when the disease presents for the worker concerned a grave danger which cannot be attenuated or eliminated by a modification of the environment, it can be acceptable that the occupational health physician prescribes genetic tests to detect susceptibility to disease. The law does allow him to prescribe whatever complementary tests may be necessary for the detection of an affection which is a contra-indication for a form of employment.

Prescription of such examinations can only of course take place in conditions which comply with the law, i.e. after written consent has been given by the applicant or worker and with protection of privileged information in the results of the tests to which the employer cannot under any circumstances gain access.

The person concerned must always be informed of the nature and object of the test and also of the consequences of the results of that test on the possibility of retaining or obtaining the post in question. However, the person's right not to know the results is difficult to observe if it turns out that inaptitude for work is found.

Instances of a study of genetic traits being useful for preventing work-related diseases are rare indeed in the present state of scientific knowledge. The use of genetic testing in occupational medicine must therefore be exceptional and rigorously restricted to cases on a limited list for which the risk for the individual is sufficiently established and available tests sufficiently reliable and pertinent. Such screening should in no case be systematic nor should its use ever have as a consequence the reduction of preventive action against occupational risks by privileging the elimination of the most genetically exposed workers instead of improving the working environment. Adequate assurance in this respect will only be achieved through a modification of the status of occupational health physicians who presently are employed by the company. So long as their status is not one of independence, their role remains most ambiguous (4) .

Laws on bioethics state unequivocally that employers are excluded from direct access to genetic screening tests, but one cannot be certain in the present economic context, that pressure might not be put upon applicants for a post in order to obtain genetic information about them. Nor can one exclude the possibility that the candidates themselves might wish to produce the information spontaneously if it were in their favour. Although it seems difficult to totally eliminate this risk, it could be reduced by a strict limitation of conditions of prescription of tests.

use of genetic testing in the insurance sector

The 1994 laws on bioethics exclude the possibility of insurance companies making use of genetic tests. However, this prohibition can be reconsidered when the law comes up for revision by July 1999 after an assessment of its application by the parliamentary bureau of evaluation. On the same date expires the moratorium adopted by the French Society of Insurance Companies according to which insurance companies made a commitment not to use information obtained by genetic tests. Attention should therefore be given in the meantime to an exploration of objections which might then be raised to a continuation of the prohibition. Genetic testing is pertinent to insurance matters when an evaluation of the risk requires knowledge on the state of health of the person insured, i.e. life and health insurance. Theoretically, the latter should not be affected by any developments in "predictive medicine" since in France it is an obligation and is based entirely on solidarity. And yet, the public health systems and the protection they give are most in danger of destabilisation or even disintegration. The principles on which they are based are in fact already very weakened by the de facto exclusion of an increasing number of individuals who, for economic reasons cannot benefit from social protection. This process could be accentuated by the development of genetic predisposition tests which by demonstrating that individuals are not equal as regards health, could sap the foundations of the principles of solidarity based to a large extent on ignorance as to the future fate of the individual.

For private insurance schemes based on a risk selection at the outset, the situation is rather different.

In fact, at the present time, an insurance company can quite legally ask for medical information to evaluate the risk it is underwriting. The law dated 12/7/1990 which provides for penal sanction of discrimination based on a state of health, is not applicable when such discrimination is exercised for the purposes of insurance. The insurance company may therefore ask the future policy holder to submit to a complete medical examination. A questionnaire must generally be filled in and frequently includes questions which, indirectly, are related to genetic traits: family history, hypertension, hypercholesterolemia, obesity...

The policy holder is held liable for the answers he gives to the questionnaire. A voluntary insurance policy is in fact a contract based on good faith, since it is on the basis of these statements regarding health that the insurance company will be able to assess the risk they are covering. Any omission, error, or false statement leads to a cancellation of the guarantee. Through medical selection the population of the insured is classified into homogenous groups and, according to the principles of mutuality, the large number of insured persons pay the costs of an unfortunate minority. In practice a disputable restriction has been applied to that principle to the effect that the "good risks" do not have to pay for the "bad risks", since equity and equality are two different concepts. So the higher risks in private life insurance schemes in fact form a special group whose premiums are higher or guarantees are reduced. In some cases, insurance companies refuse to cover the higher risks. On the contrary, the public social insurance schemes and the mutual schemes are based on principles of equality and solidarity so that all those insured pay for the excess cost of the "bad risks". However, even in countries such as France where the population generally is covered by these schemes, economic constraints and principles of liberal economy are a serious threat to their persistence and private insurance is increasingly filling the gap.

In the double context of a lively development of genetic tests and of a reinforcement of liberal economic thinking, it seems highly unlikely that private insurance schemes who already request familial data to better evaluate the exact risk insured, will of their own volition give up taking into account or asking for information of a very much more precise and extensive nature that genetics can now supply. Yet, following that route would be a very serious step in the direction of questioning fundamental values of equality of rights and solidarity between all human beings. This is the essential point : it may be considered acceptable for matters of secondary importance ("minor risks") to adapt to market conditions for a population with an adequate standard of living, but it certainly is not to drive into that mode of private insurance the "major risk" on the grounds that it would henceforth be genetically detectable and assessable. As have stated other groups reflecting on these matters, the French National Consultative Committee for Ethics considers it necessary that the present legal prohibition in France from using for that purpose genetic testing should be maintained. The very spirit of human rights is at risk here.

The law clearly forbids the insurance company from demanding that the policy holder undergo genetic tests, but may it ask him to impart the results of a genetic test previously undergone for medical or research purposes ? The essence of an insurance contract being a loyal exchange of information, knowledge of a genetic risk by the insured person only, such knowledge being withheld from the insurance company, the latter and other insured persons could be negatively affected by an unequal contract relationship.

However the law, which punishes the use for other purposes of genetic data collected in the interests of medicine or research, would seem to prohibit the insurance company from making such a request. The insurance companies themselves accepted the restriction for the duration of a five year moratorium.

This total prohibition which can lead to loss of symmetry in the supply of information, is justified by the risks that use of these tests by insurance companies represents as regards privacy of individuals directly concerned and that of their families. It is also justified by the

threat it would represent for the mutual insurance systems. The threat depends very much on the way in which medical tests are used. If they continue to be employed only in at-risk families as is the case now, they would only affect a small proportion of the insured population and would probably have no influence on insurance mechanisms.

If testing is used for mass genetic screening of the population at large, there will be increasing opportunities to distinguish between categories of insured persons who will progressively be called upon to manage their own risks to the detriment of the principles of mutual solidarity. However, the multiplicity of tests will probably lead to the balance of genetic risk distribution being restored throughout the population, all the more so since certain factors which predispose for one disease may be a protection against another. Nevertheless, even though genetic factors are not totally pertinent for an evaluation of risk, evident public enthusiasm for a genetic approach to health problems is such that they may be over emphasised compared to other criteria which are more difficult to quantify scientifically such as those related to behaviour or to the environment. Genetic information might well be used by the insured persons themselves if it seemed to improve chances of obtaining a favourable insurance policy. As in the case of employment, one cannot hope that legislation will prevent an insured person from revealing any information in his possession if this is likely to be an advantage.

In fact, both in insurance and employment, all the economic mechanisms of our "liberal" societies lead, sooner or later, to extensive use of genetic information. It would seem that in the long term, it is only through discussion in society of the part to be played by solidarity in the collective workings of that society that may be avoided the serious and foreseeable effects of the arrival of an ever increasing number of genetic tests on the social scene.

IV. Some reflections on the responsibilities of society towards individuals

Knowledge of genetic matters through the use of tests opens a new chapter in public health policies and the responsibilities of the authorities in this respect. Preceding chapters of this report have shown this to be so on several counts.

If these tests are organised on a massive scale, they will present society, in public or private matters, with important ethical problems to solve mostly in the fields of evaluation and information.

Rules will have to be established for the technological transfer of genetic tests to the public health system and to the users of genetic information taking such problems into account. Above all else, equality of access to these tests within the public health system must be guaranteed.

1. Evaluation

evaluation of genetic tests

Conditions of exactitude and reliability which need to be drawn up for the application of these tests will be covered by the implementation decrees mentioned in article 1 of the law of 4th February 1995 "providing various social measures".

Evaluation of genetic tests based on their reliability, their specificity and their sensitivity, conforms to rules usually applicable in biological testing.

The high degree of technicality and diversity of genetic tests implies specialised laboratories as this is an essential condition for sustained technical quality of results and of their interpretation.

Procedures for habilitation and quality control must be established in the immediate future.

evaluation of extensive application of these tests

For tests to be performed on a vast number of people, feasibility and reliability pilot studies must be undertaken before starting. The results will need to be examined with discernment since a pilot study is carried out in privileged circumstances which do not necessarily tally with those of a routine testing procedure (quality and motivation of participants, including, frequently, tested individuals themselves).

Evaluation raises problems :

- what is the predictive value of tests and according to what criteria should this be judged ?

- what is the value of preventive and curative action which will be recommended to those elements of the population selected by genetic tests ?

Predictive value of the tests

An evaluation of the predictive value of the tests is based on two concepts :

a) positive predictive value for the tested individual : that is the proportion of affected subjects in the population for whom test results are positive.

- It may be a very large proportion in the case of a presymptomatic diagnosis of a dominant single gene disease such as Huntington's chorea.

- It may be small, as is the case at present of genetic testing for predisposition to myocardial infarction.

- It may be difficult to evaluate because of the coexistence of hereditary forms detected by the genetic test and a greater number of sporadic forms as is the case of breast cancer.

b) the prevalence of carriers of the gene of susceptibility, that is the fraction of the population at large which is at risk and who might benefit from preventive action when the genetic risk factor is recognised, either for the index case or for descendants.

In a few cases, even with low prevalence in the population, the positive predictive value of the test and the value of prevention justify screening; phenylketonuria is a case in point. At the opposite end of the scale, on the basis of probabilistic tests should one select a group of increased-risk individuals for a frequent ailment when general preventive action can notably reduce the risk of incurring the disease ? Such would be the case, for instance, of myocardial infarction since a campaign focused on prevention aimed at the general public would be more effective than a strategy centred on an at-risk group.

This opposition between benefit for the individual or for the population at large will be the most difficult problem to solve when a choice of health policy is made.

Evaluation of preventive and curative methods

Evaluation of preventive measures applied to a population selected through genetic tests for susceptibility will be particularly difficult for multifactorial diseases. But such an evaluation is essential even if it means monitoring over many years.

Difficulties encountered in the evaluation of the usefulness of mammography for mass screening of breast cancer in the early stages of the disease are an example of the complexity of the problem.

evaluation criteria

Evaluation cannot just be founded on medical criteria such as onset of the disease, its severity, life expectancy after diagnosis.... Such data is quantifiable but requires lengthy and careful evaluation.

Long term harmful effects must also be considered. The question arises for instance for immuno-suppressive therapy in order to prevent the onset of Type I diabetes. Nor must quality of life be omitted and this is even more difficult to evaluate :

- quality of life at the time of genetic screening and consequences of learning the results on personal behaviour (anxiety, stigmatisation) and on the life of the family and in the working environment (parenthood projects, education, career);

- quality of life connected to the constraints brought about by prevention : prenatal diagnosis and medical abortion as the only "solution" for single gene diseases, physical and psychological stresses induced by the observance of preventive action for multifactorial conditions.

evaluation of reactions to screening and prevention

A genetic screening and prevention programme will only be effective if it is accepted by the target population and the medical profession.

Population

The way in which the risk of onset of a severe illness is viewed varies a great deal in different groups and individuals. Many factors play a role : frequency of the condition generally, cases known in the family or elsewhere, characteristics of the clinical expression of the disease which make it possible to recognise an affected individual (Down's syndrome, or myopathy, for instance), high media profile of certain diseases through the activities of dynamic groups.

Inversely, certain diseases although frequent, remain obscure for various reasons: no characteristic phenotypic expression (cystic fibrosis) secrecy observed by unhappy families (frequently occurring in cases of mental retardation, for instance fragile X syndrome).

Previous studies may be of benefit to decide on attitudes to preventive action. Thus, studies already carried out on the subject of prenatal diagnosis of severe genetic conditions show a high degree of acceptance of the diagnosis and of the possibility of therapeutic abortion.

For multifactorial diseases, cancers in particular, studies have already been made of participation in screening operations for cancer of the cervix and breast cancer and have shown some of the difficulties encountered.

The acceptability of a screening protocol is a determinant factor in the results obtained. Participation ratios and proportion of individuals ready to accept the protocol in its entirety (compliance ratio) will also be determinant. Experience acquired in screening for breast cancer shows that 60% must be attained for the benefits of the measures to be acceptable collectively.

The medical profession

Participation by the medical profession as a whole is essential for a screening and prevention policy to be successful. But prevention has social implications which modify the relationship between physician and patient.

Apart from the physician's knowledge concerning the value of the methods and his personal analysis, several factors may influence his behaviour :

- fear of liability if he does not inform his patients;

- the difficulty of informing families. The physician is confronted with a complex situation: on the one hand, the obligation of protection of privileged medical information and of not informing directly members of the family of a risk discovered in one of his patients who refuses to warn them of the situation, and on the other hand the possibility of a complaint by members of the family about the physician who did not inform them of a risk when the family finds itself in a medically disastrous situation which could have been avoided if they had been informed in good time;

- financial concerns.

The reactions of the medical profession to indications for mammography as a means of breast cancer screening is an illustration of such behaviours. Various studies have demonstrated that it is best not to recommend mammographies before the age of 50 because of the absence of benefit from such screening for women aged 40 to 50. In spite of recommendations to that effect, it was found (in Sweden and North Carolina) that physicians continue to recommend mammographies on an individual basis independently of health programmes.

evaluation of costs

It has often been said that prevention is less costly than curative action and that the public health budget will save money by it.

Similarly, scientific publications about genetic tests have stated that if such tests are made general the cost price of each test will be significantly lowered. In fact, the test itself represents only a small part of the cost.

When costs are evaluated, both direct costs such as for the predictive and preventive phases, the resources mobilised to organise the campaign, on the one hand, and indirect costs such as loss of income induced by absenteeism on the other hand, must be considered and integrated.

a) Cost of genetic testing proper including all components :

- sampling, dispatch of samples, the test itself, storage of samples and data, quality control.

- information before testing, communication of results by qualified personnel, explanations of various kinds, in particular responding to telephone queries, secretarial work...

For genetic counseling (for genetic diseases) a calculation was made that on average, qualified staff spent up to one or two hours on each patient. In some cases, such as Huntington's disease, much more time has to be spent.

Studies on screening heterozygotes for cystic fibrosis insist on the relatively low cost of such tests as soon as they are practised on a large scale. But the modalities and the cost of information which will have to be given individually when the results are available are not considered. In the United States, it is thought that if such a policy was to be generalised, the process of informing parents would completely saturate the facilities of genetic clinics and that the cost of screening one affected foetus would be as high as 300 000 dollars.

b)Cost of prevention for those selected by a susceptibility test.

For this kind of prevention, there will frequently be a second phase of selection of at-risk

individuals by repeat tests (mammography, coloscopy, testing of the stool for occult blood...), the cost of which must be added.

c) Cost of the constraints of prediction and prevention, defined in terms of repercussions on the life style of those involved in screening programmes.

All of these evaluations have an influence on public health policy in which the best interests of the individual and society's will to meet the cost of this policy for the greater benefit of the multitude will be in conflict.

In economic terms, the cost to the community of such screening must be adequately evaluated in relation to other expenditures.

Insofar as choices have to be made optimising expenditure and ranking objectives, policy makers must adopt a clear position on the importance they attach to genetic diagnosis.

In the present state of affairs and subject to the reservation that research remains non-limited and entitlement to testing with due medical justification is accepted, there seems to be no reason why genetic diagnosis should enjoy greater priority than other procedures, either because the reliability of the test is disputable, or there is no effective therapy, or because the condition is not systematically and solely related to a particular gene defect.

Although it appears necessary to improve the community's management of truly preventive medicine, it would be hazardous to attempt to manage genetic predisposition with the help of seemingly preventive measures in view of the impossibility of calculating costs with any accuracy and uncertain effectiveness.

2. Information

Society's responsibility is situated at various levels : medical information imparted to those concerned, pedagogical information, information given to the general public.

individual medical information

Training of qualified medical staff

Human genetics in general and molecular genetics in particular have only recently made progress so that most practitioners were not taught these subjects in the course of their medical training.

Molecular biologists use rather esoteric language which seems mainly composed of acronyms so that it is difficult for the practitioner to come to grips with this branch of preventive medicine. In addition, clinical and epidemiological genetics differ in their conceptual approach, which is a further complication.

It is however essential that each patient should obtain a better quality of information than what is provided by the media or by friends and relations. Medical staff must therefore be trained in clinical and epidemiological genetics in medical schools and above all, for the time being, through refresher courses for practising general practitioners and specialists.

Ethical issues arising from the storing of information

The usual rules relating to confidentiality of information and their computer storage have already been mentioned above.

A special problem is the storage of information concerning genetic traits so that they can be transmitted from one generation to the next, i.e. 20 or 30 years on. Two examples are given to illustrate the problem :

- in the course of prenatal diagnosis for a couple of which one parent is a carrier for a balanced chromosomal translocation, the same balanced translocation is diagnosed in the foetus. Pregnancy is continued and a live birth ensues. How should this information be kept safe so that in 20 or 30 years' time the offspring is informed of the possible risk for descendants ? It would be a paradox for the child not to benefit from a diagnosis his parents were given the benefit of;

- an identical problem arises for families affected by an X-linked inheritance for which an extensive familial study has been undertaken. How will female carriers be informed and who will be required to do so when they reach the age when procreation becomes a possibility ?

The problem is therefore a dual one :

- how should information about a family be stored for at least a generation ?

- how should at-risks individuals be informed when such knowledge becomes useful?

In countries where screening for heterozygotes for a frequent and severe recessive condition, such as beta-thalassemia in Italy or Greece, the public is at present aware of the problem since it has come across the disease. However, thanks to screening and selective abortions, only very few affected children have been born in the last ten years and older sufferers have died. Memory of the frequency and severity of the disease is attenuated, and yet the risk remains identical for the population; information on the risk must therefore continue to be given.

pedagogical information

Emphasis must be placed on the necessity of pedagogical information on the diversity of genetic traits and their mode of transmission.

It is well to recall that after Pasteur's achievements, schoolchildren were taught about the dangers of infection. Good education could prevent the stigmatisation of carriers of genetic traits which are, either one of the components of the genetic "burden" we all bear (everyone is heterozygous for some harmful mutations), or one of the expressions in the general public of a common trait.

Secondary education is probably the best venue to enhance understanding of these matters in biology and philosophy classes. Meetings organised with secondary schoolchildren have shown that they are very ready to broach such subjects.

Associations representing families concerned by a genetic condition and the positive part they can play in the transmission of information must also be kept in mind although some aspects of their action in this respect is disputable. In certain cases, links of trust and solidarity between their members enable these associations to become excellent givers of useful medical and scientific information.

Similarly, they can help physicians to understand the non-medical aspects of experiencing the disease which may contribute to better mutual understanding and explain or correct possible misunderstandings regarding proposed therapy and prevention. Huntington's disease is frequently quoted as a model since the associations participated fully - before the first markers were even announced - in reflection on ethical conditions to be met in presymptomatic screening programmes.

However, "it is of the greatest importance that those in charge of such associations be constantly aware of the dangers of misinformation, and in particular the danger of raising false hopes, which could be accentuated by a desire to achieve record performances when collecting funds".

(Opinion n° 45 of CCNE, dated 31st May 1995, on ethical issues raised by the transmission of scientific information concerning biological and medical research).

information of the public

One cannot be too careful about the quality of information supplied by the media, which in an effort to provide sensational news, may be a source of false hopes. Opinion n° 45 of May 1995 quoted above, drew attention to the responsibility incurred by scientists and the media in this respect.

Apart from recommendations of a general nature expressed in the opinion, the following particular point must be emphasised : "economic and financial pressures must be opposed". Since diagnoses of susceptibility and prevention strategies target great numbers or even the whole population, they represent a sizeable market and "the increasing role of money is such that the veracity and independence of information could be compromised".

The influence of media pressure on prevention policies is already noticeable in certain fields such as efforts to reduce addiction to tobacco. It is increasing in the field of genetic tests since industrialists have invested in molecular genetic research and wish to obtain returns on their investment by large scale testing.

This could be the case for instance as regards genetic testing for breast cancer which is of great benefit in familial forms but not to be recommended for women generally.

Annex

Examples of genetic screening

1. Familial studies

situations for which no preventive action can be offered

In these situations, a presymptomatic test reveals those who have inherited the mutant gene, but no preventive action for them can be offered.

This is the case in Huntington's disease. After considerable thought on the subject in associations of families affected by the disease and medical practitioners, a protocol was drawn up for the application of presymptomatic testing.

In every clinic, a multidisciplinary team takes on the management of a patient who wishes to discover whether he is or is not a carrier for the mutation. The team includes a genetician, a neurologist, a neuropsychologist, a psychologist, a social worker and a nurse. They make sure the applicant fully understands the procedure and its possible repercussions on his private and working life. The test comprises several phases : information, evaluation, results, and follow-up. Several interviews over a period of months are arranged with members of the medical team before any testing is undertaken.

This phase before the test is essential. The applicant is given information about the disease and its mode of transmission and care is taken to make sure this is fully understood. It is absolutely necessary that the applicant should feel totally responsible about the procedure. During the evaluation phase any pathological tendencies or depressive syndrome which should be treated before testing can be discovered. Absence of neurological symptoms or of disturbed intellectual faculties are verified.

Finally, the applicant is prepared so that he is able to anticipate any problems arising out of the results, favourable or otherwise. The follow-up phase is always necessary, but the organisers of the French programme have found that very frequently patients disappear after getting their results and do not wish to come back for the follow-up. There is

nevertheless a consensus to the effect that follow-up must be offered systematically and the means made available to provide it.

As long as there is no therapy for Huntington's disease, medical management must be pluridisciplinary to assist the applicant throughout this difficult enterprise motivated by the wish to know his true status. The multidisciplinary team must inform those undergoing tests of any progress in prevention or therapy.

situations in which preventive action can be offered

In such situations, a presymptomatic test means that carriers of the mutant gene can be given the opportunity of benefiting from *preventive medical supervision and possibly curative action.*

This is the case of familial polyposis (coloscopy to detect the appearance of polyps and removal before malignancy occurs, or colectomy).

In these situations, individuals who have not inherited the mutant gene also benefit from presymptomatic genetic diagnosis since it frees them from the necessity of special medical surveillance (for instance repeated coloscopies).

The following ethical issues arise in the context of familial studies :

a) mode of information to members of the family about the existence of risk and possibilities of presymptomatic diagnosis;

b) information to each at-risk individual about the tests, their value, understanding the results and consequences on life not forgetting information about the constraints brought about by medical follow-up;

c) when follow-up should begin and frequency of examination;

d) decision on a therapeutic strategy;

e) evaluation of strategies over the long term, for instance in the case of familial cancers, the onset of other malignant sites.

There are situations where the hereditary forms of the disease are rare compared to the sporadic forms. This is the case for hereditary forms of breast cancer. Great care must be taken about information to be given to young women who have not inherited the mutant gene. Risks of sporadic forms of breast cancer also exist for them (1 in 10 approximately) and they should consider observing the same supervision as the general population. They should not therefore be told that there is no risk. Generally speaking, those undergoing tests must understand that the existence of a predisposition gene for cancer does not mean that one can know what kind of tumour is likely to appear, when it would appear, or even if it will appear. Nor does the absence of a predisposition gene guarantee a cancer free life.

2. Screening programmes for the general public

The development of presymptomatic or probabilistic tests for the onset of severe disease in adults might lead to considering their use in mass screenings for the general public and the establishment of medical supervision methods. The existence of genetic markers in the familial form of breast cancer might motivate mass screening for women carrying one of the mutations the frequency of which is estimated at 1 in 250 women. It would seem to be one of the more frequent sets of dominant traits which, a priori, would justify a screening strategy.

Supposing solved the technical difficulties associated with an analysis of multi-gene mutations, many ethical problems still remain to be settled, such as :

a) the predictive value of the genetic test:

° at what age should screening be done and when should follow-up programmes be implemented for women screened positive ? Too early a screening would lead to several years of anxiety;

° although carriers of a mutant gene run a very high risk of developing a cancer (about 80%), the sporadic forms of breast cancer are much more frequent since they affect 1 woman in 10. So that for 250 women undergoing a test, to detect 1 case of a familial form, about twenty breast cancers will be later found among the women who do not carry the mutant gene. Is there any benefit for women who were reassured by a negative test ? Is there any benefit for public health ?

b) Preventive measures offered to carriers of the mutation :

° benefit from early medical supervision due to genetic screening must be evaluated bearing in mind present monitoring methods such as mammography the benefit of which measured in years of survival and quality of life is still disputed;

° possible harmful effects of repeated mammographies must be evaluated;

° usefulness of some preventive measures such as oophorectomy and bilateral mastectomy preventively must be evaluated as well as their physical and psychic consequences.

Furthermore, when considering policies for probabilistic diagnosis and strategies for prevention, economic pressures should not be forgotten in a health sector which potentially could be highly lucrative.

On the one hand, developing tests requires vast investments in research and returns on investment are hoped for.

On the other hand, these tests are possibilities of income for medical professions.

BIBLIOGRAPHY

ALLEN W., OSTRER H., Anticipating unfair uses of genetic information, Am. J. Hum. Genet., n° 53, 1993, 16-21

BAIRD P.A., Identifying, people's genes : ethical aspects of DNA sampling in populations, Perspectives in Biology and Medicine, vol. 38, n° 2, 1995, 159-166

BILLINGS P., BECKWITH J., Genetic testing in the workplace : a view from the USA, TIG, vol. 8, n° 6, 1992, 200-202

BOUGNIERES P., CAILLAT-ZUCMAN S., Gènes de susceptibilité au diabète de type I, Médecine Thérapeutique, n° 1, 1995, 143-152

BOURGUIGNON F., DUBY J.J., Médecine prédictive : nouvelles inégalités ou nouvelle solidarité, Risques, n° 21, 1-3 1995, 125-137

BREMOND A., COURTIAL I., Dépistage du cancer du sein, Médecine Thérapeutique, n° 1, 1995, 375-382

DONALDSON C., Using economics to assess the place of screening, Journal of Medical Screening, n° 1, 1994, 124-129

EDELMAN B., Génétique et liberté, Droits, n° 13, 1991, 31-42

EWALD F., MOREAU J.P., Génétique médicale, confidentialité et assurance, Risques, n° 18, 4-6/1994, 111-130

GORDIS L., The scope of screening, J. Med. Screening, n° 1, 1994, 98-100

GUAY H., KNOPPERS B.M., PANISSET I., La génétique dans les domaines de l'assurance et de l'emploi, Revue du Barreau, Tome 52, n° 2, 4-6/1992, 185-343

HARPER P.S., Direct marketing of cystic fibrosis carrier screening : commercial push or population need ?, J. Med. Genet., n° 32, 1995, 299-250

HARPER P.S., Insurance and genetic testing, The Lancet, vol. 341, 23/1/1993, 224-227

KAHN A., Tests génétiques et assurance, Risques, n° 18, 4-6/1994, 95-109

KNOPPERS B.M., Confidentiality in genetic testing : legal and ethical issues in an international context, Medicine and Law, n° 12, 1993, 573-582

LABERGE C.M., KNOPPERS B.M., Rationale for an integrated approach to genetic epidemiology, Bioethics, vol. 6, n° 4, 1992, 317-330

LABRUSSE-RIOU C., Les implications juridiques de la génétique, Revue du Droit Public et de la Science Politique en France et à l'Etranger, 1990, 1365-1393

LEVY MARCHAL C., Epidémiologie du diabète insulino-dépendant de l'enfant, Médecine Thérapeutique, n° 1, 1995, 139-141

LYON-CAEN G., Génétique et droit du travail, Revue Internationale du Droit Economique, n° 1, 1993, 61-74

MARTIN G., Tests génétiques et assurances, Revue Internationale du Droit Economique, n° 1, 1993, 53-60

MAZEN N.J., Tests et empreintes génétiques : du flou juridique au pouvoir scientifique, Les Petites Affiches, n° 149, 14/12/1994, 70-78

Mc EVEN J.E., Mc CARTY K., REILLY P.R., A Survey of Medical Directors of Life Insurance Companies Concerning Use of Genetic Information, Am. J. Hum. Genet., n° 53, 1993, 33-45

Mc EVEN J.E., Mc CARTY K., REILLY P.R., A Survey of State Insurance Commissioners Concerning Genetic Testing and Life Insurance, Am. J. Hum. Genet., n° 51, 1992, 895-897

MOATTI J.P., Evaluation économique de la prévention : les dangers de l'idéalisation, Santé Publique, n° 2, 1991, 53-57

MOTULSKY A., Predictive genetic diagnosis, Am. J. Hum. Genet., n° 55, 1994, 603-605

MURRAY T.H., Genetics and the moral mission of health insurance, Hastings Center Report, 11-12/1992, 12-17

OTTMAN R., Gene-environment interaction and public health, Am. J. Hum. Genet., n° 56, 1995, 821-823

POKORSKI R.J., Genetic information and life insurance, Nature, vol. 376, 6/7/1995, 13-14

RODOTA S., Genetics, prediction, individual rights, Journal International de Bioéthique, vol. , n° 3, 1993, 199-203

SANDBERG P., Genetic information and life insurance : a proposal for an ethical european policy, Soc. Sci. Med., n° 11, 1995, 1549-1559

SCHNEIDER K.A., PATERRAUDE A.F., GARBER J.E., Testing for cancer genes : decisions, Nature Medicine, n° 1, 1995, 302-303

SHICKLE D., CHADWICK R., The ethics of screening : Is "screeningitis" an incurable disease ?, Journal of Medical Ethics, n° 20, 1994, 12-18

SIEGLER M., Ethical consequences of genetic prediction, in Primum non nocere today, Elsevier, 1994

STOPPA-LYONNET D., ESSIOUS L., THOMAS G., BONAITI-PELLIE C., Prédispositions génétiques au cancer du sein, Médecine Thérapeutique, n° 1, 1995, 327-335

TERRENOIRE G., Médecine prédictive, l'épreuve de l'expérience : dépistage présymptomatique de la maladie de Huntington, Sciences Sociales et Santé, vol. XI, n° 2-3, oct. 1993, 99-121

THOMAS G., Dix ans de recherches sur les prédispositions génétiques au développement des tumeurs, Médecine Sciences, n° 11, 1995, 336-348

WEBER J.L., Know thy genome, Nature Genetics, n° 7, 1994, 343-344

WRIGHT C.J., MUELLER C.B., Screening mammography and public health policy - the need for perspective, The Lancet, vol. 346, 1995, 29-32

Genetic Testing and Insurance. The Ad Hoc Committee on Genetic Testing, Am. J. Hum. Genet., n° 56, 1995, 327-331

Idéologies de la prévention, AGORA. Ethique, médecine, société, n° 30, printemps 1994

UK call for regulation of genetic testing, Nature Medicine, vol. 1, n° 9, sept. 1995, 855-856

Use of Genetic Testing by employers - Council on Ethical and Juridicial Affairs, American Medical Association, JAMA, 2/10/1991, vol. 266, n° 13, 1827-1830

REPORTS

FRANCE :

J.F. MATTEI : Rapport à Madame le Ministre de la Santé Publique et de l'Assurance Maladie, sur l'exercice de la génétique médicale, 25/6/1995

F. SERUSCLAT, Office parlementaire d'évaluation des choix scientifiques et technologiques : Rapport sur les sciences de la vie et les droits de l'homme, "Evaluation des conséquences des progrès de la génétique", 1992

Académie de Médecine : Rapport sur le diagnostic génétique et la thérapie génique, 1995

UNITED KINGDOM :

Nuffield Council on Bioethics : "Genetic Screening Ethical Issues", dec. 1993

DENMARK :

Danish Council of Ethics : "Ethics and Mapping of the Human Genome", 1993

SWITZERLAND :

Académie Suisse des Sciences Médicales : Directives médico-éthiques concernant les examens génétiques sur l'homme, 3/6/1993

EUROPE :

Conseil de l'Europe, CDBI : "Ethique et génétique humaine", dec. 1993

INTERNATIONAL :

UNESCO, Comité International de Bioéthique : Rapport du Groupe de travail sur le dépistage et les tests génétiques, 1994

Notes

1. See annex, table of principal single gene predispositions in the development of dominant inheritance tumours.

2. Resolution of the European Parliament of 16th March 1989 on ethical and legal problems in genetic engineering, art. 13 to 20.

Council of Europe : Recommendations of the Committee of Ministers of 10th February 1992 on genetic tests and screening for medical purposes, principles 6 and 7.

3. At the present time, only *Austria* has a law which prohibits the use of genetic tests by employers and insurance companies (Law of 12th July 1994).

In *Belgium* , a law dated 25th June 1992, prevents insurers from demanding genetic tests before a contract is signed.

In *Denmark* , a draft bill provides for the prohibition of genetic testing by employers and insurers.

In the *Netherlands* , insurance companies adopted in 1990 a five year moratorium during which they have agreed not to use genetic test when the risk is insured for less than a certain amount.

In the *United Kingdom* , The Nuffield Council on Bioethics recommends that insurers do not demand genetic testing before a contract is completed. They also recommend a moratorium during which insurers would not use the results of genetic screening when the risk is insured for a small amount. They do not propose any specific legislation forbidding the use of genetic testing by employers, but recommend that such tests only be used for occupational diseases and with certain conditions.

A resolution by the *European Parliament* dated 16th March 1989 and a recommendation of the *Council of Europe* dated 10th February 1992 recommend that genetic tests should not be permitted for employers and insurers.

4. This is also a valid comment regarding insurance company physicians.