
Genetic Screening

Genetic Screening

Report of a committee of the Health Council of the Netherlands

to:

The Minister of Health, Welfare and Sports

No. 1994/22E, The Hague, 19 December 1994

“Genetic screening should enable people to escape their fate by giving them the freedom to make an informed choice and adopt a chosen course of action which they regard as acceptable.”

(Health Council of the Netherlands, Committee Genetic Screening, in this report).

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Executive summary

Health Council of the Netherlands: Committee Genetic screening. Genetic Screening. The Hague: Health Council, 1994; publication no. 1994/22.

The human genome project is a joint initiative on the part of the industrialised countries aimed at providing financial incentives to accelerate the process of charting human genetic material (DNA). The project has helped to identify, localise and clarify the structure of an increasing number of genes which play a role in the origin and development of disease (pathogenesis). This is leading to a greater understanding of genetics and, as a result, to improved techniques for diagnosing diseases, above all those in which genetic factors play a part. In the long term it will also provide aetiological insights which offer the prospect of improved scope for treatment.

The committee which has compiled this report on genetic screening welcomes this increase in knowledge. However, it does not close its eyes to the fact that, for human beings, the application of knowledge may have disadvantages as well as advantages. This applies to knowledge in general and to knowledge of genetics in particular. The early detection of hereditary diseases can reduce and prevent suffering. It can offer people choices in situations where previously their fate was preordained, yet it can also cause suffering. Moreover, the inaccurate interpretation of genetic information has caused a great deal of damage in the past. This is one of the reasons why the committee deals extensively with the possible advantages and disadvantages of genetic screening and with the conditions which must have been fulfilled before screening is carried out. One of these conditions is that those who participate in genetic screening must act voluntarily, after proper information of what is involved. In order to guarantee that

screening remains voluntary, the committee considers it vital that an adequate level of care for the handicapped be maintained.

Scope of the report

The committee has opted to define its remit broadly. It takes genetic screening to mean any kind of test performed for the systematic early detection or exclusion of a hereditary disease or a predisposition to such a disease, or in order to determine whether a person carries a predisposition which may produce a hereditary disease in offspring. All members of a predetermined target group are invited to undergo screening or urgently informed about it. In the case of screening it is the care system which takes the initiative; those invited have not (yet) been led to seek medical help because of physical signs, symptoms or anxiety. The committee has also taken account of the family testing customarily performed in clinical genetics centres because aspects of this work are relevant when considering genetic screening. By broadening its terms of reference the committee is also able to deal with the detection of congenital abnormalities by means of prenatal ultrasonography.

Hereditary disorders

About 3,000 genes which, when affected by abnormalities, are known to be related to hereditary disorders have now been identified and described. In some cases these disorders are heredo-familial, i.e. they have existed in families for generations, yet they can also arise suddenly. Hereditary disorders manifesting at birth are termed congenital abnormalities (e.g. spina bifida, hare lip, clubfoot, Down's syndrome). They can however also occur in later life; examples include not only some form of Alzheimer's disease and Huntington's chorea, but also some forms of cancer, cardiovascular disease and a number of psychiatric illnesses. Every year in the Netherlands about 800 children are born with congenital disorders linked to chromosomal aberrations. About 2,000 have disorders transmitted as mendelian dominant or recessive due to mutant genes, and between 5,000 and 8,000 are born with congenital abnormalities caused by the interaction of various deviant hereditary traits or environmental factors. The number of people who in later life develop diseases whose onset is determined by the interaction of genetic and environmental factors is even higher.

It is now technically possible to carry out genetic screening for a number of disorders. Genetic screening may involve chromosome testing, be carried out to determine the presence of mutations directly, or it may involve biochemical

examination of substances indicating the presence of a mutation or a heightened risk of congenital abnormalities or hereditary disorders. In addition, ultrasound scanning can be used at the prenatal stage to detect anatomical defects in the fetus. There are more screening possibilities for families containing patients known to suffer from a hereditary disease than for groups of people selected at random. The reason is that, with some hereditary diseases, even in the case that the gene related to the disease is not exactly known, kindreds can be looked at (linkage research) to establish whether they acquired the chromosomal region containing the gene which (partly) causes the disease congenitally from their parents.

Screening throughout life

It is possible for people to undergo genetic screening at different times throughout life. For example, it can be carried out prenatally or prior to conception, the main aim being the early detection of a heightened risk of giving birth to children with a disorder which is untreatable and will seriously undermine their quality of life. There is also neonatal screening, which is focused mainly on the early detection of treatable disorders, and screening performed in later life, primarily to determine the risk of acquiring a disease in cases where the risk can be reduced by preventive measures. The committee provides two tables listing pilot programmes currently underway either in the Netherlands or abroad to detect hereditary disorders or risk indicators. The programmes in question cover congenital anatomic defects, congenital hypothyroidism, Down's syndrome, haemoglobinopathies, phenylketonuria, hypercholesterolaemia, neural tube defects, Duchenne muscular dystrophy, fragile X syndrome, prostatic cancer and cystic fibrosis.

Effects of genetic screening

People in the target groups who are offered genetic screening are thus always faced with having to make a choice. Deciding not to take part may also have consequences. The state of the art in medicine is therefore not the only consideration; in the case of genetic screening, psychological, ethical and legal perspectives are equally important. The social consequences also merit attention.

Psychology

Little research has so far been done into the psychological aspects of genetic screening. However, research data on the psychological experiences of people who have acquired heredity data after specifically asking for it is available. The committee considers such information relevant to any discussion of the psychological aspects of genetic screening, despite the fact that the situation in which it is obtained differs from the normal screening procedure in two important respects. First, genetic screening usually is not performed in response to a specific request. Second, people invited to undergo screening usually have no prior personal knowledge or experience of the disorder which may be detected.

When it comes to the psychological consequences of genetic screening, four main issues can be identified. The first concerns the psychological factors which partly influence a person's decision to accept an offer to be screened. The decision to participate or not should be based on information which is correct and understandable, without even indirect pressure to participate. A high rate of participation should not be a goal as such. The way in which screening is offered can also influence the way in which society views people with identifiable handicaps; balanced information will ensure that they are not seen as the result of missed opportunities for prevention.

The second issue centres on the psychological consequences which the results of screening have for the subjects and their families. Screening can give confidence and reassurance. However, sufficient attention must be paid to the anxiety which may be engendered by the invitation to undergo screening and by the outcome of the examination; heightened apprehension about health and the presence of an abnormality may persist, even after the absence of the mutation that is sought has finally been confirmed. The way in which the results of screening affect the subject's perception of self is also important. Adequate counselling and the provision of information in advance that is both balanced and accurate can play a crucial role.

Thirdly, there is the impact which the results of screening may have on the lives of the subjects and their families. Unless effective treatment is available for improving the quality of life of a person with a disorder, it is mainly a question of using the information to make decisions about forming relationships, having children, lifestyle and how to live the rest of one's life. Counselling and guidance must be based *inter alia* on an understanding of the psychological factors involved.

The fourth issue concerns the possible psychological consequences for people who have decided not to take part in a screening programme and who are then confronted with the birth of a child suffering from a disorder which screening would have detected. If they did not take this possibility sufficiently into account when they

decided not to participate in screening, they may experience feelings of guilt and remorse. Proper information is the only way to prevent this happening.

Ethics

The committee assessed the moral dimension in accordance with the ethical norms governing medical practice. Doctors have a duty to do good, and a moral obligation to do no harm; they must show respect for the autonomy of the individual and the principles of solidarity and equality of access to care. A genetic screening programme enables people to discover whether a hereditary disease poses a risk to themselves or their offspring. If treatment is available for the condition in question at the time the facts become known, screening can have significant benefits for the individuals concerned. On the other hand, an invitation to undergo screening confronts people with risks of which they were largely unaware and can also make them worried. Moreover, the options available in such a situation are not entirely free of drawbacks. Before a decision is taken to implement a genetic screening programme consideration must be given to whether the principle of “do no harm” justifies confronting people with choices which are often very difficult to make.

Voluntary participation based on information that has been properly understood is absolutely essential in the case of genetic screening. The government must ensure that the population at large has sufficient knowledge on heredity. It must for instance be clear to everyone that all people have some mutations in their genes. Proper education can be given already in primary schools, by the media, in written leaflets and so on. In 1989 the Health Council presented it like this.

An invitation to be screened puts a certain pressure on the autonomy of the individual. This in turn creates an added obligation to pay a great deal of attention to the context in which the offer of screening is made and the question of how the options open to the subject are put to him or her during the screening process. Social environment may also be a factor which influences the individual’s freedom to choose. The committee concludes that the screening of children to detect disorders which are untreatable and which only become manifest in later life should be rejected out of respect for the autonomy of the individual.

If genetic screening meets a number of preconditions and has a positive balance of advantages and disadvantages, the principle of equality of access to health care justifies inviting people to undergo screening rather than waiting for them to request it. After all, this is one way of ensuring that the test is not only available to those who are already aware that it exists. An unfavourable test result can lead to social stigma. Society must ensure that the results of screening do not pose unwarranted obstacles when it comes to access to prevailing insurance policies or employment contracts or

other agreements. Too great a degree of uncertainty on this point may constitute grounds for not carrying out the screening programme.

The committee points to several conditions which in a social context must be fulfilled if genetic screening is to be provided in a proper manner. In order to make it possible for individuals to choose, society must show solidarity with those who are faced with having to make the choices. Respect for the autonomy of the individual calls for solidarity, and the obverse is also true. The choices that have to be made in these issues must be respected by society. The solidarity that exists within society with regard to children and adults who suffer from a hereditary disorder must be preserved. After all, the welfare of such people is heavily dependent on the opportunities which society offers them, and society can also influence the choices which parents make in respect of their children. The scope for counselling, integrating and making provisions for handicapped people is therefore important, and the government has a responsibility to monitor the activities which enable these aims to be achieved. Only when these have been guaranteed can parents who are expecting a seriously handicapped child really choose between having the child and terminating the pregnancy.

Ethical considerations concerning the scope for genetic screening lead to the conclusion that considerable caution is required when deciding whether to provide this kind of testing. The advantages that come with such programmes in the form of improved scope for treatment are nearly always accompanied by disadvantages. Prior to any offer of screening being made, it would appear highly desirable to examine, by means of properly designed pilot studies and independent assessment, whether the advantages clearly outweigh the disadvantages.

Law

Taking account of legal principles and fundamental rights, the general legal framework governing medical practice and the more specific regulations, particular attention is warranted from the legal viewpoint for three aspects of genetic screening: the assessment of screening programmes, the legal position of those invited to take part and the combination of screening and scientific research.

The Population Screening Act requires that central government approve certain screening programmes before they are implemented. The question of whether genetic screening is subject to a statutory licensing requirement is determined primarily by the scope of the Act. The latter defines population screening in broad terms, as follows: “a medical examination which is carried out in response to an offer made to the entire population or to a section thereof and which is designed to detect diseases of a certain kind or certain risk indicators either wholly or partly for the benefit of the persons to be examined”. The key word here is “offer”. The committee considers the definition of

population screening contained in the Act to be rather loose because the key term “offer” is too inexact. It nevertheless concludes that genetic screening, as defined in the report, falls within the scope of the Population Screening Act. The committee endorses the line taken by government in not wishing to include in the Act the family testing, which is currently undertaken in centres for clinical genetics. There is, however, a grey area in which the question of whether, for the purposes of the Act, population screening also covers this kind of testing needs to be looked at on a case-by-case basis.

A licence is refused if the screening in question is scientifically unsound, if it conflicts with the statutory regulations governing medical practice or if it involves risks for the subjects which outweigh the likely benefits. The rules pertaining to population screening performed to detect serious diseases or abnormalities which can neither be treated nor prevented are even tighter; a licence is granted only if special circumstances constitute grounds for doing so. The committee endorses the view of government that screening for untreatable disorders calls for considerable caution, particularly in cases where the disorder in question only manifests itself in later life. However, a problem does arise if the screening is aimed to decisions concerning offspring, as is the case with prenatal screening and tests carried out prior to conception to determine whether a disorder can be transmitted as mendelian recessive. Given that the aim of the Population Screening Act is to protect people who are involved in screening programmes, there is in the opinion of the committee no justification for banning testing of this kind from the outset. It therefore advocates that the law be applied in such a way as to leave scope in theory for these forms of screening to be performed, albeit after a thorough judicial review pursuant to section 7 subsection 1.

Genetic screening programmes that are subject to licensing requirements will be examined by the body which grants the licence, advised by the Health Council. The committee believes that some form of independent assessment is also desirable in the case of programmes that do not need to be licensed, with the exception of small scale family testing. The criteria it formulates in the report can be applied in both cases. The question is to what extent the examination of genetic screening programmes for which no licence is required needs to be formalised. Here the professional organisation may have a task. The committee regards a statutory obligation as unnecessary, although expertise and independence do need to be guaranteed. It recommends that examination be carried out by a national committee.

In its report “Heredity: science and society” (GR89), the Health Council focuses in detail on the position of those who undergo tests to detect hereditary disease, also if such tests are carried out in the context of genetic screening. The committee endorses the report’s conclusions and recommendations.

If a screening programme takes the form of a research program, it should also be regarded as a medical experiment, which has legal consequences. Two different

situations can be identified. The first concerns screening which is not subject to a licence requirement under the Population Screening Act. Programmes of this kind will be covered by the Medical Experiments Bill when it comes into force. Programmes which are subject to licensing requirements and which are also medical experiments will only be examined pursuant to the Population Screening Act.

Social considerations

Apart from the psychological, ethical and legal aspects, social considerations also play a role in genetic screening programmes. The committee deals with the possible consequences from the population genetics viewpoint, with financial aspects and with the consequences of screening for access to employment and insurance.

Population genetics is a branch of science which focuses on the epidemiological spread of mutations in genetic material and on their possible causes and effects. A genetic screening programme may influence the occurrence of a particular mutation in offspring. It is therefore worthwhile obtaining a picture in advance of the consequences which implementation of the programme may have for future generations. This point is relevant only in the case of prenatal or preconception screening.

The committee considers the influence of genetic screening in the aforementioned respect to be no more than marginal. Only if the fact of carrying an autosomal recessive trait in itself resulted in selection could screening have consequences from the population genetics viewpoint. It is precisely on such grounds that selection on the basis of being a carrier or non-carrier must be guarded against, since the effects on human health are unknown.

The committee concludes that social attitudes and the behaviour which they engender have more significant consequences from the population genetics viewpoint than genetic screening. This is not to say that the consequences of genetic screening for the disease frequency in the population are marginal too.

As stated previously, the committee believes that the acceptability or otherwise of genetic screening programmes must be judged by a national committee. The committee should round off its assessment by examining whether the principle of equitable distribution justifies making health care resources available for implementing the programme. Such an assessment requires an insight into the costs involved and the savings which may result. However, too much itemisation of costs and savings could easily lead to social pressure to participate in screening programmes and go for the most economically advantageous option. Such pressure must be countered vigorously. The committee cannot overemphasise the fact that genetic screening must enable

people to escape their fate by giving them the freedom to make an informed choice and adopt a course of action which they regard as acceptable.

As mentioned above, the Health Council reported in 1989 on the possible consequences for access to employment and insurance of genetic testing. The report played a part in the formulation of the government position paper on predictive medical examination, in which the government indicates that in the case of medical examinations prior to appointment, legislation in combination with self-regulation is an option. When it comes to medical examinations for life assurance and disability insurance, the government regards the insurers' current moratorium as effective.

The committee considers the above position paper too weak. In a previous position paper the government had pledged to examine after two years whether self-regulation would make legislation superfluous. A report by the TNO Institute of Preventive Health Care makes it clear that at present this is by no means the case.

The committee is also extremely worried by the fact that, as far as the insurance situation is concerned, the government has resigned itself to things remaining the way they are. This means the possibility of new forms of uninsurability arising. The committee believes that legislation is urgently required. This is especially true in view of the increasing role genetic screening may come to play in the future, possibly resulting in more, in most cases rare, diseases becoming uninsurable. It therefore believes it important to expedite the draft legislation initiative regarding medical examinations, which incorporates most of the recommendations made previously by the Health Council.

Assessment of screening programs

All in all, the committee takes the view that the pros and cons of carrying out genetic screening - of whatever kind - require careful consideration. This is in the first place the responsibility of the body which provides the screening, and should take place prior to a programme being introduced. In cases where such a programme is classed as population screening requiring statutory licence pursuant to the Population Screening Act, the Act itself provides for examination by an independent body (i.e. the Health Council) before it can be carried out. The committee also considers assessment necessary when screening is not subject to a statutory licence requirement. It makes an exception for family testing as currently performed in clinical genetics centres. The type of assessment advocated by the committee can be carried out by a national committee on medical ethics.

To ensure that assessment is performed systematically and carefully, the committee provides criteria based on the considerations contained in the report. For the provider who is considering introducing such a programme, these criteria can also play a useful role at an earlier stage. The committee expects that their application will encourage the increasing knowledge of matters connected with genetic screening to be properly used.

Introduction

1.1 Request for a report

On 5 November 1991, the State Secretary for Welfare, Health and Cultural Affairs requested the President of the Health Council of the Netherlands to inform him on current scientific capabilities with regard to screening for hereditary diseases (annex A). He further requested that screening methods and risk indicators for non-hereditary diseases be taken into consideration. The State Secretary also indicated that screening falls within the scope of population screening, as defined in the Population Screening Act (WBO) recently passed by the Dutch Parliament.

Undercapacity in the secretariat meant that the President of the Council was unable to inaugurate the committee (which was charged with responding to the request for a report) until 23 November 1992 (annex B). In this chapter, the committee sets out its own interpretation of this task and makes some preliminary observations.

1.2 Demarcation of the scope of the report

The committee understands ‘genetic screening’ to mean any kind of test performed on people for the systematic early detection or exclusion of a hereditary disease, the predisposition to such a disease or to determine whether a person carries a predisposition which may produce a hereditary disease in their offspring. In the following pages, the committee provides a further explanation of this definition, and of the boundaries which were drawn during the preparation of this report.

The committee understands ‘early detection’ to mean: the search for disease, predisposition or carrier status in those who have not (yet) been led to seek medical aid because of physical signs, symptoms or anxiety. In the case of carriers, detection occurs at a time when there are still opportunities for genetic counselling, or further tests, with regard to reproduction. In screening it is the care system which takes the initiative with regard to detection. The committee understands ‘screening’ to mean determining in advance those who are eligible for early detection (the target group) and approaching this group in a systematic way. Here, ‘systematic’ is taken to mean that (in principle) every member of the target group is specifically invited to take part in (or is expressly informed concerning the opportunities offered by) early detection of the disease, predisposition or of carrier status.

The definition of *genetic screening* therefore has the following distinguishing characteristics:

- hereditary disease, predisposition or carrier status
- no reason for those involved to seek assistance
- systematic approach to the target group.

All of these characteristics must be present before the term *genetic screening* can be used. In the committee’s view, characteristics such as the organisational form, the scale involved, the place where early detection is actually carried out and the question whether it is a new or a previously accepted part of the health service) are not of overriding importance for the definition. In any case, such characteristics can vary from one screening programme to another. Therefore, screening need not take the form of large scale population testing.

The committee acknowledges that even the definition selected here is still not totally sound. By way of illustration: From the viewpoint of public health, a comprehensive publicity campaign which causes virtually all members of the target group to request early detection has the same implications as issuing individual invitations to the members of a target group. The character and the extent of such publicity campaigns tend to obscure the distinction between individual requests and making an offer. The committee sees the express provision of information as constituting an offer. Another point is that genetic testing in relatives (necessary in order to respond to individual requests for genetic counselling) can also be included within the definition. In the field of genetics, it would appear to be difficult to draw clear borders between individual genetic testing, genetic testing within families, and genetic screening. These show considerable similarities in terms of the desired effects (enabling people to make meaningful choices), the possible risks and the conditions for good implementation and supervision. As a result, within the framework of this report, the committee has opted for an overly broad interpretation of the concept of genetic

screening rather than an overly narrow one. This means that the committee has also included in its deliberations the family testing as currently performed in clinical genetics centres. However, this in no way implies that the committee feels that the status of such family testing should be changed in any way whatsoever. It is simply that the committee views family testing from a different perspective to that usually adopted by the medical profession. The profession sees family testing as constituting individual medical aid, while it views screening as studies involving (large parts of) the population. The committee considers that screening is not necessarily (by definition) a large scale activity while family testing is not necessarily a small scale undertaking. The committee will return later on (7.2) to the matter of the relationship between the concepts of 'genetic screening' and 'population screening' (within the context of the Population Screening Act) and to the role played by family testing.

There is yet another reason for applying a broad interpretation of the concept of genetic screening. Screening during the prenatal phase involves the use of ultrasonography, which also detects non-hereditary foetal defects. It is the committee's view that the search for such defects (which is irrevocably linked to this technique) also falls within the scope of this report.

The State Secretary also requested that consideration be given to testing for non-hereditary disorders. The committee thinks that, from the viewpoint of the technology used, there is actually very little difference between the early detection of hereditary diseases and of diseases lacking a hereditary component. Exceptions to this are certain factors which play a part in infectious diseases. Thus, when examining the question of genetic screening, problems could (in principle) be encountered which are involved in other types of disorders. However, the objectives and the social implications of genetic screening often extend much further, since such screening can also have repercussions for others (in this instance for descendants or for other members of the family). This is something which genetic screening has (to some extent) in common with the detection of infectious diseases such as tuberculosis or AIDS. However, the committee has not studied the special aspects and specific implications associated with the detection of infectious diseases. Since it considers the investigation of genetic screening to be a complex matter in itself, the committee will restrict itself to this topic in the present report.

The committee will make no statements regarding the desirability of testing for specific diseases. However, it does address several distinct clinical pictures in annex G. The objective is to show that - dependent upon the disorder - highly varied hereditary mechanisms, times of screening, diagnostic capabilities and other considerations can play a part in the decision on whether or not to implement a given screening

programme. Such considerations might relate to public health, the health of individuals and to other aspects, including those of a psychological, ethical, legal or social nature.

1.3 Preliminary observations

In its 1990 Annual Report on the health service, the Council included a comprehensive summary of forms of population screening, both current and potential (GR90). As that report also noted, testing for a variety of disorders already makes up part of the health service's normal activities. In the Netherlands, screening is used for extremely common diseases such as breast cancer and cervical cancer. Screening is also part of monitoring during pregnancy (including rhesus sensitisation, diabetes and high blood pressure). It also covers the 'heel prick' (blood test) given to newborns for the detection of phenylketonuria and hypothyroidism. These forms of screening are generally felt to be quite useful. While usually producing a clear test result, they also allow insightful prediction of the repercussions of this result for the test subject (or her child). Finally, these forms of screening clarify the way in which the heightened risk can be influenced. These results of screening can be seen as positive, however such results will not always be equally obvious. The result of screening sometimes has to be expressed in terms of probability. There may be some uncertainty regarding the diagnosis or the outlook for the future. The optional courses of action involved include therapeutic or preventative considerations, but there are also drawbacks. Besides those who are accurately informed that the characteristic in question either was or was not detected in the course of screening, others may be given an incorrect result. Situations like this make it clear that screening also has its drawbacks. Accordingly, prior to the introduction of a screening programme, the following question should be answered: Does the target group stand to gain sufficiently from the screening to justify subjecting people to the difficult choices which are associated with such a programme?

Research in the field of genetics is currently making rapid strides. The committee considers scientific knowledge to be of value, and is of the opinion that society can use such knowledge to its advantage. However, there should be secure guarantees to ensure that such knowledge is not abused. If it appears that, in several places in this report, great emphasis is placed on possible drawbacks then this is due to the committee's desire to reduce such drawbacks to the bare minimum when introducing programmes for genetic screening. This in no way constitutes an implicit rejection of genetic screening itself.

The committee would also like to request, in advance, that due consideration be given to the care of the handicapped. Screening can now be used for the early detection of predispositions to an ever increasing number of disorders with a hereditary component. This is especially the case with autosomal dominant and sex-linked

hereditary disorders. There is usually an awareness within the affected families of the occurrence of such disorders. However, there are also improved prospects for the early detection and prenatal diagnosis of recessive hereditary disorders and of other congenital disorders which often spontaneously occur in a family. In such cases, termination of pregnancy is usually one of the optional courses of action. In discussions of the issue, however, it has been proposed that this might lead to reduced acceptance of the handicapped and to people being less prepared to maintain community services for them at the current level of care. A development such as this would be disastrous, and would jeopardise the future parents' freedom of choice in the event of such difficult decisions. The committee would like to point out that screening will never lead to the total elimination of all congenital abnormalities, nor indeed can this ever be the objective of such programmes. This is because mutations continue to arise spontaneously, as do detrimental combinations of risk factors.

1.4 Structure of the report

In 1989 the Health Council published a report entitled 'Heredity: science and society' (GR89). This examined the issues surrounding early detection of hereditary disorders and of carrier status for the relevant genes. The committee will summarise the background information and present it in this report. Chapter 2 is a brief introduction to hereditary disorders. Chapter 3 contains a discussion of the techniques which are used to detect hereditary disorders and carrier status. In chapter 4, the committee examines the various periods in life during which genetic screening can occur, in addition to the associated technical and social aspects. Chapters 5, 6, 7 and 8 address various aspects, including those of a psychological, ethical, legal or social nature. In chapter 9, the committee sets out the criteria against which, in its view, programmes for the implementation of genetic screening must be assessed. In annex G, the committee briefly considers 18 disorders in which hereditary factors play a significant part. The aim of this is to elucidate the problems associated with various diseases.

Hereditary disorders

2.1

General

Human genetic material is located inside the cell nucleus, in 22 pairs of non-sex-determining chromosomes (autosomes) and two sex-determining chromosomes (XX or XY). Genetic material also occurs outside cell nuclei, in the mitochondria. The genetic information consists of between 50,000 and 100,000 genes. A gene is a length of DNA which carries information relating to one particular function. All individuals inherit one set of chromosomes from the father and another set from the mother. As a result, there are always two copies of each autosomal gene. The genetic information contained in the mitochondria is inherited from the mother alone. Knowledge of this area is still far from complete. Currently it's clinical use is restricted to testing, within patients' families, for a relatively small group of hereditary diseases. These types of hereditary disorders have not been addressed by this report.

In the course of time, variations have arisen in the structure of numerous genes throughout the general population. Gene mutations are caused by molecular 'errors' in DNA, which are partly caused by environmental factors. Such 'errors' arise during the cell division. The error may consist of the substitution of one or more building blocks (point mutation), loss of (part) of a gene (deletion) or of larger rearrangements such as insertions, duplications or the repetition of a given sequence of building blocks (repeat).

While most mutations are quite harmless, some of them affect functional characteristics. If it arises in somatic cells, the mutation is not passed on to the

offspring. However, if the mutation occurs in a sex cell then this may indeed be passed on to any future children. Such a mutation may have occurred quite recently, either before or during an individual's initial phase of development. In such cases there are no previous reports of occurrences of the associated disorder within the family. Such disorders therefore occur spontaneously, but they are genetically transmissible. More usually, the mutation concerned will have been in the family for many generations. Dependent upon the moment when the disorder manifests itself, it is possible to discriminate between congenital abnormalities (spina bifida, harelip, club foot, Down's syndrome) and hereditary diseases occurring later in life (such as some forms of Alzheimer's disease, Huntington's disease, some cancers, cardiovascular diseases and several psychiatric illnesses).

In recent decades, scientific research in the fields of biochemistry, cell biology and (molecular) genetics has produced many new insights into the molecular and cytogenetic backgrounds of hereditary disorders. A great deal of research effort is currently being devoted to the international 'Human Genome Project'. Partly because of this undertaking new developments in this area are coming thick and fast. Even the understanding of heredity and its complexity is changing rapidly. The main objective of the Human Genome Project is to chart human genetic material. Recognisable structures (so-called markers) are located at more or less regular intervals along all chromosomes. These simplify the localisation of a gene on a chromosome. Once a gene has been located, attempts can be made to determine the sequence of building blocks which make up that gene. The insights and technology which this has generated create new opportunities for the early diagnosis of patients and the identification of carriers of chromosome abnormalities and gene mutations. The next step is to determine the function of such a gene and of the protein produced by that gene. Such knowledge can be used to develop new therapeutic techniques.

Genetic disorders can be classified in a number of different ways. One commonly used system is to distinguish between chromosomal abnormalities and gene mutations. This is based on the presence or absence of visible, morphological abnormalities of the chromosomes.

2.2 Chromosomal abnormalities

Chromosomal abnormalities are taken to mean morphological abnormalities of chromosomes which can be seen with the aid of a light microscope. This includes abnormalities in the number of chromosomes. These features usually arise during the development of the sex cells or during the first few divisions of the fertilised egg cell. The older the pregnant woman, the greater the chance of a numerical chromosome abnormality occurring in the foetus. The chances of structural chromosome

abnormalities are increased if one or both parents have been exposed to external influences such as radiation or cytostatic drugs. At least half of all spontaneous abortions are caused by chromosome abnormalities in the foetus. The use of modern techniques has shown that, despite of this natural selection, there are chromosome abnormalities in 0.92% of live births (Jac92). At least half of these cases involve multiple congenital deformities, a mental handicap (retardation) or disorders of sexual development and function. This affects about 900 newborns each year in the Netherlands. In a small percentage of cases, the chromosomal abnormality is inherited from one of the parents, who is a (healthy) carrier. In the affected parent, for example, a piece of chromosome has become detached and has then re-attached to another chromosome. The situation in the parent concerned is described as a balanced translocation. Following the birth of a child with a chromosome abnormality, the chance that subsequent children will have same disorder is highly dependent upon which parent is the carrier of the translocation and which chromosomes are involved. The chance of a repetition of a simple defect in the number of chromosomes (e.g. a supernumerary chromosome 21, as in Down's syndrome) is usually quite low (1 to 2%).

2.3 Gene mutations

Gene mutations are variations in the structure of a gene, and they can give rise to hereditary disorders. An abnormality in a single gene which (partly) causes a disorder is described as a monogenetic abnormality. Cases where more than one abnormal gene is involved are described as multifactorial abnormalities. Dependent upon the pattern of inheritance, monogenetic abnormalities can be further classified into autosomal dominant, autosomal recessive and sex-linked disorders.

With an autosomal dominant mutation, disease may develop if only the copy of the gene inherited from the father or only that inherited from the mother contains a mutation. With autosomal recessive mutations, the genes from both parents must contain the mutation. In this way, recessive mutations are passed - unnoticed - from generation to generation. Only where both parents are carriers with mutations in the same gene, will each of their children have a large chance (25%) of being born with the hereditary disorder concerned. With autosomal dominant mutations, the parents have a 50% chance of passing the mutation and the disorder to their child.

Together, dominant and recessive hereditary disorders occur in 0.5 to 1.5% of live births, some of them only appearing later in life (Mck92). This involves about 2,000 new patients per annum in the Netherlands.

With sex-linked disorders, the mutation is situated on the X chromosome. Instances of dominant and recessive hereditary sex-linked disorders are known. This distinction

is only important for women since, with transmission of a recessive trait, the mutation can be compensated for by the non-mutated copy of the same gene on the second X chromosome. The most common X chromosome disorder in the Netherlands is colour blindness (about 5% of newborn boys). Other sex-linked disorders, such as haemophilia, occur much less frequently.

In the case of multifactorial transmission the appearance of disease is determined by a combination of (usually unknown) external factors and inherited genetic predisposition. The hereditary component for the development of the abnormality is determined by the interplay of various abnormal hereditary traits. Congenital abnormalities arising in this way occur in 2.5 to 4% of live births in the Netherlands, an annual total of 5,000 to 8,000 individuals. Some well known examples of such abnormalities are spina bifida, congenital heart defects and club foot. Following the birth of a child with a deformity of this type, there is a heightened chance that subsequent offspring will be similarly affected. This also applies to the child's own descendants. Furthermore, an increasing number of diseases which occur later in life are being found to belong to the group of diseases which show multifactorial transmission.

To date, about 6,000 genes have been described and located. Associated hereditary disorders have been described for about 3,000 of these, disorders which are associated with mutations in those genes.

Detection techniques

3.1 Screening test

Because of the circumstances in which it is used, the initial test carried out in the context of early detection is also referred to as a screening test. This is usually a relatively simple test whose results indicate whether the test subject has a greater than normal chance of possessing the trait in question. If this is indeed the case, then further diagnostic work is carried out. However, the definitive diagnosis can still be girded with an error margin. This general model of screening does not necessarily apply in all cases. Detection sometimes takes place by means of a combination of diagnostic tests which may or may not be carried out in sequence. Sometimes detection is achieved directly, by means of the definitive diagnostic test.

3.2 Chromosome testing

As previously stated, major chromosome abnormalities (e.g. abnormal number, large piece missing, linkage of an extra piece onto another chromosome) can be detected by examining chromosomes within cell nuclei, under the light microscope. At a given stage of cell division, the individual chromosomes can be rendered visible, after which they can be evaluated for number and for external characteristics. The test requires either a small amount of blood or, if carried out during the prenatal phase, either chorionic villi (tissue projecting from the placenta) or cells from a sample of amniotic fluid. If the cells to be tested come from a blood sample, then the test will take several

days. Amniotic fluid for this test should be withdrawn between the fifteenth and eighteenth week of pregnancy. This test takes about two weeks since the cells first have to reach the appropriate stage of cell division. Chorionic villi to be used in this test are taken between the eleventh and thirteenth week of the pregnancy. Since these villi generally contain a sufficient number of cells in the appropriate stage of cell division, the test results can be available within one week. The time gained is of importance in that it shortens the period of uncertainty. If necessary, a termination of pregnancy can usually be carried out up to the thirteenth week of pregnancy (on an outpatient basis, by means of suction curettage). Where a choice has to be made between using chorionic villi or amniotic fluid as a source of cell material for chromosome testing, various factors (besides the time involved) have to be taken into consideration. Two such factors are cytogenetic reliability and the risks to the foetus which are inherent to the procedure. If the time factor is not critical then the question of whether to opt for using chorionic villi or amniotic fluid involves a delicate weighing up of the benefits and drawbacks (Chr93). It is also possible to draw blood from the unborn child (by umbilical puncture) for the purpose of testing for chromosome abnormalities and other disorders. However, there are only a limited number of situations in which this is indicated.

Chromosome testing can be used for the diagnosis of a number of diseases. When carried out by experienced staff, this type of testing is highly specific and extremely sensitive, which gives it considerable predictive value. While the test usually only involves the individual concerned, very infrequently it is necessary for other members of the family to be tested (usually the parents).

3.3 Biochemical examination

In some cases, monogenetic gene mutations may either block the synthesis of certain enzymes or lead to the production of enzymes with abnormal structures, either situation will disrupt metabolic processes. The resultant diseases can be detected by checking whether certain products of normal metabolic processes are present in body fluids such as blood and urine (metabolite studies). About one hundred rare clinical pictures can be detected by this means (GR92). With several clinical pictures, it is possible to find out directly whether the correct form of the enzyme is present (enzyme diagnosis). In addition to patients, (healthy) carriers can be identified in this way. The test is restricted to the individual concerned. However, if an abnormality is detected, this will often lead to the testing of other family members, who may request testing to see if they are carriers.

Monogenetic gene mutations can also lead to the production of abnormal proteins involved in oxygen transport (haemoglobins; as with thalassaemia and sickle-cell

anaemia) and to abnormalities in the blood-clotting process (in haemophilia). The presence of such abnormalities can be established by means of haematological, biochemical or DNA testing.

The above-mentioned tests have a clear relationship with the product of an abnormal gene. In addition, there are biochemical screening procedures which are based upon measurement of the levels of certain substances in the blood, for example. Although such substances have no known (direct) relationship with the structure of an abnormal gene, they are nevertheless associated with certain abnormalities. Within the framework of this report, the most relevant test of this type is prenatal testing by means of the triple test.

It has been known for 10 to 15 years that measurement of the amount of alphafoetoprotein in the blood of a pregnant woman can indicate a heightened chance of neural tube defects or of chromosome abnormalities in the foetus (Mer84). Over the years, attempts have been made to increase the predictive value of this test by incorporating the measurement of additional substances. The original triple test involves measuring the levels of alphafoetoprotein, hCG (human chorionic gonadotrophin) and oestriol. These are used in combination with the duration of the pregnancy, and the age and weight of the mother, to calculate the probability that the woman in question is carrying a foetus with either Down's syndrome or an open neural tube defect (Wal88). Recently published work (Spe93) has indicated that the best results are obtained by measurement of the levels of alphafoetoprotein and of the free beta chain of hCG, in combination with the age of the expectant mother. The test is carried out between the fifteenth and the eighteenth week of pregnancy. Recent research has shown the concentration of PAPP-A (Pregnancy Associated Plasma Protein-A) to be very promising for the first trimester of pregnancy (Lit94).

Another form of biochemical testing which can reveal the presence of a risk factor is the determination of the amounts of cholesterol and triglycerides in the blood. Increased levels of these substances indicate a risk of cardiovascular diseases which is statistically greater than normal.

The measurement of proteins produced by cancer cells is another form of biochemical testing which can give an early indication that the person concerned is suffering from some form of cancer. Some examples of this are the measurement of carcino-embryonic-antigen (CEA) levels with some types of intestinal cancer; prostate specific antigen (PSA) with prostatic cancer; and cancer antigen 125 (CA-125) with ovarian cancer (Can93).

3.4 DNA testing

A small amount of DNA is generally sufficient for DNA testing and any nucleated body cells can be used for the purpose. With the technique of PCR (Polymerase Chain Reaction), a method of replicating DNA, it is even possible to perform tests on DNA from just a few cells, or even from a single cell. This method can be important for prenatal testing using foetal cells isolated from the mother's blood, or which have been taken from an embryo produced by test tube fertilisation (so-called pre-implantation diagnosis). DNA testing can be subdivided into so-called linkage-testing and the direct detection of mutations.

Linkage-testing is based on the fact that markers (recognisable DNA variants) can be found in the immediate vicinity (usually on either side) of the abnormal gene, and which are usually passed on to the offspring together with the gene concerned. Linkage-testing is used in cases of hereditary disease in families, to find out which markers the patients possess. It is then possible to indicate (on the basis of the presence or absence of those markers in various members of the family) which individuals are carrying the abnormal gene associated with the disease. Since the link between the marker and the disease gene is sometimes severed by recombination, the link between a given marker and the presence of a disease gene is never absolutely reliable. There remains a small, but real, chance of error. The reliability of the test must be determined for each individual family. It is dependent upon the distance between the marker gene and the disease gene on the chromosome. Due to a great increase in the number of traceable markers, there has been a corresponding increase in the number of families and clinical pictures for which linkage-testing can be used with reasonable reliability.

The direct detection of mutations within the gene is only possible for those clinical pictures where the structure of the gene concerned has been clarified, together with the relationship between abnormalities of that gene and the expression of the clinical picture. This type of DNA testing can be restricted to a single individual and can, in principle, be used as part of screening. While the test is highly specific, sensitivity varies from clinical picture to clinical picture, dependent upon the part of disease related mutations that are detected.

3.5 Testing with ultrasonography

From the twelfth week of the pregnancy, ultrasonography can be used to detect structural and functional abnormalities in the unborn child. The ultrasonography test which is generally carried out is primarily aimed at testing the vitality, growth and position of the foetus, the position of the placenta and the detection or exclusion of

multiple pregnancies. If this type of test reveals indications of foetal abnormality, follow-up testing with advanced ultrasonography techniques is required to establish the precise nature of the abnormality involved. Such follow-up testing requires exceptional expertise and special equipment. It is also carried out if other observations have revealed a heightened risk of abnormalities which can be detected by ultrasonography. This is the case, for example, if the foetus exhibits abnormal growth or if a previous pregnancy resulted in a child with an abnormality of the brain, heart, kidneys, urinary ducts, skeleton, etc, which is detectable by ultrasonography. In well equipped centres, where there is a heightened risk of particular structural abnormalities, a specificity of 98% and a sensitivity of 93% have been achieved (GR90a). The values of these test characteristics decline sharply where unselected populations are screened for congenital abnormalities (Ber93, Buc93, Ewi93).

Time of screening

4.1

Introduction

The screening of patients and the identification of carriers can take place at different times throughout life. Which moment is most appropriate and the most desirable is dependent upon the objective, the technical options, and the psychological, ethical, legal and other social aspects. According to the committee, the objective of any form of screening should be: to give those affected the opportunity to make informed choices from several alternative courses of action. This includes options relating to procreation, termination of pregnancy and change of lifestyle. The technical options are in part determined by available knowledge concerning the cause of a disease and the extent to which such knowledge has been used to develop tests. The committee will address the psychological, ethical, legal and other social aspects in the following chapters.

Dependent upon the time of life, a distinction is made between screening prior to conception, as well as prenatal, neonatal and (other) postnatal screening. In tables 1 and 2, the committee has indicated screening programmes associated with genetic diseases which are currently being carried out in the Netherlands and which are the subject of (pilot) studies being carried out abroad. The tables also include disorders in which testing can remain limited to high risk families. In this report, the committee will cite a number of examples of disorders for which (from a technical perspective) testing is currently possible, or will become possible within the foreseeable future. The examples have been chosen so as to illustrate the various psychological, ethical, legal and logistical issues which play a part in screening. The committee would also like to make

Table 1 Summary of testing for hereditary disorders and hereditary risk factors in the Netherlands.

age group	disease / condition	target group	type of test	follow-up test required	nature of material required
prenatal	erythrocytes - blood group (ABO rhesus)	all pregnant women	serological	no	mother's blood and possibly also father's blood
	thrombocytes blood group	if indicated	serological	no	idem
	diabetes	all pregnant women	biochemical	yes	mother's blood
	tests for carriers of balanced chromosome abnormalities, of sex-linked diseases or of recessive hereditary diseases	if indicated (family / habitual abortion)	cytogenetic, biochemical and/or DNA testing of pregnant women and possibly also of partner	no	parents' cells
	haemoglobinopathies and sickle cell anaemia	if indicated (particular ethnic groups in the population)	Hb electrophoresis	no	parents' blood
	congenital structural abnormalities, including neural tube defects	if indicated	ultrasonography	often	
	abnormalities in the genetic material of the foetus	if indicated	chorionic villus biopsy; amniocentesis placental biopsy; biochemical; DNA; cytogenetic	sometimes	foetal cells or chorionic cells
	chromosome abnormalities and neural tube defects	pregnant women (various centres)	triple test	yes	mother's blood
neonatal	phenylketonuria	all newborns	biochemical	yes	blood
	hypothyroidism	all newborns	biochemical	yes	blood
prior to conception	tests for carriers of balanced chromosome abnormalities, of sex-linked diseases or of recessive hereditary diseases	if indicated (family / habitual abortion)	cytogenetic, biochemical and/or DNA testing of pregnant women and possibly also of partner	no	cells
later life	hypercholesterolaemia	if indicated (family)	biochemical; DNA	yes	
	carcinoma of the colon	if indicated (family)	biochemical; DNA	yes	
	carcinoma of the ovaries	if indicated (family)	DNA	yes	
	carcinoma of the breast	if indicated (family)	DNA	yes	
	MEN-2A	if indicated (family)	DNA	yes	
	fragile X	mentally	DNA, cytogenetic	no	

Table 2 Examples of (pilot) tests for hereditary disorders and risk factors abroad (above and beyond those cited in table 1).

age group	disease/ cond.	target group	type of test	follow-up test required	country
prenatal	cystic fibrosis	parents	DNA (identification of carriers)	no	Great Britain, Germany, United States, Australia and Denmark
neonatal	cystic fibrosis	all children	biochemical	yes	Australia, Great Britain
	haemoglobinopathies	all children	biochemical	no	Great Britain, various Mediterranean countries
	DMD	all newborn boys	biochemical DNA	yes	Belgium, Germany, Wales, France, Cyprus, USA, Canada
	rare metabolic diseases	a: if indicated (family) b: all children	biochemical	yes	a: Great Britain b: several states of the USA
prior to conception	cystic fibrosis	secondary school pupils and couples	DNA (identification of carriers)	no	USA, Canada
	Tay-Sachs disease	young adults	biochemical (identification of carriers)	yes	Israel, USA
other	prostatic cancer	adults	biochemical	yes	USA
	haemochromatosis	if indicated (family)	biochemical	yes	Australia

it clear that just because it makes mention of a disease, this does not necessarily mean that it considers screening in such situations to be either useful or acceptable. As stated, the sole purpose of the summary is to illustrate the various issues associated with screening

4.2 Screening prior to conception

The aim of screening prior to conception is to gain insight into the chances of hereditary diseases occurring in the offspring and to do so at a moment when all possible options with regard to procreation are still open. These options include choosing to avoid having offspring of one's own; acceptance of the risk possibly in combination with the use of prenatal diagnosis (now being possible for an increasing number of diseases); the use of donor insemination or of in-vitro fertilisation (using donor sperm cells or egg cells, or combined with preimplantation diagnosis (see 4.3)) and the adoption of a child.

Screening prior to conception is currently possible when any of the following occur in a family: an X-linked hereditary disorder, some autosomal recessive and some autosomal dominant disorders, a familial chromosome translocation or frequent spontaneous abortion. Genealogical investigation and the collaboration of members of the applicant's family are often essential in this regard. Other than matters relating to the family, screening prior to conception to find carriers is only possible for clinical pictures in which carriers of the abnormal genetic material can be identified by abnormal proteins, cells or chromosomes or for those in which the gene and its mutated versions (associated with the clinical picture) are known.

The drawbacks are a degree of intrusion by medical science into the process of procreation, the possibly irksome repercussions which the knowledge gained might have for other members of the family or for access to employment and private insurance, and the psychological burden of being faced with difficult choices. In the case of recessive hereditary disorders (which only occur if both of a child's parents are carriers of a mutation in the gene concerned), some research workers prefer to minimise the drawbacks by only carrying out the screening if both parents participate. Furthermore, they will only report the presence of the trait in question if the test indicates that both partners are carriers. If only one of the partners is identified as a carrier, no mention is made of this.

Screening to identify the carriers of mutations which are associated with commonly occurring recessive hereditary diseases is also carried out (in the form of experiments) on secondary school pupils (Mit93). The information can then be given within the context of the class. The question remains, however, as to the effectiveness of screening at this time with regard to use of the knowledge gained in later life, at the time of procreation. The committee feels that, in general, there should be a reluctance to include children in the target group. In each case it will be necessary to judge whether the intended benefits are sufficient to justify a degree of intrusion into the child's (future) autonomy.

Regarding screening prior to conception within more or less limited target groups, one could cite clinical pictures such as cystic fibrosis (CF), fragile X syndrome, hereditary haemoglobinopathies, Tay-Sachs disease and infantile spinal hereditary muscular dystrophy (Werdnig-Hoffmann disease). These are severe disorders which become apparent at birth or shortly afterwards, and for which there is no cure.

4.3 Prenatal screening

The aim of prenatal screening is to create courses of action for those involved. This is achieved via the early detection of couples with a heightened risk of having children with a hereditary or foetal disorder or by collecting information of importance to

obstetric policy. The term 'prenatal screening' implies that a pregnancy is already under way. Prenatal screening is chiefly used to detect neural tube defects, Down's syndrome and congenital anatomical abnormalities. In addition, prenatal diagnosis is carried out (if indicated) for other disorders, such as those cited for screening prior to conception, and for parents with a heightened risk (usually evident from the family's medical history) of having offspring with a severe hereditary disorder.

The range of tests for hereditary or congenital abnormalities which can be carried out during pregnancy is increasing rapidly. Furthermore, these tests can be carried out at ever earlier stages of pregnancy. Prenatal testing for the detection of couples with a heightened risk of having children with a hereditary disorder can be used for all clinical pictures in which the familial genetic defect in question has been identified and located. In practice, prenatal testing is almost always associated with severe, untreatable disorders.

The earliest time actually precedes implantation of the fertilised egg cell. This so-called pre-implantation diagnosis is still restricted to the realms of scientific research. There are currently several dozen children throughout the world, who were born following such testing. The testing is carried out on egg cells or fertilised egg cells after several cell divisions. The testing focuses either on establishing the presence or absence of a commonly occurring genetic mutation in the family or (in connection with the above) upon discovering the sex of the foetus. Testing is inextricably linked with the procedure of in-vitro fertilisation (IVF). The target group for this test consists of (married) couples who, following the usual prenatal diagnosis, have repeatedly had to resort to termination of pregnancy, or those who object to the usual prenatal diagnosis mainly because it involves the termination of a pregnancy. There are also (married) couples who not only have a heightened genetic risk but who are also dependent upon IVF for initiating their pregnancy.

Testing a foetus during pregnancy can be carried out either via ultrasonography or using cellular material from the foetus or from the future placenta (chorion). Routine testing using ultrasonography is especially aimed at the collection of information for the obstetric policy. Advanced ultrasonography is used to establish the presence of anatomical abnormalities in the foetus. Cellular material can be obtained by taking chorionic villus biopsies, amniotic fluid or foetal blood. The invasive nature of such tissue sampling means that this type of testing involves a (small) risk of losing the pregnancy or of premature birth. Experiments are currently being carried out to determine whether foetal cells (or cells from the placenta) isolated from the mother's blood (or from a vaginal swab) could be used for the purposes of such testing.

The most common indication for the testing of chorionic villi or of cells derived from amniotic fluid is a heightened risk of Down's syndrome due to the age of the mother. Such testing may also be carried out if there is prior knowledge of other

heightened risks of a foetal organic defect. This would be the case, for example, if such a heightened risk emerged from complications which occurred during pregnancy (foetal growth disorder, abnormal quantity of amniotic fluid). Another instance would be if abnormality came to be suspected as a result of routine ultrasonography.

At the prenatal stage, tests are carried out either on the mother alone or on both parents. Screening of the mother involves, first and foremost, factors which are known to be able to affect pregnancy (high blood pressure, diabetes, antibodies against Rubella, blood group and blood group antibodies. In addition, the triple test (3.3) can be used to establish whether or not there is a heightened risk of having a child with Down's syndrome or an open neural tube defect. If it emerges that there is indeed a heightened risk, then this screening can be followed by concentrated diagnostic testing of the foetus, either by means of ultrasonography or by using cells from the amniotic fluid. In a number of countries, the triple test is offered to all pregnant women, as a matter of routine. In the Netherlands, however, this test is only available on a limited scale. Blood group sensitisation is sufficient reason for carrying out a blood group test on the father-to-be.

Furthermore, in the prenatal stage, the tests described in association with screening prior to conception can be carried out on one or both parents. The aim is to identify carriers of hereditary mutations or chromosome variants. Where necessary, this is followed by the focused testing of foetal cells.

The perception of the pregnancy is affected by prenatal screening, both in a positive and a negative sense. On the one hand, parents with a high chance of having offspring with hereditary or congenital abnormalities can be relieved of all anxiety and uncertainty. On the other hand, such screening confronts the parents with the possibility that their child might be born handicapped. If subsequent diagnostic testing establishes that an abnormality is indeed present, then the available courses of action involve decisions on whether to continue the pregnancy. The woman (or married couple) concerned can either prepare for the birth of a child with the handicap in question or decide to have the pregnancy terminated. Numerous considerations may be involved in a decision like this. In either case, comprehensive information is required about the relevant clinical picture, especially if the woman is unfamiliar with the disease in question.

Prenatal screening, in combination with prenatal diagnosis, can contribute to the avoidance of illness in the population (Cor93). The annual review of the Dutch working group on prenatal diagnosis (Nederlandse Werkgroep Prenatale Diagnostiek) has revealed that 8903 tests (chorionic villus biopsy, amniocentesis or placentocentesis) conducted on 336 pregnancies revealed the presence of an abnormality (numerical chromosome abnormality, other unbalanced abnormality, neural tube defect, other congenital abnormality, with the exception of anatomical abnormalities detected by the

use of ultrasonography). Of these 336 pregnancies, 243 were terminated. Where the abnormality concerned was trisomy 21, trisomy 13, trisomy 18 or triploidy, about 90% of the pregnancies were terminated (WPD93). The possible reasons for not terminating the pregnancy are: acceptance of the risks by the parents, intra-uterine death of the foetus before the test results are obtained, pregnancy is too far advanced to be terminated because of a non-lethal abnormality, abnormality of the sex chromosomes or an abnormality with an uncertain prognosis. The termination of pregnancy should be viewed in the light of the fact that, if prenatal diagnosis was not available, some of the pregnancies would never have been initiated. This is because, in such a situation, the parents involved would have refrained from having (further) offspring (Fre90).

4.4 Neonatal screening

The aim of neonatal screening is the prevention of (or timely intervention in) hereditary disorders, by means of timely diagnosis, genetic counselling, provision of information, treatment and counselling. With some untreatable hereditary disorders, the possibility of timely genetic counselling is mentioned. The purpose of this is partly the avoidance of uncertainty in a long-term diagnostic process, the prevention of subsequent feelings of guilt and of regret on the part of the parents (who feel that they have responded wrongly towards a developing disorder in their child) and the timely identification of those at risk within the family.

For diseases in which invalidity can be prevented by timely intervention following birth, the best option is neonatal screening. This may take the form of biochemical/endocrinological testing or DNA testing. Just a few drops of blood (obtained by means of the 'heel prick') are all that is required for either test. In most cases, an abnormal result has to be confirmed, and subsequent diagnostic testing is also required.

Because of the form of organisation involved and the limited physical stress imposed on the person being screened, neonatal screening offers the prospect of a high degree of participation. Neonatal screening for phenylketonuria (PKU) and hypothyroidism (CHT) is applied to virtually all newborns in the Netherlands and is widely accepted. Usually, the parents are only given very general advance information about the purpose of the screening. The information to be provided to parents (which is necessary in connection with obtaining their consent) becomes much more comprehensive and complex as the screening is expanded to cover additional diseases. Such an expansion is conceivable, now that it is possible to identify the carriers of ever greater numbers of diseases by means of DNA testing. With regard to simultaneous screening for various clinical pictures, a committee of the Institute of Medicine in the

United States has advised against combining too many tests, in view of the limitations imposed by the requirement to provide full information (Ins93).

At a number of pilot areas throughout Europe, in addition to the routine screening for phenylketonuria and hypothyroidism, neonatal screening for Duchenne type muscular dystrophy (DMD) is also being carried out (Ros93). If the proportion of those carrying mutations in the gene for MCAD disease (Mid-chain acyl Co-enzyme A Dehydrogenase: involving fatty acid metabolism) in the Netherlands is found to be high then consideration could be given to the possibility of screening for this disease (which responds well to treatment if identified in time).

4.5 Screening in later life

This screening relates especially to clinical pictures which manifest themselves later in life and which, to some extent, are multifactorial in origin. The aim of such screening is to establish whether there is a genetic predisposition to the disease. If screening indeed reveals the presence of such a predisposition, intensive monitoring can sometimes lead to detection of the disease itself at a very early stage, while it is still treatable. Furthermore, the person involved can attempt to prevent expression of the genetic predisposition, by the avoidance of certain environmental factors.

The number of clinical pictures in which it is possible to detect the presence of a hereditary component will increase as more genetic information becomes known. This sometimes relates to diseases which are extremely prevalent, in which the hereditary form can be a subgroup of a widely distributed clinical picture. In such a case, extra consideration will have to be given to the information provided. Some examples of diseases for which screening can be carried out (as a result of family indication) in later life are hypercholesterolaemia, hereditary forms of breast cancer, cancer of the colon and Alzheimer's disease.

Psychological aspects

5.1

Introduction

The committee considers certain research data to be important to any discussion of the psychological aspects of genetic screening. This data concerns the psychological experiences of people who, after having explicitly requested medical aid, have obtained information about heredity or who have been submitted to genetic testing. This mainly relates to people (individuals or couples) who have been confronted with a specific disorder within their own family. As a result, they wanted to know what chance there was of a (or another) child being born with the disorder in question or what their own chances were of contracting the disorder in later life.

There are two respects in which this situation is essentially different from the offer of certain heredity tests in the context of genetic screening. With the latter firstly, there is no explicit request for medical aid (see 1.2). A second essential difference is that, with genetic screening, many of those involved lack prior knowledge or experience with the disorder which is the subject of the screening. Despite these differences, it would seem to be worthwhile to extrapolate (to some extent) the psychological effect of genetic screening from the first situation. This is because little research has been done into the psychological effects of genetic screening itself. As regards the relationship between the provision of information on health and the use of such information to determine behaviour, the committee refers the reader to more general literature (Dam93).

The committee would like to state, in advance, that research into psychological repercussions is often somewhat fragmentary in nature. In addition, there is no research into the psychological repercussions experienced by those who (either consciously or compelled to do so by circumstances) abandoned the option of genetic testing and who were subsequently confronted with a genetic disorder.

5.2 Screening prior to conception

The aim of screening prior to conception is to inform, in good time, those (young) adults who request such information about whether or not they have a heightened chance of having a child with a recessive disorder. Those involved are hereby given the opportunity to make a free and informed choice from various options with regard to having children, or to elect not to have children of their own. The committee addresses, in order, the following issues: the extent to which offers to identify carriers are accepted, the possible effect of being a carrier on self-perception and in terms of social stigma, and the use of the information obtained for family planning purposes.

5.2.1 *Accepting the offer*

The extent to which offers of screening are accepted, is highly dependent on the physical setting in which screening takes place and the way in which a programme is introduced. This applies not only to screening prior to conception but to all types of screening. Research in the field of cognitive psychology (Tve81) has shown that the wording and the context within which a problem is formulated influence subjective evaluation of the risk, as well as the ultimate decision. Firstly it is important whether information is formulated in terms of profit and loss. Another factor which has a part to play, is whether a given course of action is proposed as a means of reducing risk, or of eliminating risk altogether.

The roles of each of these factors were investigated in an experiment (Huy90) whereby a hypothetical situation was created which involved Down's syndrome. In one instance the statement of the problem included information about the chances of having a child with Down's syndrome in a given situation. In the other instance the chances of having a child without Down's syndrome were quoted. As regards the second factor, on the one hand, prenatal diagnosis was introduced as a test aimed at reducing the chances of giving birth to a handicapped child. On the other hand it was presented as an opportunity to exclude the possibility of having a child with Down's syndrome.

The hypothetical decisions were clearly influenced by the way in which the problem was stated. One consequence of this is that with a screening programme for CF, for example, it is crucially important to choose the right formulation, one which

will clearly indicate that such screening cannot lead to the detection of all the various mutations involved.

In addition, it holds true for all forms of screening that the more personal the approach and the fewer steps that people have to take for themselves, the greater the extent of participation. This was demonstrated in trial projects in Canada in which almost all 15 to 17-year-old secondary school pupils were invited to participate (as whole classes) in screening to identify carriers of Tay-Sachs disease or of CF. Not surprisingly, about 70% and about 40% respectively chose to take advantage of the opportunity (Mit93). Besides lack of interest, the reasons for non-participation were mainly fear of having blood samples taken and, more particularly, of AIDS. Another reason was that the individuals concerned did not have their parents' signed letter of informed consent with them. In the case of CF screening, the degree of participation rose to 70% if a mouth-rinse was used for the study instead of blood.

The committee states that a high degree of participation is not necessarily an indication of the success of a screening programme. It may just as well be an indication of excessive compulsion or persuasion. A psychologically interesting point is that various studies have shown that, of those questioned, the percentage supporting the offer of screening to identify carriers of CF always exceeded the percentage of those who actually participate in such screening (Dec92, Kat90, Wat91).

5.2.2 *Self-perception*

The psychological effect on self-perception of being a symptom-free carrier of mutations, including the insight gained into the state of one's own health, has not yet been adequately studied. Marteau (Mar92) established that carriers of mutations in the Tay-Sachs gene have a less optimistic view of their own future health than do non-carriers. She indicated that inadequate information could be responsible for this (Mar90). As a result, some people become confused regarding the fact that being a carrier has absolutely no repercussions for the health of the individual concerned. Evers-Kiebooms in Flanders has established that carriers of the CF gene also have less positive feelings about themselves than do non-carriers, when thinking about the results of tests for CF carriers. Indications of social stigmatisation were also found. In comparison with carriers of mutations, non-carriers attribute markedly less positive feelings to most of those who are carriers of a mutation in the CF gene. In addition, carriers attribute less positive feelings to other carriers than to themselves. In this study, the negative view of carrier status was more accentuated in those without personal experience of the disease. Existing prejudices can, of course, play a part in this.

The population at large has only a limited knowledge of actual clinical pictures. This means that those experts in heredity (and other practitioners) with whom people

come into contact in connection with screening for carriers have a very delicate task. The nature of the information given can either enhance or reduce the stigmatising effect (Eve94a). Since the research described above deals with relatively subtle measurements, it does not entirely contradict Watson's findings (Wat92) that most carriers were not unduly worried about their carrier status. Indeed, 'conscious' worrying seemed to occur only very seldom.

5.2.3 *Use of information for family planning*

The committee will now examine the use to which information about carrier status is expected to be put when planning pregnancies. In this connection, it is important to take as reference the weighting of 25% hereditary risk by couples who are familiar with the disorder in their family or in their population. To some extent, good information can substitute for prior experience with the disorder in question.

Firstly, the committee would point to the situation regarding thalassaemia in Sardinia (Cao81). In the period 1977-1980 about 85% of high-risk couples employed prenatal diagnosis during pregnancy. As this population is extremely familiar with the disorder concerned, the strategy of screening and of prenatal diagnosis was widely accepted. The screening programme resulted in a drastic reduction in the incidence of thalassaemia among the newborn.

In Belgium, studies of the parents of children with CF revealed that for two thirds of them the risk involved in another pregnancy significantly influenced their plans regarding such pregnancies. Many of them either postponed the next pregnancy or elected to have no further children. At least 53% of the parents of a firstborn with CF had no successive pregnancies within an average follow-up period of about seven years. Both the perceived risk and the presence (or otherwise) of other children in the family were important factors with regard to later reproduction (Eve90). The importance of these two factors and of the possibility of prenatal diagnosis has also been described for a range of other disorders (Fre90). The latter study also illustrates the complex, irrational and painful process of reaching a decision about subsequent pregnancies. Parents who already have a child with a particular disorder can find it difficult to decide whether they should have any more children, even where prenatal diagnosis is possible. Both guilt feelings with regard to the first child and the maintenance of a positive attitude to the treatment of that child can interfere with reaching a decision regarding prenatal diagnosis.

Parents must be assisted to clearly distinguish between caring for the child that they already have (and other associated problems) and the new responsibilities with regard to a future child (where the chance that it will have the disease in question is known in

advance). Accordingly, in the field of clinical genetics, the prevailing view is that treatment and genetic counselling should be provided by different individuals.

The above passages suggest that, after genetic screening, couples in which each partner carries a mutation in a recessive gene will be influenced by information about the genetic risk and (to an even greater extent) by individual perceptions of this risk. The committee would like to emphasise the importance of simple and well-balanced information about the disorder to be detected and about the real significance of carrier status. This is important with regard to obtaining informed consent from the person to be tested. It is also important for the promotion of well-adjusted self-perception on the part of carriers and for the avoidance of misapprehensions regarding their chances of having a child with the disorder in question. In addition to verbal information, it is also extremely important to provide folders which should be read before a decision is reached about participation in the screening programme. Patients, the parents of patients and patients' associations can all offer useful contributions to the production of such a folder.

Balanced information is also needed to acquire an adequate perception of people with the handicap in question, and to develop respect for them. The younger the people involved in screening, the greater the importance of good, prior information. In order to ensure that information will be well understood, it is important that sufficient basic material about human genetics be taught in secondary schools. This can include class discussions, folders, videos etc. Once such a basis has been established, this can be used by information provided in the context of genetic screening. Besides screening prior to conception, these general remarks about information are also relevant for the other three types of screening.

In conclusion, the committee would also like to address the importance which the results obtained by genetic screening have for the family. If a person is shown to be a carrier of a mutation, this information is also important to brothers, sisters and, possibly, for other members of the family. This aspect should not be neglected, either in terms of prior information or during the personal counselling given in conjunction with details of the test results. As Kooij puts it, quite correctly, 'it is still not clear what influence screening will have on marital relationships, relationships with other members of the family and what responsibilities this will involve with regard to the immediate family, more distant relatives and future descendants. It is quite clear, however, that what screening reveals in one individual will clearly have direct consequences for another' (Koo94).

5.3 Prenatal screening

The offer of prenatal screening is often the first time that future parents will be confronted with the tangible possibility that their child could have a severe disorder and that some severe disorders can be detected. This leads to an ambivalent situation in which a much-wanted pregnancy is perceived as being provisional and is discussed in terms of whether or not their child might have a disorder. This situation can place future parents in a state of emotional confusion. Just being confronted with the possibility gives rise to anxiety and stress. The first spontaneous expectation on the part of the parents is to be reassured that their child is normal. In fact, correct prior information should negate this expectation, without giving rise to excessive anxiety. Often, prenatal screening first assesses the risks, after which (dependent on the degree of risk involved) a decision can be made with regard to further testing. Beekhuis, quite correctly, points out that this difference between diagnostic tests and tests to evaluate the degree of risk involved should be made quite clear to the participants (Bee93). Psychological tests on risk perception have shown that most people find it difficult to correctly understand chances and to deal with the associated level of uncertainty (Bil87, Vle87).

Prenatal screening can influence views about pregnancy in other ways. Widespread prenatal screening can create an unwarranted sense of security, rather than the more realistic view that pregnancy and birth involve many uncertainties which cannot be monitored. This may give rise (incorrectly) to the common belief that all congenital abnormalities can be prevented. Consequently parents are, to a great extent, considered to be responsible for their children's abnormalities.

Sociological sources warn against the excessive intrusion of medical science into the lives of pregnant women (Kat86, Kat93, Lip91). These authors indicate that pregnancy is increasingly being seen as a production process. Authors with feminist-sociological leanings believe that this creates an individualisation of problems relating to handicap and disease, a load which falls principally on the mother's shoulders.

The committee would now like to explore psychological investigations of the anxiety which can be induced by prenatal screening. This applies both to the determination of carrier status for CF in pregnant women and to the screening of the mother's blood to detect children with Down's syndrome and neural tube defects (triple test). The committee will then briefly illustrate the consequences of terminating pregnancy for genetic reasons, since this is the most common option if a severe abnormality is discovered as a result of an amniocentesis or a chorionic villus biopsy.

5.3.1 *Anxiety engendered by screening*

As far as investigations into the screening of pregnant women for CF are concerned, the emphasis is usually placed on the level of participation rather than on the psychological effects. Williamson specifically points out the ephemeral nature of the anxiety experienced by pregnant women who have been shown to be carriers of a CF mutation. His study incorporated a programme whereby the partners of the women examined were only tested if the women were found to be carrying a mutation (Wil93). Mennie also suggested that the stress associated with the establishment of carrier status would only last for a short time (Men93).

In none of the studies yet carried out has the effect of such temporary anxiety on pregnant women been investigated. This transient anxiety could be reduced by only carrying out a screening programme for CF during pregnancy if both partners are tested at the same time. This strategy has been used in various studies, one of them a pilot study in Edinburgh (Liv93). The advantage of such an approach is that, straight away, consideration is given to the information to be provided as a result of the existing pregnancy, together with the confirmation of carrier status for both parents. In this way, it is possible to avoid the anxiety experienced (however temporarily) by pregnant women who have been identified as carriers of the mutation while they are awaiting the results of tests performed on their partner. Only in relatively few cases (less than 5%) do such tests reveal that the partner also carries a mutation. From the psychological viewpoint, setting up screening programmes which are only carried out if both partners participate, has the associated advantage that both partners are directly involved in all decisions. One drawback is that this creates additional practical problems with regard to the organisation of the screening. Another is the ethically sensitive issue of the offer of screening being withdrawn if the partner is unwilling to participate.

Where both the pregnant woman and her partner are carriers, and are aware of this, they usually opt for prenatal diagnosis, although they may not necessarily intend to terminate the pregnancy (Wil93). However, the numbers involved are too small to allow any conclusions to be drawn.

With the triple test, a result which indicates heightened risk inevitably provokes anxiety and stress. The level of anxiety can be further reinforced by lack of information or clarity in the interpretation of test results (Mar93). A heightened risk does not necessarily imply that the unborn child actually has the disorder. It is therefore necessary to explore the consequences of informing people that they have a heightened risk. According to Burton, anxiety falls back to its initial level if further diagnosis establishes that the abnormality which gives rise to such concern is unlikely to be present after all. Her study gave no indication that the expectant mother's attitude,

either to the pregnancy or the child itself, was affected in any way at all (Bur85). Marteau, on the other hand, has shown that diagnostic test results which fail to confirm the risk do not necessarily reduce anxiety to the base level. Her studies revealed that, even after a period of several weeks, women with increased risk were still significantly more anxious than those for whom the triple test indicated that there was no heightened risk (Mar93). In this context, Christiaens has shown just how important it is that the concept of risk assessment be adequately explained. The pregnant women must be made well aware that the triple test is about risk assessment rather than diagnosis (Chr94).

Opinion is divided regarding the desirability of applying ultrasonographic screening to all pregnant women (regardless of their risk level) during the first trimester or at the start of the second trimester. Quite a large number of diagnoses are missed (Chi92). Within the context of this section it should be noted that Green emphasised the importance of non-verbal communication between the obstetrician and the patient. Even quite subtle differences in the verbal explanation of the ultrasound images can have a significant influence on the pregnant woman's level of stress and anxiety (Gre90). However, there is a lack of soundly based scientific research on this topic.

5.3.2 *Termination of pregnancy for genetic reasons*

If, after a test result has indicated the existence of heightened risk, prenatal diagnosis reveals the presence of a severe disorder, most parents decide to terminate the pregnancy. The consequences of terminating a pregnancy due to the detection depend to a great extent on the personality of the woman concerned and upon the situation (Les82). Many authors point out that such consequences are often underestimated. In addition to loss of the pregnancy, the individual must also come to terms with their decision to terminate a much-wanted pregnancy. According to Thomassen-Brepols, more than half of the individuals involved take more than a year to come to terms with the situation (Tho85). The loss of a much-wanted child and of the feeling of biological worth involves an extended process of mourning. The individual has to set things straight regarding conflicting emotions and the clash between the image of a much-wanted child and that of a handicapped child. Nevertheless, in subsequent pregnancies, most women again opted for prenatal diagnosis (Bra92; Les82). In this connection, research is required to clarify the similarities and differences between the sorrow of parents who have a child with the abnormality (both with prior knowledge via prenatal diagnosis, and without) and of those who, following prenatal diagnosis, decide to terminate the pregnancy.

Pregnancies which are terminated on the basis of the sex of the foetus, where a male foetus would have a 50% chance of an X-chromosome-linked abnormality, form a

distinct group. Numerous case histories have shown how difficult it is for people to come to terms with this situation.

Little systematic research has been carried out into the effect of the lethality (or otherwise) of the disorder on the process of mourning and of dealing with the termination of the pregnancy. In the course of a study carried out in Flanders, a large group of adults was shown to be about evenly divided between those who would terminate a pregnancy if it was established that the child would die soon after birth and those who would do so if the child were to have a severe chronic disease (Eve94b). Feelings of guilt occurred less frequently in cases involving a lethal disorder (Spy92).

It is important to point out here that the emotional reactions and the process of mourning which follow the termination of pregnancy on the basis of genetic indications are frequently underestimated. This aspect has indeed been confirmed by follow-up research in the Netherlands (Kor92). A significant proportion of the respondents reported that they had undergone a long and difficult process of mourning. Such mourning often lasted for longer than six months, involving a variety of emotions and problems. The subjects were depressed, drained and quickly irritated, experiencing concentration problems and insomnia. Loss of the child was accompanied by a loss of the individual's own identity. Many women, and some men, experienced a sense of failure. In addition, some had feelings of guilt, e.g. for having passed on the disease or for having decided to terminate the pregnancy.

As regards the psychological repercussions of prenatal screening, one striking fact is that many studies reveal faulty methodology - which makes it difficult to draw unambiguous conclusions. Another notable fact is that very little consideration is given to any psychological repercussions suffered by the father.

5.4 Neonatal screening

Something common to all forms of neonatal screening is that they can reveal the presence of a disorder in a child at a time when the parents do not expect to be confronted by this or have had no reason to become concerned about it, since no symptoms have yet appeared. Informing parents about an adverse diagnosis can provoke violent emotional reactions. Gradually, they will have to come to terms with the implications of the diagnosis, both at a cognitive and an emotional level.

5.4.1 *Treatable disorders*

In essence, it will be easier to come to terms with the situation where effective intervention in the disease process is possible. This situation mainly occurs in neonatal screening for phenylketonuria and hypothyroidism (the 'heel prick'). Besides the

obvious advantages which neonatal screening has for the child itself, the prospect of therapy is a positive element for the parents. It helps them come to terms with being unexpectedly confronted by the fact that their child has a severe disorder. This would explain the positive experiences associated with both types of screening programme. Neonatal screening also offers the parents of a child with phenylketonuria a great deal of prior information concerning their risk of having another such child in subsequent pregnancies. This is clearly a fringe benefit of the screening programme, even though it necessitates good counselling and requires those involved to come to terms with the situation, psychologically.

The results of tests which, with the benefit of hindsight, mistakenly indicated the presence of an abnormality will (as with prenatal screening) give rise to anxiety. This anxiety can be limited by the provision of adequate prior information, follow-up tests and counselling.

5.4.2 *Untreatable disorders*

Neonatal screening can now be used for disorders such as Duchenne muscular dystrophy, which manifest themselves during childhood, have a rapid and progressive course and cannot be treated (Omm94). The untreatable nature of these diseases is a critical factor for the parents, in coming to terms with the situation, psychologically. The development of the disease in their newborn is quite outside their control. Here, the importance of the test result for the newborn has to do with better counselling, early adjustment by the parents to the developing disorder on the one hand and reducing the interval between diagnosis and the appearance of the first symptoms - a period which can cover many years of false hopes (Par94). The test result offers parents additional courses of action with regard to a subsequent pregnancy. There is also the option of early counselling and support, and of avoiding of feelings of guilt and regret arising from any inappropriate treatment which their child might receive in the period preceding diagnosis. The above sections have served to illustrate the importance of timely information and counselling when planning further pregnancies, as well as that of prenatal diagnosis. There has been too little follow-up of families with children in which Duchenne muscular dystrophy was diagnosed neonatally to enable any statements to be made regarding the effects on planning of further pregnancies and on relationships within the family.

With neonatal screening for Duchenne muscular dystrophy, sufficient consideration must be given to the possible repercussions for the relationship between the parents and their newborn as well as to the normal emotional growth of the child and its developing interaction with the family. Very little information is available on this topic. For this reason alone, good information (for an informed consent) and an

adequate network of psycho-social assistance are extremely important with this type of neonatal screening. The psychological and social effects are currently being systematically evaluated in Cardiff. Within a few years, this should reveal the effects which an early diagnosis of Duchenne muscular dystrophy has on the child itself and on the family.

From a psychological perspective, it is important to weigh the parents' suffering and their emotional reactions in response to an early diagnosis against the anxiety, uncertainty and the emotions which accompany appearance of the initial symptoms in the absence of a diagnosis. It should not be forgotten that the latter also involves a protracted diagnostic process and a possible procession of various medical specialists. The prevailing view within the parents' associations is that the sooner diagnosis is made after birth, the better parents are able to prepare themselves to accept and live with Duchenne muscular dystrophy.

5.5 Screening in later life

There is currently no experience of the psychological effects, at population level, of screening (young) adults for hereditary diseases which manifest themselves in later life. Such experience is mainly restricted to predictive testing for Huntington's disease. This is carried out solely in families in which the disease occurs. There seems to be much less demand for predictive testing than was initially anticipated. In addition, it seems that the group which allows the test to be carried out is a select group with a greater average self-awareness than the average population (Dec94). Most publications agree on the principal motives for requesting the test: to get the facts or to remove anxiety and uncertainty; family planning and having existing children checked.

Research in Canada, the United States, Great Britain, in Flanders and in the Netherlands illustrates that a predictive test (carried out within a good counselling context) has no obviously negative repercussions. After being told that they carry a mutation in the Huntington gene, people always experience strong emotional reactions and a difficult period while they come to terms with the situation. Nevertheless, it appears that most persons tested, having received their test result, manage to get with their lives without any severe psychological problems. They also have the feeling that they can improve the way they organise their lives, even if this effect is smaller than they had thought. There is still insufficient experience to establish what influence early discovery of the mutation has on detecting the first symptoms of the disease and on the diagnostic process. On the other hand, determining the absence of a mutation also has repercussions. The threat of the clinical picture is, in a manner of speaking, part of the family. Once this threat is lifted from a person, a period of adjustment to their new identity is required (Tib93).

The question is now: what does the above teach us regarding genetic screening for other hereditary disorders which are expressed during adulthood? In this connection, it is certainly important to consider the inventory of psychological, ethical and social problems prepared by the European Community Huntington's Disease Collaborative Study Group (Bal93). If the screening involves severe disorders for which no therapy is available, it is extremely unlikely that screening outside the affected families will be acceptable. Within the families, intensive prior counselling is required as well as adequate counselling after the person has been informed of the result. This is even more important if the person involved is unfamiliar with the disorder.

Screening for a genetic predisposition to breast cancer or cancer of the colon is a different proposition entirely. This is because, once the presence or absence of a mutation has been established, frequent check-ups or radical surgery can be considered or eliminated, as the case may be. In this case, as with other hereditary disorders where the presence of a mutation often involves a markedly heightened risk rather than an unambiguous diagnostic result, it will be psychologically very difficult to interpret the information correctly and to find the best way of living with the uncertainty. Pilot projects have already been set up with the aim of investigating the psychological repercussions of what is an extremely delicate matter. There is a total lack of knowledge regarding women's understanding and perception of a medically determined genetic 'susceptibility' for breast cancer. Nor is there unanimity about the way in which to approach screening for a genetic predisposition and about what, in reality, can be predicted (Dur93).

In the case of some multifactorial disorders in particular, the situation can be psychologically very complex. On the one hand, the person involved will learn that they have a heightened risk of getting the disorder, on the other hand, they will find out what behaviour or adjustments to their lifestyle will be required to reduce this risk. The prospect of having partial control over some matters will, to some extent, facilitate the process of coming to terms with the heightened risk. In this context it is important to give due consideration to the findings in health psychology. Just knowing about something is certainly not enough to produce changes in behaviour. The tension resulting from the existence of the heightened risk coupled with an inability to modify behaviour can give rise to considerable stress after screening for multifactorial disorders. For the time being, nothing whatsoever is known about the repercussions of the detection of heightened risk for the self-perception of the person being tested. It is unclear to what extent some people already come to see themselves as patients at an earlier point in time.

5.6 Concluding remarks

In summary, there are four distinct dimensions to the psychological repercussions of genetic screening.

The first dimension relates to psychological factors which partly serve to determine acceptance of the offer of screening. The committee considers a free and well informed choice to be more important than obtaining the highest possible level of participation. Accordingly, it is the committee's view that a great deal of attention should be paid to the form and terminology of the concrete information and to the setting in which the offer of screening is made. These elements will also have repercussions for the way in which society views people with a detectable handicap. Well balanced information helps to avoid a situation in which they are seen as the result of missed prevention.

The second dimension concerns the psychological repercussions of the result of screening for the person being tested and their family. Sufficient consideration must be given to the anxiety which can be caused by the offer of screening and by the result. Even after the absence of disease, risk of disease or carrier status has been conclusively determined, heightened concern about health and handicap can persist. The effect of confirming a test result is also important for self-perception. A crucial part can be played by well balanced, correct, advance information and adequate counselling.

The third dimension concerns the part which the result of screening can play in the life of the person involved and that of their family. Unless efficient therapeutic agents are available, agents which can improve the quality of life of a person with the disorder, the emphasis is on the use of the information in making decisions about entering relationships, reproduction, further augmentation of life and in deciding the individual's lifestyle. Those psychological factors which come into play here must be included in counselling and support.

The fourth dimension concerns the psychological repercussions which can occur in those who have decided to forgo participation in a screening programme and who are subsequently confronted with the birth of a child with the disorder in question. They may experience feelings of guilt and regret if the possibility of such an event was not sufficiently considered during the process of arriving at their decision. This effect can also be obviated by means of adequate provision of information.

Ethical aspects

6.1

Introduction

This chapter deals with the ethical issues associated with genetic screening. Several of these are also encountered in genetic testing carried out as a result of an individual request for genetic counselling, and with the family testing which is often an extension of this. These issues have already been comprehensively dealt with in an earlier report produced by the Health Council (GR89). Accordingly, in this report, the committee will focus mainly on the issues raised by an offer of screening (or the express provision of information about screening) which is made without any prior request for medical aid.

Such an offer differs in a number of relevant (from the moral standpoint) ways from a request for testing. The simple fact that such offers are made by health workers on the basis of their professional expertise and social function, imparts a degree of legitimacy. The personal opinions and motivation of the person making the offer have a part to play in the making of the offer, although this subjective element can be partially repressed if the offer is made in writing. An offer is, by definition, not entirely free from value judgements, however. In principle, all screening involves an approach being made to 'healthy' people. They are hereby alerted to the existence of a health risk of which they were generally unaware or only vaguely aware. The offer of screening places people in a situation in which they are forced to choose. Even if they decide not to pursue the offer of screening, a choice and a decision are still involved. Caution is called for, partly because screening involves large groups of people.

For various reasons, the requirement for caution applies even more to genetic screening.

- The options and courses of action often relate to pregnancy and reproduction.
- The information obtained can also be of importance to other members of the family, even if they are not participating in the screening programme.
- Some cases involve a risk-evaluation test or (with some diagnostic tests) evaluation of residual risk, which makes it difficult for the participants to interpret the result.
- A long period of time may pass between the determination of a genetic predisposition to a disorder and the actual manifestation of that disorder.
- Usually it is not known whether or not people are able to cope with being informed about the result of the tests.
- It is not yet certain which disorders and combinations of disorders will be detectable by screening in the future.
- In the past, it has been shown that knowledge of this field within the community is open to incorrect interpretation and abuse, which can lead to extremely harmful forms of discrimination. Opportunities for abuse and causes of discrimination are still present in society (Gar94).

The above means that genetic screening involves a considerable moral responsibility for those offering it. This responsibility not only affects the recipients of the offer of screening but also other members of their family. It is important to find out, in advance, whether participants in the programme could be harmed. Certainly, when it comes to screening for hereditary disorders, the test result can have a negative influence on peoples' personal wellbeing and social performance. In view of the increasing plurality of our society, differences in culture and religious background must also be borne in mind. Against this are ranked the benefits of genetic screening, such as:

- The individual has a greater range of options.
- More courses of action become available to individuals, bringing the opportunity to exert greater control over their own lives.
- (Long-lasting) sorrow and suffering can be reduced and, sometimes, avoided altogether.
- The offer of screening promotes more equal access to the health service.

In this chapter, the committee will examine whether (and if so, to what extent) the offer of genetic screening complies with ethical standards governing the practice of medicine, namely:

- being of benefit to the individual
 - the moral obligation to do no harm
 - showing respect for the autonomy of the individual
-

- justice, equal access and solidarity.

A book (in Dutch) has been written on this subject (Wer90).

6.2 Doing good, not harm

6.2.1 Genetic screening in general

A programme for genetic screening enables people to discover what their chances (or those of their descendants) are of having a hereditary disorder. If such knowledge becomes available at a time when courses of action are still open, then such screening can be of great value to those involved (Kui89).

A good example is the clinical picture of phenylketonuria. In this instance, the severe neurological trauma produced by a hereditary enzyme defect combined with the use of certain foods can be prevented (after timely detection of the predisposition) by a long-term diet. Detection is by means of tests on the blood of newborn babies, obtained by means of the 'heel prick'. Another example is genetic screening prior to conception. If people are aware of the risk at that stage, all possible courses of action regarding their offspring are still open. Genetic screening also creates opportunities to discover, at an early stage, a susceptibility to disorders which occur later in life. That risk may perhaps be reduced by adapting environmental factors and lifestyle.

However, there are also disorders where screening leads to an early appreciation of the risks but where it offers few courses of action (or none at all) by which the person involved can influence that risk. The benefit to be gained by timely discovery of the risk is then of an entirely different order of magnitude than in the previous example of phenylketonuria. Certainly, where an offer is involved, prior consideration will have to be given to the question of whether such an offer is ethically sound. In addition, the individuals to be tested should be made fully aware of the significance and the possible usefulness of the screening for them. Besides the varying degrees of benefit, genetic screening also has its drawbacks.

In the case of genetic screening, prior to the offer being made, the individuals to be tested will generally be unaware (or only vaguely aware) that they are exposed to a genetic risk. Accordingly, the offer can give rise to anxiety and uncertainty. Subsequent detection of the trait in question during testing will only serve to boost this anxiety and uncertainty still further. On the other hand it clarifies courses of action, which can eventually lead to feelings of relief and certainty. However, this does not apply to those who are incorrectly given such a result. In their case, the anxiety generated by the news cannot be justified and, with hindsight, any follow-up testing (with all the associated risks) will be seen to have been unnecessary. In the prenatal

situation, such follow-up testing can take the form of amniocentesis or a chorionic villus biopsy. Both tests involve a slight risk of miscarriage or of damaging the unborn child.

In those cases where screening failed to reveal the presence of the trait in question, the misplaced feelings of relief and certainty can later revert to grief, anger, disillusionment and distrust of medical information, if the couples concerned go on to have children with that particular disorder. On the other hand, the sorrow caused by the appearance of such a disorder may be alleviated by the knowledge that everything which could be done had been done. For this reason it is of the utmost importance that the person to be tested be made fully aware, in advance, of the degree of certainty offered by the test. The committee would like to point out that studies of the effect of incorrect results must be included in the continuous evaluation of any screening programme.

Another difficulty is that benefits and drawbacks don't always effect the same persons. It is extremely difficult to weigh the benefits to some against the drawbacks for others. This is because grief and other emotions are incommensurable and are, in any case, difficult to evaluate. In such cases, an attempt must be made (by means of sound, independent assessment) to establish whether the benefits outweigh the drawbacks for the group of participants as a whole and whether, therefore, the offer is permissible. For any given screening programme, the main consideration must be its desirability rather than its technical feasibility.

In order to avoid turning the benefits of genetic screening into drawbacks, a check should be carried out (before the offer of screening is made) to determine whether there are adequate facilities in the Netherlands to guarantee the quality of the offer. This applies to the provision of written and verbal information, the performance of the test, the follow-up testing, the realisation of the courses of action and to the facilities in the area of counselling (Mod92).

6.2.2 *Screening prior to conception*

The aim of genetic screening prior to conception is to determine the risk of a future child having a hereditary disorder and to find out about the various courses of action which are available. The great benefit of screening at this time of life is that all courses of action are still open. As was noted in the previous chapter, if persons are aware that they are the carrier of the hereditary trait for a disorder, this can have a negative psychological effect on their perception of their state of health or on their self-esteem. The risk of self-stigmatisation is by no means entirely fanciful. As yet, nothing is known about the possible influence of screening on the relationship between partners, or how it affects the chances of finding a partner (Koo94). Furthermore, there are some

diseases (including cystic fibrosis) where it is not yet possible to detect all carriers of the trait in question. In this context in particular, the importance of providing good information cannot be understated.

6.2.3 *Prenatal screening*

Besides being in the interests of the parent(s), prenatal screening can also be in the interests of the unborn child. The expectant parents can opt for a particular course of action, based on their personal views. Screening can be in the interests of the unborn child if the disorder in question leads to a short life of severe and degrading suffering. However, with some disorders there is the problem that their course and severity can vary markedly from individual to individual, and that these aspects cannot always be established prenatally.

With prenatal screening, results which indicate the presence of a predisposition to a disorder usually involve severe disorders for which no treatment is available. In such cases, the available courses of action are rather limited when compared to screening carried out prior to conception. The only choice available to the parents of the unborn child are to terminate the pregnancy or to accept the birth of a child with the disorder. The trauma experienced by those having to make such a choice should not be underestimated. A much-wanted child does not automatically become unwanted simply because a disorder has been detected. Prenatal screening can affect parents who had not previously been identified as having a heightened risk. Such couples are completely unprepared for this sort of choice. If the offer of screening limits the options in this way, then counselling and support are of great importance. This applies just as much to counselling the parents during the process of reaching a decision, as to counselling which is given once the decision has been taken. Following the termination of pregnancy or the birth of a child with the disorder, the parents should (if they so wish) be able to call upon support, counselling and assistance.

Prenatal screening can sometimes produce findings which are either unforeseen or unrelated to the original request for screening. Accordingly, the situation cannot be avoided in which comprehensive ultrasonography produces information about possible abnormalities which were not being specifically sought. Such matters as non-paternity can also be revealed in the course of prenatal screening. The participants in a screening programme must not be suddenly startled by information which they had not requested. Those offering screening programmes should ascertain, in good time, what information the participants do or do not wish to receive.

6.2.4 *Neonatal screening*

Neonatal screening is particularly important when timely intervention can prevent severe physical or mental handicaps. In such cases, the benefit to the child is evident. From the viewpoint of the child's welfare, the committee feels that neonatal screening is also worth considering in those cases where timely discovery can lead to an improvement in the course of a disorder. With untreatable disorders, the benefits for the child are less evident. It is the committee's opinion that neonatal screening should only be considered for disorders which manifest themselves during early childhood. In its 1989 report, the Health Council elucidated this situation for the clinical picture of Duchenne type muscular dystrophy (DMD). The Council cited the possible advantages as: timely provision of information to the parents concerned and to other members of their families regarding the risk of repetition; more rapid detection of the disorder whereby the parents are spared an often long and sometimes inefficient passage through the health service system; and timely adjustment to the special tasks and measures which go hand in hand with the disorder. The Council cited the drawbacks as the risk of the premature intrusion of medical science and uncertainty about the severity of the disorder. The following can be appended to the conclusion of that earlier report regarding the benefits and drawbacks: improved insights mean that prediction of the severity and the course of the muscular dystrophy is now much more accurate. In addition, the sex-linked inheritance of this disease means that the mother's female relatives also have chance being carriers and it is now possible to offer such individuals timely tests for carrier status.

6.2.5 *Screening in later life*

Screening in later life relates to hereditary forms of cancer and a number of other disorders, e.g. of the nervous system. In the case of cancer, the courses of action sometimes consist of radical preventive surgery, intensive monitoring and early surgery or of changes in lifestyle.

For those diseases in which non-hereditary factors are involved, certain information is required when determining predisposition. Thus, it is most important to establish the certainty of the prognosis, the scope of the repercussions if there is no early detection and the options with regard to intervention. In the case of multifactorial disorders, a careful analysis of the benefits and drawbacks of screening is a complex matter. Quite how the genes involved interact with one another is largely unknown, as is the influence of environment, diet and lifestyle upon the manifestation of the hereditary risk. In such cases, courses of action usually involve dispensing with various types of

behaviour which are generally damaging to health. If, after being informed that they do not possess the hereditary susceptibility in question, people go on to draw the conclusion that, as far as this aspect is concerned, they can do as they like, then it is doubtful whether screening will lead to health gains at the level of the general population (Cla94).

It is often unclear what options are available with regard to screening for multifactorial disorders. The tests are used to evaluate risks, and the results will be difficult to interpret. Great caution is required because it is uncertain that people will actually manage to gain any personal benefit from the information obtained.

6.3 Respect for the autonomy of the individual

6.3.1 *Genetic screening in general*

Voluntary participation on the basis of well understood information is an absolute precondition of genetic screening. As it stated in section 6.1, the committee feels that the very fact that the screening is offered by the health service makes it difficult for the target groups involved to disregard the offer. In a certain sense, an offer puts pressure on the autonomy of the individual. This creates the additional obligation to devote great consideration to the way in which the offer is made and in which courses of action are proposed during the screening process. It is essential that individual freedom of choice be safeguarded throughout the entire process.

The information to be provided should be the best possible, and it should be conveyed by the health professionals involved. Midwives, gynaecologists, general practitioners and other primary health care workers should possess adequate knowledge of the field of genetics. They must subscribe to the purpose and the use of a given test, since the hazards posed by incomplete or incorrect information would otherwise be too great. Possible participants should be given broad details of the potential importance of participation, and of the repercussions. The information about the clinical picture in question should be so formulated that people can develop a clear idea of what is involved. Realistic information should be provided concerning the limitations of the test. Such information should be given in writing, accompanied by a verbal explanation.

It is essential that offers direct or stimulate people as little as possible. After having been fully informed, people should remain free either to disregard the offer or to react to it by submitting an individual request. Participation in a test should not be made to seem so self-evident that a decision not to take part has to be defended. Accordingly, the situation must be avoided where expansion of the options available leads to a restriction of individual freedom. However, this involves a precarious balancing act. If

the benefits of screening are abundantly clear and are generally subscribed to within the target group then, if the offer is refused, respect for autonomy compels those offering screening to ascertain whether the information provided has been clearly understood. However, in such circumstances, it should be clear that the aim is simply to provide information and not to influence, to offer options rather than attempting to produce more 'acceptable' behaviour. People's right to self-determination demands respect for individual decisions.

Besides the way in which an offer is made, the social environment can also exert influence and place the autonomy of the individual under pressure. Individual choices can result in a collective mechanism which, in turn, can lead to social pressure. Those offering counselling must bear this in mind and be alert to it. The responsibility for resisting this pressure rests also with the government. The government must ensure that the population at large has sufficient knowledge about heredity. Realistic information must be used to moderate the far-fetched expectations that people often have regarding genetic screening, both in the positive and negative senses. Thus the situation must be avoided whereby society becomes unable to deal with diseases and disorders. Furthermore, in order to reduce the danger of stigmatisation and discrimination as much as possible, it is best that 'primary' information about heredity and genetic screening be made available as widely as possible rather than limiting it to a specific target group. It should be made clear to everybody that all of us carry various mutations within our genes. In this connection, reference could be made to information presented as part of the basic secondary school curriculum, in the media, via written material in the form of folders, etc. The Health Council made a recommendation to this effect in the 1989 report (GR89). In this respect, the government must also continually emphasise the value of the autonomy of the individual. For these reasons it is important to reject genetic screening programmes imposed by the government or those whose primary aim is to benefit society. Programmes with such objectives have been all too often abused in the past (Gar94).

Finally, the committee concludes that respect for autonomy means that screening children for untreatable disorders which only become manifest in later life must be rejected.

6.3.2 *Prenatal screening*

With prenatal screening, the unborn child's right not to know can be frustrated if parents decide to continue the pregnancy in a situation involving a severe, untreatable disorder which only manifests itself in later life. Where an offer is made of screening for such disorders in the prenatal phase, the obligation to the unborn child (whose

autonomy can be impaired but whose views cannot be heard) must be a major consideration.

6.3.3 *Screening in later life*

The aim of screening in later life is to offer the person being tested more options with regard to courses of action. The hereditary nature of disorders means that any information obtained will also be of interest to other members of the family. This may lead to a stressful situation in which the person being tested wishes to be informed of the result, while one of his relatives does not wish to know. This can occur, for example, if a person wishes to know whether or not he is at risk of a hereditary form of cancer. Other members of the family may not wish to learn of this via screening.

6.4 **Justice and equality of access to care**

6.4.1 *Genetic screening in general*

Where a treatable disorder can be detected at an early stage by genetic screening and where such screening is not especially burdensome an offer can be justified (rather than waiting for a request) on the basis of equality of access to health care. This avoids the situation in which the test is only available to those who are aware of its existence. Consideration should also be given to the question of whether the offer will lead to the optimal use of health service resources.

The principle of equal access means that similar cases must receive similar treatment. It does not mean, however, that anyone can claim rights on all services. It is sometimes quite justifiable to restrict an offer to that part of the population which has a demonstrably heightened risk. A restriction applies, by definition, to a pilot population screening programme. In such a case, however, equity demands that the criteria for admission are set out clearly and that no-one is excluded unfairly.

When the offer of screening is directed at part of the population, a situation must be avoided in which screening leads to discrimination. One prerequisite is that there should be a sufficient basis for the screening within the population group concerned. Furthermore, the significance of such screening should be correctly interpreted within the general population. It is therefore imperative that people be aware that genetic abnormalities occur at different frequencies in different population groups.

When a screening test produces a result which indicates that the trait in question is present, this can have a negative influence on a person's ability to function within society. This particularly applies to employment and private insurance cover. The organisers of screening programmes are expected to identify possible problems in

advance, make an inventory of them and inform those involved about them. Society will have to see to it that the results of genetic testing do not form an unjust impediment for access to employment, to the customary insurance cover or anything else. Too great a degree of uncertainty on this point may constitute grounds for not carrying out the screening programme.

6.4.2 *Prenatal screening*

The principle of justice is also involved in the ongoing discussion within the Netherlands regarding which target group can most appropriately be screened for Down's syndrome (DS) and other chromosomal abnormalities. Such screening is routinely offered to pregnant women aged 36 and above, given the heightened risk of such disorders in older women. Diagnostic testing is by means of amniocentesis or a chorionic villus biopsy. In the absence of screening, about 30% of all children with Down's syndrome are born to women in this age group. However, diagnostic testing can also be carried out in pregnant women who (according to the result of pre-screening using the triple test) have a risk of the same order of magnitude as women aged 36. By this means, the diagnosis can be determined in approximately 60% of the affected pregnancies and an indication is also given of a possible open neural tube defect. It then emerges that there can be a conflict of ethical principles. Besides the principle of justice, there is also the principle of doing no harm. Five percent of the women taking the triple test will be confronted with a test result which indicates a heightened chance of a foetus with DS. However, with only 1 out of 70 such women will follow-up testing confirm that the foetus is indeed so affected. Since participants find it difficult to interpret the results of risk-evaluation tests, the screening will give rise to unfounded anxiety in a number of cases. In addition, where insufficient information has been provided in advance, a number of women will be (wrongly) reassured by the pre-screening. Even if all pregnant women take part in the screening, 40% of children with DS will not be detected.

6.4.3 *Screening in later life*

As a result of genetic research, the number of disorders in which hereditary factors are known to be involved will tend to increase. While the scope of future screening techniques is still unknown, the interest being displayed by industry makes it likely that this will involve a substantial number of tests. There will be an ever increasing number of tests for disorders which manifest themselves in later life, and which are partially or entirely hereditary in nature. The use of such tests leads to queries about the financing of provision (Cla94), an evaluation of merit, options for choice in reproduction,

reassuring people about their future, and opportunities for therapy or intervention. Studies have been carried out in association with screening for Huntington's disease (not in the context of any such screening programme), which is a dominant, hereditary disease. These studies have revealed the necessity for psychological support in the case of far-reaching predictions about the future.

6.5 Solidarity

The committee also wishes to explore various conditions that must be satisfied within society before responsible genetic screening can be offered. In order to make individual choices possible, society must display solidarity with those who are confronted with such choices. The right to self-determination requires solidarity, and vice versa. Where such critical issues are concerned, personal choices must be respected by society.

Solidarity requires that the population be adequately informed with regard to heredity. By this means a situation will be achieved in which people are aware that, since everyone carries mutations within their genetic material, everyone carries hereditary risk factors. General information available to all should emphasise the point that most congenital disorders cannot be predicted. Many arise by chance errors during formation of the sex cells, by unforeseen combinations of hereditary traits and by disturbances during pregnancy or at birth. The committee wishes to emphasise that screening cannot possibly result in the eradication of all hereditary abnormalities, nor indeed can this be the objective of such programmes.

In this context, it is important to note that, within our society, solidarity with children and adults with a disorder must be constantly stimulated. The committee is extremely disturbed by signs that such solidarity is already coming under mounting pressure. The welfare of people with a handicap is highly dependent on the opportunities for development which society offers them. In addition, the choices which parents make with regard to their offspring can be directed by the opportunities offered by society to cope with handicaps.

Opportunities for the support, counselling and integration of people with a handicap are critical in this respect. People with a disorder represent a minority group in our society. This means that they are dependent on political decisions, a preferential policy, etc. It is one of the responsibilities of government to safeguard the requisite activities. Only if these are guaranteed will the parents of an unborn child with a severe handicap have a real choice between terminating or continuing the pregnancy.

6.6 Concluding remarks

Ethical reflection on the options with regard to genetic screening leads to the conclusion that great care is required in deciding whether to offer these screening programmes. While these programmes offer benefits such as an increase in the number of courses of action available, they almost always have their drawbacks. It is imperative that well planned test studies and independent assessment be carried out before such programmes are offered, in order to discover whether the benefits clearly outweigh the drawbacks. From the ethical point of view, genetic screening programmes must also satisfy various preconditions.

Legal aspects

7.1

Introduction

In this chapter, the committee will consider the position of genetic screening with regard to the law. In law, as in ethics, there are a number of general principles which have a bearing on genetic screening. These include principles of justice and civil rights. In addition, genetic screening is part of the health service, an area in which there are many legal standards which are also applicable to medical practice in the context of screening. Finally, specific legislation has been produced with regard to population screening. From the legal point of view, there is much that could be said about general principles, precepts and standards, since these often have a distinct meaning in law (Gev89). Since this aspect was dealt with comprehensively in a previous report, however, the committee will now address itself mainly to those parts of the law which are incorporated in legislation.

With regard to general principles, there are the tenets of self-determination, of equality and of social and individual civil rights. The latter are set out in international treaties and in the Dutch Constitution. Accordingly, the right to health care enshrined in article 22 of the Constitution is interpreted as follows: ‘the government will take steps to promote public health’. Besides the provision of equality of access to care, this obviously also means that it is the government’s duty to strive for prevention, by initiating or promoting certain forms of screening for example (Com92; Com94).

Social civil rights create obligations for the government while individual civil rights are aimed at protection of an individual’s liberty from encroachment by the

government or by society. The principle of self-determination can be found in articles 10 and 11 of the Constitution. These formulate the right to protection of an individual's personal privacy and of their physical integrity. Beyond their individual significance, principles of justice and civil rights also stimulate the development of specific, concrete rules of law via legislation and jurisdiction. Some examples of this type of legislation are the Data Protection Act (WPR), the Medical Treatment Agreements Act (WGBO) and the Population Screening Act (WBO). The latter is particularly important in the context of this report.

The general legal framework governing medical practice, as it applies to the health service as a whole, is also of importance to genetic screening. Some examples are the rules governing planning and financing of health service facilities, government supervision, (planned) quality legislation, legislation relating to the authorisation and capability of those performing medical procedures and to the civil and disciplinary liability of health workers. Examples of such legislation include the Hospital Provisions Act (WZV), the Individual Health Care Professions Act (BIG), the bill for the Quality Act concerning Health Care Institutions and the above-mentioned WGBO. This general legal framework will not be discussed further here.

A third area of the law which is implicated with genetic screening is that of (access to) employment and insurance. The committee has decided to deal with this issue (including the legal aspects) in the chapter on social aspects.

Taking account of legal principles and fundamental rights, the general legal framework governing medical practice and the more specific regulations, particular attention is warranted from the legal viewpoint for three aspects of genetic screening: the assessment of screening programmes, the legal position of those invited to take part and the combination of screening and scientific research. The committee will now explore these three points further.

7.2 Examining planned screening programmes

7.2.1 *Scope of the law*

The Population Screening Act (WBO) requires that central government approve certain screening programmes before they are implemented. The minister provides the licence, having first obtained the views of the Health Council. What the legislator had in mind here was population screening which carries a potential psychological or physical risk. Population screening which requires a licence can be subject to rules drawn up by an order in council. The law makes no specific demands of population screening which does not require a licence. Such studies are, however, subject to general legal standards and general rules governing medical practice.

As to whether genetic screening is subject to statutory licence requirement, it is necessary to consider the sphere of action of the WBO. Two important questions here are: does genetic screening constitute population screening as defined in the WBO? and, if so: under what circumstances is a licence required? Testing which does not constitute population screening as defined in the WBO will not require a licence.

The law uses a broad definition of population screening, to wit ‘a medical examination which is carried out in response to an offer made to the entire population or to a section thereof and which is designed to detect diseases of a certain kind or certain risk indicators either wholly or partly for the benefit of the persons to be examined’. The key concept here is the term ‘offer’. By way of clarification, the government has indicated that this is an allusion to testing carried out at the initiative of a physician or medical institution amongst persons who, in principle, display no physical signs. The examples quoted were neonatal screening (phenylketonuria and congenital hypothyroidism) and prenatal screening e.g. for neural tube defects and Down’s syndrome. According to this explanation, testing based on indications is not included in the definition. The government cited the example of the individual genetic testing and counselling given by clinical genetics centres.

The committee defines genetic screening (see 1.2) as: ‘any kind of test performed for the systematic early detection or exclusion of a hereditary disease or a predisposition to such a disease, or in order to determine whether a person carries a predisposition which may produce a hereditary disease in offspring’. The committee considers such testing to be ‘systematic’ when all eligible members of the target group are actually invited or are informed of the opportunity. The committee considers ‘early detection’ to mean testing of people who have not (yet) had any reason (due to physical signs, symptoms or anxiety) to seek medical assistance.

The committee considers the definition of population screening contained in the Act to be rather loose because the key term ‘offer’ is too inexact. Nor does the clarification provided by the government eliminate all areas of doubt. It is nevertheless, the conclusion of the committee that genetic screening, as defined in this report, falls within the sphere of action of the WBO. This is clearly in line with the intentions of the legislator. However, there remains the question of whether the usual family testing carried out in clinical genetics centres (which the committee considers to fall within its remit) is also covered by the WBO. The genetic testing of relatives (family testing) is either carried out because it is required for the (requested) diagnosis for the person requesting advice, or for other family members who, in turn, may also have an interest in genetic testing as a result of the diagnosis. In principle, when a physician initiates family testing for people who display no physical signs, this falls within the scope of the WBO (given the systematics of that legislation). Nevertheless, the legislator did not intend family testing (as presently carried out at clinical genetics centres) to be subject

to the WBO. While it is conceivable that there are widely divergent views on this topic, the committee nevertheless concurs with the legislator in this regard. The question is what weight should be allotted to the form of organisation, the background to the offer, the size of the family to be tested, the extent of the expected risk and the degree to which the family members to be approached are familiar with this. There will inevitably be a grey area, one in which the family testing in question must be evaluated to establish whether this also constitutes population screening as defined by the WBO.

According to the WBO, a licence is required for population screening in which use is made of ionising radiation; population screening for cancer and population screening for serious diseases or abnormalities which can neither be treated nor prevented. The genetic screening which is the subject of this report will require a licence if such screening is aimed at detecting either a hereditary form of cancer or severe diseases or abnormalities which can neither be treated nor prevented. The legislator's view is that termination of pregnancy constitutes neither treatment nor prevention. From this formulation the committee infers that prenatal screening for Down's syndrome (regardless of the method used) will therefore require a licence. However, it is the government's wish that prenatal screening of pregnant women aged 36 and above be excluded from the WBO. The position with regard to the triple test is not entirely clear. In the light of the WBO, the committee feels that the government's view regarding the 'classical' screening of pregnant women of 36 or over is not entirely consistent. This is the price paid for the somewhat inexact definition of 'offer'. If this definition is given a narrow interpretation, then the government's standpoint becomes comprehensible (KEMO92). However, the committee has a broader interpretation, one in which such screening is indeed covered by the law. Given this view (and bearing in mind the nature of the screening and the aim of the legislation) it is the opinion of the committee that not only the risk-evaluating triple test but also the usual screening of pregnant women aged 36 or over are covered by the WBO. Whereas treatment is impossible (in the view of the legislator) there would be a statutory licence requirement. However, the committee mentions here that it considers the termination of a pregnancy also an appropriate course of action, under the circumstances.

Furthermore, the minister can make population screening subject to a statutory licence requirement (if the interests of public health promote the immediate creation of such a provision) due to the nature of the test method to be used or that of the disease or risk indicator to be detected. This option (an urgent decision made in the light of a changed understanding regarding aspects of the testing) will be excluded from consideration in this report.

7.2.2 *Conditions to the granting of licences*

Under what circumstances would a licence be refused? If the screening in question is scientifically unsound, if it conflicts with the statutory regulations governing medical practice or if it involves risks for the subjects which outweigh the likely benefits. Standards have been made more rigorous with regard to population screening for severe diseases or abnormalities for which no treatment or prevention is possible. A licence will only be granted if this is warranted by exceptional circumstances (article 7, section 3). The legislator's aim in toughening-up standards was to incorporate an additional consideration. The condition amounts to 'No, unless...' and is virtually tantamount to complete prohibition. However, the government recognises that the potential benefits of population screening are not limited to prevention and treatment alone. It is the government's view that, even where no treatment is possible, early detection can sometimes offer considerable psychosocial benefits. The committee concurs with the legislator that genetic screening for untreatable disorders should be handled with great restraint, all the more so when such disorders only manifest themselves in later life. However, a problem arises if the screening is aimed at decisions about possible offspring, as with prenatal testing and testing prior to conception for recessive hereditary disorders. These types of screening are predominantly aimed at severe, untreatable disorders. The committee considers that a prohibition on such forms of screening right at the outset (article 7, section 3 can be interpreted to this effect) is indefensible, given the aim of the WBO (the protection of those involved in population screening). The committee therefore advocates that the law be applied to screening in such a way as to leave room for manoeuvre (but only after assessing it against article 7, section 1).

Having first obtained the views of the Health Council, those responsible for awarding the licence will assess genetic screening programmes into hereditary forms of cancer against the three main criteria: scientific soundness, conformity with the statutory regulations governing medical practice and a favourable balance between benefit and risk.

The obligation to obtain a licence will not apply to all genetic screening programmes. One such example is the screening of newborns for phenylketonuria. In addition, with some genetic screening programmes, it will not be yet possible to determine whether the obligation to obtain a licence is applicable. An example of this is family testing for hypercholesterolaemia. In order to avoid the repercussions of this severe disease, if the test result is adverse then advice is given about eating habits and lifestyle which can be beneficial to health and (sometimes) about medication. Does this mean that prevention or treatment are possible, as defined by the WBO? The law is

somewhat nebulous on this point also. If the obligation to obtain a licence does not apply to a given population screening programme, the WBO loses its significance and the problem gains an extra dimension. This has caused the committee to conclude that additional conditions must apply to those population screening programmes which are not covered by the WBO. It is the committee's view that the implications of population screening in general (and of genetic screening in particular) require the incorporation of a period of appraisal before the decision is taken to proceed with implementation. The committee recommends that planned genetic screening programmes be subject to routine (independent) assessment. The criteria which the committee has formulated in this report could be used in the course of such assessments. The question is to what extent should such assessments be formalised. In the first instance it is certainly the responsibility of the profession to evaluate new methods and to gather the requisite data. While it takes the view that a legal obligation is not required, the committee believes that it is essential to safeguard professionalism and independence. The committee considers that, aside from sufficient alertness on the part of the financiers, there should also be an evaluation by a national committee.

By order in council, further conditions and rules can be imposed on any population screening which is subject to licensing requirements. This would allow the protection (against the risks involved in the screening) for persons to be tested to be further regulated. Rules are imposed by order in council with regard to screening which also constitutes scientific research in the field of medicine. These rules govern the way in which consent is given and in which those involved are informed about the aim of the screening, its nature, its repercussions and the protection of the personal privacy of the persons to be tested. The committee explores the latter condition further in section 7.4.

7.3 The legal position of (candidate) participants

A number of legal standards relating to the position of participants in a population screening programme (including genetic screening) derive from civil rights in the area of protection of personal privacy and physical integrity, (proposed) legislation and jurisprudence. In this connection, one particularly important rule is that the presumptions which are common in curative medicine (such as consent for minor procedures) cannot be used in population screening programmes. This does not relate to weighting factors against which planned screening must be assessed, but rather to standards that generate preconditions which must always be met by any screening programme which is implemented. However, the committee feels that before a decision is made on whether or not to initiate a given programme, there should be clarity about the way in which the preconditions are to be met. The screening protocol can provide a decisive answer to this question.

In its report entitled 'Heredity: science and society' (GR89), the Health Council comprehensively examined the position of those undergoing genetic testing, also if this occurs within the framework of genetic screening. The committee endorses the recommendations and conclusions of that earlier report. For the purposes of clarity, the major points of that report will be reviewed here - with the accent on genetic screening.

Obtaining the informed consent of participants is of crucial importance. Participation in screening should be completely voluntary, which implies that neither direct nor indirect compulsion should be applied. The information provided in advance is essential for genuine informed consent. It is the committee's view that candidate participants should be informed as completely as possible about matters which are vital to their personal interests. Besides the purely medical considerations (the aim of screening, its nature, its risks and its repercussions), the committee also has the social aspects in mind. These include possible problems with access to employment and insurance, as well as stigmatisation by social environment.

While participants have the right to be informed of the results of screening, they are also entitled not to be notified of (some or all of) these. Knowledge of future disorders, in particular, can be most intimidating. It can have an effect on entering relationships, obtaining employment or obtaining approval for insurance cover. A person's right to protection of their personal privacy means that they are not obliged to receive information in general. Health workers will have to respect the wishes of participants. The right not to know is set out in the WGBO as follows: 'If a patient has indicated a desire not to be informed, then no information will be provided, except where the patient's interests in this regard are outweighed by the harm to the patient or to others which could follow from this'. In all probability, where people voluntarily agree to take part in genetic screening, the desire not to receive certain information after the screening has been concluded will only relate to chance findings or unexpected results. It is therefore necessary to notify all participants in advance of the possibility of chance findings and to ask them if they wish to be informed about this. After due consideration (as indicated in the Act), however, the health worker can decide to pass on certain information despite it.

Information collected within the context of screening is covered by professional secrecy and, where systematically accessible registration is involved (which will quickly be the case), by the WPR. No assumptions may be made regarding the use of data for purposes other than the population screening in question. The granting of such consent may not be assumed. The professional secrecy involved in family testing can lead to complex issues. On this point, the committee would make reference to an earlier report by the Health Council (GR89). Caution is also required when dealing with body tissue obtained for the purposes of genetic screening. The above-mentioned report (GR89), which includes guarantees relating to the storage and use of cellular material,

also describes the position of the ‘donors’. In addition, the committee would also make reference to the report entitled ‘Proper use of Human Tissue’ (GR94a). This report incorporates a proposal for standardising the use of body tissue for purposes other than the original purpose for which it was obtained. The committee endorses both reports on this point.

The position of legal competence deserves special attention. Young juveniles and those who have reached their majority but who are still not legally competent cannot take an independent decision to participate. Nor can young children exercise their right not to know. The question is, to what extent can legal representatives act as proxies with regard to granting consent? If the screening programme is being carried out purely in the interests of participants who are not legally competent then the granting of such consent by a proxy can be justified. Consideration should be given to the question of whether screening involving children can be postponed until they are of an age at which they can (in part) agree to participate. Within the WGBO, the limit is set at 12 years of age (reaching a decision with the help of the parents) or 16 years of age (making an independent decision). Genetic screening can also be carried out when it is only *partly* in the interests of the persons being tested. An example would be a pilot study or where a programme also constitutes scientific research. It is the committee’s view that, in such situations, prior consideration should be given to the extent to which participation by legally incompetent individuals is either useful or necessary. If this is the case, then agreement by proxy is generally acceptable. The committee will now proceed with a further exploration of those issues surrounding the convergence of screening and scientific research.

7.4 Combination of genetic screening and scientific research

A screening programme can take the form of human-centred scientific research. This is the case, for example, if participants are examined during screening (partly) with a view to furthering scientific knowledge, if additional studies or diagnostic tests are carried out, or if participants are subjected to certain extra examinations, procedures or rules governing behaviour. The aim of such interventions may be to assess the method(s) to be used, such as diagnostic procedure or information folder, whether on a small scale or a larger scale. In such a case, screening can also be considered as a medical experiment - which has certain legal repercussions. Another situation involving convergence occurs if information or body tissues gathered for the purposes of screening are also used for scientific purposes. The committee will explore both situations more fully.

Again, where a screening programme is also a medical experiment, two different situations can be distinguished. First, there is screening for which no licence is required

under the terms of the WBO. Once it has come into force, the Medical Experiments Bill (WME) will apply to such programmes. This bill, which is currently passing through the Dutch parliament, sets out conditions to be met by experiments. It also includes the condition that any such experiments can only proceed after first receiving a positive advice from a recognised medical ethics committee.

In theory, any population screening programme which is subject to licensing requirements and which is also a medical experiment has to be assessed twice: once when the licence is granted and again when the experiment is being assessed. In order to avoid such duplication of assessment, the WBO states that assessment on the basis of the WME can be omitted. The WBO states that granting of a licence can be refused 'if such screening does not serve the interests of public health'. This means that the importance of the scientific part is a point for evaluation, one which must be amply substantiated in the course of the licence application. In addition, rules will have to be established in an order in council regarding the way in which such a combined screening programme can be given the go-ahead and the way in which those involved are informed (and what information they are given) prior to the granting of consent. The order in council referred to here is in preparation. It will contain conditions with regard to information and consent which correspond to those of the WME bill. The committee feels that, as far as information and consent are concerned, great consideration should be devoted to the scientific objective. It should be made clear to the participants that the screening programme serves an additional purpose, they should also be informed about the personal repercussions which this will have for them. The participants will also have to be informed in advance if the nature and the duration of the scientific part differ from that of the screening part. The voluntary requirement for participation is equally applicable to the experiment. The same viewpoint was expressed in a recent report of a Health Council committee (GR94b).

The use of information or cellular material obtained through screening for other purposes was briefly mentioned in the previous section. The committee is aware that 'further' use of such material can be very useful. The committee would like to state, once again, that those who are in possession of such material (the research workers) cannot assume that consent has been granted for this. Participants' consent was only given in relation to screening. Their trust (that the use of information and cellular material will be restricted to screening) may not be breached. The committee considers automatic linkage (consent for screening not possible without consent for further use) to be inadmissible. Pursuant to the report entitled 'Proper use of Human Tissue' (GR94a) the committee urges that participants be consulted in good time regarding the possible further use of their material for scientific research. If the data used cannot be traced back to their source then further use after screening is permissible. Further use of cellular material which cannot be traced back to its source is permissible if those

involved have no objection to this (after being given general information). Consent is required for the use of information or human tissues which can be traced back to the source. The possibility of new findings being made at a later date requires that timely arrangements be made regarding the future provision of information on developments of this kind.

Other social aspects

8.1 Introduction

In this chapter, the committee discusses several other aspects which have to be considered when evaluating the repercussions of a programme for genetic screening. The committee would like to take this opportunity to emphasise, once again, that the primary check of the acceptability of a genetic screening programme is whether that programme contributes to the individual welfare of the participants and whether it enables them to make a well-informed, free choice regarding courses of action.

8.2 Population genetics

Population genetics is devoted to the study of the way in which mutations in genetic material become distributed within the population or parts of it (including different races and geographically isolated populations) and the possible causes and repercussions of this. Accordingly, population genetics is not primarily concerned with the burden of illness in the population but with the frequency of gene mutations in the descendants. Since genetic screening programmes have a potential influence here, it is useful to create a predictive scenario of the consequences which implementation of the programme could have on the frequency of gene mutations in future generations.

The simplest case is that of prenatal screening for a disorder based on new mutations and in which the patients involved will have no descendants. Trisomy 21, the most common form of Down's syndrome, meets virtually all of these criteria. In most

cases a new mutation is involved. The disorder will not occur (prenatally) more or less frequently in future generations as a result of screening. Mutations continue to occur and selective termination of pregnancy has no effect on the frequency within the general population. The fact that patients with this disorder do not usually have children is partly because this is discouraged by their social environment on the basis of society's views.

The issues are more complex in the case of a disorder such as cystic fibrosis (CF). New mutations are almost never involved in this case. The mutations involved arose long ago and are passed down from parent to child. Until recently, reproduction was virtually out of the question for patients with cystic fibrosis since most of them died before reaching the age of sexual maturity. While this has changed in recent years, participation in reproduction by such patients will produce only a small relative increase in the gene frequency. This increase is so small because, relative to the number of carriers, patients form only a tiny minority (in the Netherlands, carriers outnumber patients by 120 to 1). Screening for carrier status would eliminate this tiny effect if it resulted in reduced numbers of CF patients being born. In evaluating the repercussions of whether or not to screen, a complicating factor is that it is not understood why CF has such a relatively high carrier frequency. It has been speculated that the reason behind this high frequency is that carriers of mutations in the CF gene have greater resistance to certain diseases. If so, then this gives rise to a number of questions: Does the selective advantage enjoyed by carriers still apply today? Disregarding reproduction by CF patients, is the gene frequency increasing, decreasing or stable? Which of these situations is the most desirable: an increase in the gene frequency thereby giving more people resistance to some diseases although more people will be born with CF, or a reduction in the gene frequency so that fewer patients with CF will be born although there will be fewer people with improved resistance? Given the current level of knowledge, it is not possible to answer this question.

Assuming that CF screening results in a drastic reduction in the numbers of CF patients, then (in terms of the offspring of CF patients) there would be a return to the situation in which CF patients failed to reach sexual maturity. Differences could arise relative to the earlier situation if parents who are both carriers of a mutation in the CF gene terminate a pregnancy (as a result of prenatal diagnosis) and then go on to initiate a new pregnancy. Two thirds of their children without manifested CF are carriers of the mutated gene. However, the effect of such behaviour on the total frequency of the mutation within the population would be very slight.

However, the situation could change drastically if carrier status for CF were to lead to carriers suffering social prejudice or social disadvantage, either prenatally or postnatally. Given that this would have unknown repercussions for 'human health', it is

necessary to guard against selection for (non-) carrier status also on the grounds of population genetics.

The third situation for which the committee would like to indicate the possible repercussions in terms of population genetics concerns Duchenne type muscular dystrophy. In a third of these patients the mutation involved is a new mutation. This disease has a progressive course and patients die at around the age of twenty. One reason for screening could be to establish carrier status in female relatives of the patient's mother. Here also, since the patients concerned do not participate in reproduction, whether or not screening is used, this form of screening is not expected to have any repercussions in terms of population genetics. New mutations will continue to arise. A partial decrease of the frequency of the mutation in the population could occur if, as a result of prenatal screening, a decision was made to terminate the pregnancy if the foetus was a female carrier of the mutation.

It is clear from the above that social views and the resultant behaviour can have greater repercussions in terms of population genetics than genetic screening alone. This does not change the fact that genetic screening can have a major effect on the burden of illness in the population.

8.3 Costs, effects and risks of genetic screening

It is the committee's view that programmes for genetic screening should be evaluated for acceptability by a national committee (7.2). The final part of the evaluation should take the form of a check (from the point of view of fair apportionment) to see whether it is appropriate that government resources which were meant for the health service should be made available for the programme.

An awareness of the costs attached to the programme and of any possible savings is required in order to determine what resources are required. Either way, the committee wishes to include the cost of implementing the screening itself (information, organisation, implementation and evaluation). There are also the costs incurred by follow-up activities once the results have been made known (counselling and treatment). Savings (negative costs) can also be generated by the screening programme. The committee considers the possible savings to include reduction of direct expenditure, in terms of health care costs, for the handicapped people in question (reduction of the numbers concerned or reduction of the health care costs for each such person who is identified in time), as a result of early diagnosis. Considerations of cost can - and should - only play a limited part in decisions about genetic screening. There should not even be a suspicion that economising on the costs associated with a

particular disorder is a significant consideration when assessing the acceptability of a programme.

The latter aspect could, in turn, easily lead to social pressure to take part in screening programmes and to choose the cheapest course of action. Any such pressure should be vigorously opposed. It cannot be emphasised enough that the aim of genetic screening is to enable people with predispositions for disorders (in which genetic factors are a major factor in the development of the disorder, either in those persons screened or in their descendants) to escape their fate and to make a well informed free choice on the course of action which they regard as acceptable.

If a rough indication of the costs is given, relating the costs to the effects should show whether implementation of the screening programme is appropriate from the point of view of fair apportionment of the resources which are available to the health service.

8.4 Work and insurance

In the report entitled 'Heredity: science and society', a Health Council committee comprehensively explored the issues surrounding employment and obtaining private insurance which are associated with genetic testing (GR89). This focuses on two particular situations.

Firstly it relates to whether or not genetic testing in that regard is even acceptable. The Health Council rejected genetic testing initiated by employers to determine access to employment or by insurers with regard to the granting of insurance cover. It is quite possible that this code of conduct will be adopted throughout Europe within a few years (Mar94). In line with this, insurers decided on a moratorium, however this expires in 1995.

The Council considered that monitoring tests on employees are only permissible on a voluntary basis and only then if these relate to special situations where it is necessary to protect a demonstrable health interest either of the employee involved or of others. The Council urged moderation in the use of chromosome testing and DNA testing during monitoring, in view of the deficiencies of currently available tests, the lack of adequate understanding of the repercussions which this will have for the employee and the risk that the test results will be misused. They recommended a review of the report 'Mutagenicity of chemical substances' (GR81). Neither new information nor the current state of knowledge enables anything to be added to the arguments presented in 1989, nor subtracted from them.

The other situation relates to the duty of disclosure regarding information which has emerged via genetic testing (including screening) when applying for life insurance, personal work disability insurance and pension insurance. The Council urged that this

obligation be restricted. The temporary insurers' moratorium referred to previously includes a rule that candidate policy holders need not report the results of previous genetic testing if the sum insured is less than NLG 200,000. A recent initiative bill (Koh94) can be seen as an attempt to achieve a legal resolution of this issue.

In the following pages, the committee will briefly explore some recent facts which serve to underline the need for legislation, both in the area of employment and of insurance.

The committee has found that reports produced in other countries express their approval for the temporary insurance moratorium in the Netherlands (Can92, Ins93, Nuf93). This moratorium means that the insurers forego genetic testing as a condition for granting a policy while accepting a restriction of the duty of disclosure with regard to information obtained from genetic testing in the past. However, the committee is critical of the voluntary nature of the moratorium and the fact that it is only temporary.

Medical examinations in connection with the granting of employment do not generally include a request for information relating to the candidate's genetic make-up. However there is no guarantee that this will always be the case (Lou93). Occasionally, people undergoing genetic testing ask to be informed of the results at the earliest possible opportunity as such results significantly affect their chances of obtaining a new job (Nie94). This development makes it clear that self regulation has not led to a situation in which examinees feel that their position is sufficiently secure.

The committee has taken note of the government's position paper on predictive medical testing (Sim94). Regarding medical testing for employment this indicates that the option of legislation in combination with self-regulation (conditional self-regulation) is a legitimate subject of discussion for the government. The government considers the current situation to be effective with regard to medical examinations for life insurance cover and the granting of work disability insurance cover. This view disregards the fact that a person will be unable to obtain such insurance if they have a blood relative with either Huntington's disease or myotonic muscular dystrophy. The government considers the situation to be acceptable 'in view of the high probability that these diseases will also affect such candidate policy holders and because these disorders are still considered to be incurable'. The government assumes that the moratorium will be extended in 1995.

The committee considers the standpoint regarding medical examinations for employment to be too weak. In an earlier government position paper (Hir90) it was indicated that the government would review the situation after two years, to see whether self-regulation would render legislation unnecessary. The TNO report (Lou93) makes it clear that this is still by no means the case.

Furthermore, the committee is extremely concerned by the fact that the government has acquiesced to the current situation regarding insurance. This can lead to new forms of ineligibility for insurance cover. Although this affects only a minor category of the population, the committee does not consider this to be a valid argument. It is the committee's view that individuals from families in which incurable hereditary diseases occur are experiencing an infringement of their freedom to decide whether or not to take advantage of an opportunity to test their genetic predisposition. What is at stake for them is the possibility of acquiring a social benefit. They will only be granted an insurance policy if they can demonstrate that they do not possess the hereditary trait in question. Economic realities may therefore compel such people to undergo a test for which voluntary participation is generally a precondition. In addition, the existence of the (limited) duty of disclosure gives rise to the risk that, because of the (possible) repercussions with regard to obtaining an insurance policy, people forgo participation in genetic screening programmes which might be of benefit to them. The committee wonders whether the public is sufficiently well aware of the relevant legal position. It feels that legislation is urgently required. This is all the more so in view of the fact that genetic screening may well become increasingly important in future. Accordingly, this novel form of ineligibility for insurance cover can expand to cover even more (usually) rare clinical pictures. The committee therefore considers it important that some urgency be imparted to the process of dealing with the bill regarding medical examinations, which incorporates major elements of previous recommendations by the Health Council.

Assessment criteria

9.1

Introduction

As is evident from the preceding text, the committee feels that the benefits and drawbacks of carrying out screening (in whatever form) must be prudently evaluated. It is primarily the responsibility of those offering screening to make such an evaluation prior to the introduction of the programme. Where the screening in question is population screening which is subject to licensing requirements in accordance with the Population Screening Act (WBO), that legislation provides for assessment by an independent institution before a screening programme can be offered. However, the committee considers such assessment to be necessary even where genetic screening is not subject to licensing requirements under the WBO. The committee makes an exception in the case of family testing in the strict sense, as indicated in chapter 7 of this report. This specific form of small-scale family testing, which is entirely restricted to clinical genetics centres, is little different to providing medical aid for individuals. The evaluation of acceptability is then embedded in the procedure right from the outset, as it were, while competent counselling is also available. The committee feels that the guarantees here are sufficient to render independent assessment superfluous. In case of doubt, however, prior local assessment can be carried out.

In the case of genetic screening which does not require a licence on the basis of the WBO, the committee supports assessment by a national medical ethics committee. Assessment demands expertise and independence in order to evaluate the screening programme for completeness, correctness and admissibility. If changes are made after a

screening programme has been implemented then a new evaluation is required, unless it only affects (minor) points which would not produce a different result in any subsequent evaluation. The assessing committee should then be notified of any changes and of why they are deemed necessary. In the interests of systematic assessment, the committee has set out a list of assessment criteria in this chapter. These criteria derive from the considerations included in this report.

In 1968, Wilson and Jungner formulated a set of assessment criteria for the evaluation of population screening, at the behest of the World Health Organisation (Wil68; see annex C). In its report entitled 'Heredity: science and society', the Health Council of the Netherlands formulated several conditions to be met by genetic population screening (GR89; see annex D). Furthermore, in its 1990 Annual Report on the health service (within the context of preparing an inventory of existing and potential new forms of screening), the Council included a general consideration of the requisite criteria to be used in population screening (GR90b). In 1992, the Committee of Ministers of the Council of Europe formulated some supplements to the WHO criteria. These supplements related specially to genetic testing (Com92; see annex E). Likewise, the National Advisory Council for Public Health has recently defined an ethical-legal assessment framework (NRV94; see annex F). The criteria which will now be discussed dovetail with the indicated conditions.

In the practical situation, a list of mutually independent criteria which must be met by any population screening programme is a most appealing idea. Accordingly, the above-mentioned list produced by Wilson and Jungner is frequently used in this way. However, comments are regularly made to the effect that the list is not well suited to this purpose. For example, one of these criteria states that the subject of screening must be a major health problem while another states that the test should not be excessively burdensome. However, these two criteria are clearly related. While phenylketonuria is an important health problem for an individual, its low prevalence means that it cannot be characterised as a major public health problem. Nevertheless, screening for this disease is generally accepted since the requisite test (the 'heel prick') is not especially burdensome and has other useful characteristics. If a particular target group has a high risk of a particular disease then, dependent upon the available choices, a more burdensome test may be acceptable.

Table 3 sets out the criteria which, in the committee's view, must be met by genetic screening programmes, if they are to be considered admissible. It also lists those aspects about which information must be supplied to the assessing institute.

Table 3 Criteria to be met by genetic screening programmes.

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- 1 A genetic screening programme must relate to a health problem or to a condition which can lead to such a problem in those being tested or in their descendants.
 - 2 The target group of the screening programme must be clearly defined.
 - 3 The purpose of the programme must be to enable the participants to determine the presence or the risk of a disorder or carrier status, and to take a decision on the basis of that information.
 - 4 Practical courses of action must be open to the participants.
 - 5 Participation in a genetic screening programme should be completely voluntary and should be conditional on consent based on good information.
 - 6 The target group should be supplied with good quality, comprehensible information.
 - 7 A test method should be available which is suited to the objective of the screening.
 - 8 There should be sufficient facilities for follow-up testing, to carry out the selected courses of action and to inform and support the participants.
 - 9 The procedures used for the storage of medical information and cellular material must incorporate adequate measures to protect both the personal privacy of the participants and their rights regarding their personal data and cellular material.
 - 10 If scientific research is carried out within the framework of screening, the participants should be properly informed about this in advance.
 - 11 Provision should be made for continual quality assurance of the effectiveness, efficiency and safety of the test procedure, any follow-up work, as well as information and support given to the participants.
 - 12 When weighing up the benefits and drawbacks for the participants in the programme, the final balance should be clearly biased towards to benefits. To assist with this evaluation, those proposing a screening programme must provide information about:
 - a the prevalence of the disease or disorder in the target group;
 - b the natural course of the disorder, and the variation in degrees of severity;
 - c those target groups which are eligible for testing and the considerations which led to selection of the proposed target group and the proposed time of life for testing;
 - d the specificity, sensitivity and predictive value of the test method to be used and the burden which such testing imposes on participants;
 - e the available courses of action if a health problem or carrier status are revealed;
 - f the time allowed by the procedure for consideration and possible implementation of the choice made;
 - g the potential psychological, social and other repercussions (both positive and negative) of an offer and of participation or non-participation in the screening, for the person to be tested and for members of their family or for groups within the community;
 - h the likelihood of erroneous results, the possible consequences of this for participants and the measures taken to limit any harm which such an error might cause;
 - i what guarantees there are to prevent participants experiencing unjustified impediments (as a result of their participation or non-participation in the screening programme or follow-up testing) to obtaining employment or private insurance cover;
 - j The costs which are linked to the screening and to the attainment of the requisite infrastructure.
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9.2 Explanation of the criteria and of the information to be provided

A genetic screening programme must relate to a health problem or to a condition which can lead to such a problem in those being tested or in their descendants.

Here, the committee has deliberately avoided including the limiting clause that screening should focus on a major public health problem. In its supplement to this limitation, the National Advisory Council for Public Health indicates that the importance of a disorder is determined by its severity and prevalence within the population (NRV94). Accordingly, this requires that severity and prevalence be weighed against one another, something which is carried out within the context of criterion 12. Allowing for the remaining assessment criteria, this will mean that, in practice, screening programmes will generally only deal with severe disorders.

Since screening can be used with conditions which can cause health problems, this means that it can also be extended to include testing for carrier status with regard to the relevant inherited mutations.

The target group of the screening programme must be clearly defined.

The process of weighing up the benefits and drawbacks of screening programmes is not the same for any two target groups selected at random. The identity of the target group to be screened must be known before the acceptability and desirability of the screening programme can be assessed. In addition, a clear definition of the target group is required before an evaluation can be made as to whether or not the principle of justice has been satisfied (6.4). Separate justification is required for screening programmes aimed wholly or partly at legally incompetent persons (7.3).

The purpose of the programme must be to enable the participants to determine the presence or the risk of a disorder or carrier status, and to take a decision on the basis of that information.

Genetic screening programmes should be carried out for the benefit of the participants. The achievement of social objectives, such as cutting the costs of health care, must be no more than an incidental effect and never the primary aim (6.3.1; 8.2).

Practical courses of action must be open to the participants.

Information about a genetic screening programme should make it clear to participants that courses of action are available should the trait in question be found to be present. If they are to have any real meaning, the courses of action must be acceptable to the participants. The committee expressly asserts here that a choice is involved even when the only options are to continue a pregnancy or to terminate it. Great caution is called for if the available choices do not allow a choice of treatment and if the disorder only manifests itself in later life (7.2.2).

Every subsequent step in testing must involve freedom of choice. Risk-evaluating testing should include the option of foregoing follow-up testing (6.3.1).

Participation in a genetic screening programme should be completely voluntary and should be conditional on consent based on good information.

The acceptability of a programme of genetic screening is entirely dependent on the freedom accorded to those being tested to take part in the programme (or not) and to choose a course of action (6.3). Accordingly, the use of compulsion or pressure is absolutely forbidden (7.3). However, where there are great benefits to participation those offering screening are entitled to ascertain whether those who reject the offer have actually understood the information (6.3.1).

The target group should be supplied with good quality, comprehensible information.

The information provided forms the basis for voluntary consent. Such information should contain data about the disorder in question (severity, degree of predictability, mode of transmission, significance of carrier status); about the nature of the screening (risk evaluation or diagnostic) and the programme's design (who does the testing; who provides information; who should be approached for counselling and support); about the sensitivity, specificity and predictive value of the test results; about the implications which testing can have for other members of the family; about the risks and burdens imposed by testing; about the courses of action and the social repercussions which can accompany confirmation of a genetic predisposition. Where screening is aimed at a target group with no personal experience of the disorder in question, the information provided will have to be extremely comprehensive (5.2; 6.3.1).

Besides the way in which the programme is offered, with risk-evaluation screening it is important that both the positive and the negative side of the risk be explained. When drafting the written information, it is recommended that use be made of

contributions from patients, relatives of patients, parents' associations and patients' associations (5.2).

For those who receive a result which confirms the presence of a trait, more detailed information will generally be required.

A test method should be available which is suited to the objective of the screening.

This criterion is self-evident (see 12d also).

There should be sufficient facilities for follow-up testing, to carry out the selected courses of action and to inform and support the participants.

Information and support can be required before, during or after testing (6.2.1). The psychological burden imposed by an anomalous test result is an important measure of what is meant by 'sufficient' here. The greater the burden imposed by the result, the greater the demands made of support (5.2). If one of the options is termination of a pregnancy then it must be possible for this to be carried out within the legally determined period.

The procedures used for the storage of medical information and cellular material must incorporate adequate measures to protect both the personal privacy of the participants and their rights regarding their personal data and cellular material.

Any screening to be carried out must comply with a number of legal standards derived from civil rights in the area of protection of personal privacy and physical integrity, (proposed) legislation and jurisprudence. While participants have the right to be informed of the results of the screening they are also entitled not to be so notified. The data so obtained are subject to professional secrecy and systematically accessible registration is subject to the Data Protection Act (WPR). A retention period for data and cellular material must be established. Regarding the reuse of any body tissues which have been collected, the committee makes reference to a recent report by the Health Council (GR94a).

If scientific research is carried out within the framework of screening, the participants should be properly informed about this in advance.

If screening is subject to licensing requirements under the terms of the WBO, and if it involves scientific research, then it will be subject to the Medical Experiments Bill (WME), once this comes into force. In this regard, population screening which also constitutes scientific research is subject to requirements in the order in council which is being prepared within the framework of the WBO. Nor may it be automatically assumed that data derived from population screening can be used for scientific research (7.4).

Provision should be made for continual quality assurance of the effectiveness, efficiency and safety of the test procedure, any follow-up work, as well as information and support given to the participants.

This requirement is for caution, something which applies to any screening programme. With regard to genetic population screening, this requirement has received additional emphasis from the rapid pace of development in the relevant scientific discipline and since little is yet known of the psychological repercussions of genetic screening (5.6).

When weighing up the benefits and drawbacks for the participants in the programme, the final balance should be clearly biased towards benefits.

All genetic screening programmes must meet the above-mentioned requirements, in addition such programmes should clearly be of benefit to the participants. In order to determine whether this is in fact the case, the interrelationships of various aspects of the programme must be evaluated (6.2.1). Prior to the implementation of large-scale screening, it will usually be necessary to collect relevant data on these aspects by means of pilot screening within the Netherlands (6.5). Otherwise, it must be documented that data from abroad are also applicable to the Netherlands. Pilot screening will usually not provide information about all aspects since some of these (those which the study itself is intended to clarify) are still unclear.

For the above mentioned weighing up those proposing a screening programme must provide information about:

The prevalence of the disease or disorder in the target group.

The information to be provided must contain information about the number of potential patients whose condition would be detected early even without such a screening programme.

The natural course of the disorder, and the variation in degrees of severity.

The information about the course of the disorder should contain information about patients' average life expectancy, the nature and severity of the complications, the options regarding treatment, the chance of physical or mental handicaps and the like. In the case of prenatal screening, the likelihood of spontaneous abortion or foetal death during pregnancy (as a result of the disorder) should be indicated.

Those target groups which are eligible for testing and the considerations which led to selection of the proposed target group and the proposed time of life for testing.

The information to be provided must also contain a discussion of possible alternative screening strategies (4.1). When determining the target group and the moment of testing, the aim must be to make the screening as beneficial as possible. Care must also be taken that, in limiting the screening to a specific target group, this does not lead to unfair differences in accessibility (6.4.1). Consideration should be given to the question of whether screening involving children can be postponed until they are of an age at which they are able to decide for themselves (4.5; 7.3).

The specificity, sensitivity and predictive value of the test method to be used and the burden which such testing imposes on participants.

The burden imposed by screening and the repercussions of incorrect results (in the medical, psychological, legal and social senses) are the main factors determining the requirements which will be imposed on specificity, sensitivity and predictive value.

The available courses of action if a health problem or carrier status are revealed.

Following a test result which confirms the presence of the trait in question, the available courses of action should be both clearly defined and worthwhile to the participant concerned.

The time allowed by the procedure for consideration and possible implementation of the selected course of action.

The more drastic the courses of action and the more latitude for consideration of these options required by the test result, the more time will have to be allowed.

The potential psychological, social and other repercussions (both positive and negative) of an offer and of participation or non-participation in the screening for the person to be tested and for members of their family or for groups within the community.

The greater the chance of adverse repercussions, the greater the requirements imposed on the characteristics of the test, the target group to be selected and the time allowed by the procedure to consider participation in the screening programme and to decide on a course of action.

The likelihood of erroneous results, the possible consequences of this for participants and the measures taken to limit any harm which such an error might cause.

In as much as no method can totally exclude the possibility of obtaining erroneous results, it should be clear what steps have been taken to limit any harm which such an error might cause (6.2.1).

What guarantees there are to prevent participants experiencing unjustified impediments (as a result of their participation or non-participation in the screening programme or follow-up testing) to obtaining employment or private insurance cover.

The committee has addressed the matter of such essential safeguards in section 8.4. Those offering a screening programme are expected to inform those participating in the programme about any possible restrictive consequences and to do everything possible to avoid the creation of unfair obstacles. If there is insufficient certainty on this point, this can be a reason for not implementing the programme (6.4.1).

The costs which are linked to the screening and to the attainment of the requisite infrastructure.

The consideration of the benefits and drawbacks with regard to the above-mentioned data must reveal a clear benefit for the participants. If this condition is fulfilled, a check must be made to see whether use of the resources required for the programme can be justified within the total area of the health service. In section 8.3, the committee examines the way in which such information can be presented.

The Hague, 19 December 1994,
for the committee
(signed)
Dr NAJ Mul
Secretary

Prof PJ van der Maas
Chairman

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A	Request for a report
B	Members of the committee
C	Wilson and Jungner's criteria
D	The criteria of the Council of Europe
E	Criteria from the report 'Heredity: science and society'
F	The criteria of the National Advisory Council for Public Health
G	Brief descriptions of clinical pictures
	Congenital anatomical abnormalities Congenital hypothyroidism
	Down's syndrome Duchenne and Becker muscular dystrophy
	Hereditary forms of breast cancer Familial hypercholesterolaemia
	Phenylketonuria Fragile X syndrome
	Infantile spinal muscular atrophy (Werdnig-Hoffmann's disease)
	MCAD (a disease involving fatty acid metabolism)
	Cancer of the colon Myotonic dystrophy
	Neural tube defects Cystic fibrosis
	Thalassaemia Alzheimer's disease
	Huntington's disease Tay-Sachs disease
H	Concepts and abbreviations

Annexes

Request for a report

In a letter dated 5 November 1991 (No. PEP/GZ 912195), the presiding State Secretary for Welfare, Health and Cultural Affairs requested that a report be prepared with regard to ‘Signalling provided by screening’. The request for a report was phrased as follows:

The strides being made by medical technology, particularly in the area of recombinant DNA techniques, have made it possible to demonstrate carrier status for ever more hereditary disorders, to detect an increasing number of disorders in an early, pre-symptomatic stage and to establish risk indicators for diseases.

In the report entitled ‘Heredity: science and society’, which you presented on 29 December 1989, you indicated that developments relating to screening for Duchenne muscular dystrophy, some haemoglobinopathies and cystic fibrosis should be closely monitored. In particular, it was recommended that the potential of tests for carrier status using DNA techniques should be further explored at population level.

The position paper relating to your report (published by the Minister of Justice and myself on 30 November 1990), indicates that I suggested that your Council be requested to pass on news of novel developments in these areas. I am pleased to be able to follow up this resolution by requesting you to inform me about the level of technical development with regard to screening for hereditary disorders. Rather than restrict yourself to this topic alone, you are to include the areas of screening methods and risk indicators for non-hereditary disorders in your observations.

I am aware that screening comes under the definition of population screening as formulated in article 1 of the Population Screening Act. If the nature of the screening method or that of the disease or risk indicator to be detected so dictates, the population screening programme concerned can be designated as

being subject to licensing requirements (article 2). Since the bill is in its final stages in the Lower House of the States-General, I would appreciate it if an initial copy of your report could be in my hands in mid-1992 (in connection with the timely preparation of the items of subordinate legislation).

The State Secretary for Welfare, Health and Cultural Affairs

(signed)

Hans J Simons

Members of the Committee

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- PJ van der Maas, *chairman*
professor of public health; Erasmus University Rotterdam
 - JMA van den Boer-van den Berg;
medical ethicist; University of Leiden and University Hospital Dijkzigt Rotterdam
 - GCML Christaens
gynaecologist; University Hospital Utrecht
 - G Evers-Kiebooms
professor of psychology; University of Leuven (Belgium)
 - JKM Gevers
professor of health law; Academic Medical Centre Amsterdam
 - JDF Habbema
professor of mathematical decision sciences; Erasmus University Rotterdam
 - LP ten Kate
professor of clinical genetics; Free University Amsterdam
 - NJ Leschot
professor of clinical genetics; Academic Medical Centre Amsterdam
 - MF Niermeijer
professor of clinical genetics; Erasmus University and University Hospital Dijkzigt Rotterdam
 - GJB van Ommen
professor of medical genetics; University of Leiden
-

- B Verschuren
attorney at law; Amsterdam
- M de Visser
professor of neurology; Academic Medical Centre Amsterdam
- ETM Olsthoorn-Heim M.Law, *adviser*
health lawyer; Health Council of the Netherlands, The Hague
- NAJ Mul, *secretary*
immunologist; Health Council of the Netherlands, The Hague

Editorial support: AB Leussink

Secretarial assistance: MI Roskam

Wilson and Jungner's criteria

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- 1 The condition sought should be an important health problem
 - 2 There should be an accepted treatment for patients with recognised disease
 - 3 Facilities for diagnosis and treatment should be available
 - 4 There should be a recognisable latent or early symptomatic stage
 - 5 There should be a suitable test or examination
 - 6 The test should be acceptable to the population
 - 7 The natural history of the condition, including development from latent to declared disease, should be adequately understood
 - 8 There should be an agreed policy on whom to treat as patients
 - 9 The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
 - 10 Case-finding should be a continuing process and not at 'once and for all' project.
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The criteria of the Council of Europe

Criteria from the report 'Heredity: science and society'

Screening is taken to mean a study which is offered at the initiative of an institution. Such a study can be of great value to those involved when it enables a disease to be treated in time or even prevented. However such studies also have their drawbacks. The members of the target group are, in principle, all healthy people. They display no physical signs and will usually have no immediate reason to suppose that they have a disorder. Screening studies can make people unnecessarily anxious or, if an abnormality is found, they can give rise to feelings of inferiority. Such studies can also give rise to a false sense of security.

For this reason, all screening programmes must meet the requirement that their benefits outweigh their possible drawbacks. A pilot study, in which possible problems are mapped out, can be most valuable in finding out whether a given programme meets this requirement. The committee feels that all screening programmes should incorporate an evaluation study. Furthermore, in accord with a previous Health Council report (GR80), they find that a screening programme should meet the following conditions:

- 1 The natural course of the disorder in question should be well known. The group of people to be tested should also be fully informed of this.
- 2 Prevention or treatment of the disorder should be possible. Accordingly, the screening of newborns or of young adults can only be justified where prevention or of treatment (in those where an abnormality is detected) can be expected to produce substantial results.
- 3 The test used should be reliable and should have a satisfactory predictive value. Those being tested should be aware that the screening test is sometimes not diagnostically specific, so that supplementary diagnostic study may sometimes be required. The test should clearly distinguish between sufferers, potential sufferers and carriers (i.e. those who have no heightened personal genetic risk of getting a disease but who do run such a risk of having a handicapped child).

The benefits of screening for those who (correctly) receive a positive result from the screening should

be proportionate to the drawbacks for those who (incorrectly) have a positive (false positive) or negative (false negative) result. These drawbacks are: tests which (in fact) prove to be unnecessary in the case of a false positive, sometimes including surgery. In the case of a false negative, no further action is taken.

- 4 Informed consent is vitally important. Those participating in the study must do so entirely voluntarily, which implies that neither direct nor indirect compulsion should be applied. Another condition is that participants should be well informed concerning the nature and significance of the study as well as about the risks attached to it. The emotional reactions of those involved when confronted with a correct or incorrect test result or the suspicion that an abnormality is present, are often underestimated. Accordingly, when setting up a screening programme it is necessary to inform potential participants about this.
- 5 During the programme, the privacy of those involved must be respected. Screening involves a very real and distinct risk that certain individuals will be stigmatised, thereby damaging their social position. Strenuous efforts should be taken to avoid such a risk, including exercising professional secrecy.
- 6 It is necessary to maintain contact with general practitioners and others who will have access to the results of screening and who must provide support and guidance to individuals being tested.

It is essential that the benefits of screening are reasonably proportional to the possible drawbacks. It is therefore desirable that a screening programme only be introduced after having been assessed against the conditions to be imposed. With regard to screening in the area of heredity, the committee considers it important that special consideration be given to any possible risks of a psychosocial nature. In view of the nature of the disorders or risk factors involved, those tested will usually experience higher than usual levels of psychosocial stress. Several screening programmes currently involve a type of supervision, for example in the form of conditions attached to the financing of such programmes.

The upcoming legislation for population screening offers excellent prospects for assessment and control.

The criteria of the National Advisory Council for Public Health

3.3 Population screening

The first ten standards are the criteria produced by Wilson and Jungner (WHO 1968). In all cases these can be considered to be conditions to the development of screening programmes. Standards 11 to 15 are conditions governing the acceptable implementation of a programme. Programmes which are found to be inadequate can usually be modified to meet these conditions.

Within this framework, the criteria developed by Wilson and Jungner are typical in that they are not restricted to purely legal-ethical principles. They also incorporate more general social principles affecting the quality of medical practice.

1

The programme for the early detection and treatment of diseases should involve an important health problem.

Explanation: Any preventative policy must focus on the most important health problems. In view of their relatively far-reaching nature, this applies even more to screening programmes than to other preventative activities. The importance of a health problem is determined both by the prevalence and severity of the disease.

2

There must be the prospect of a worthwhile outcome to early diagnosis, in the form of treatment or counselling.

3

Facilities for diagnosis and treatment must be available.

Explanation: If early diagnosis leads to no clearly beneficial outcome, then it will be harmful rather than beneficial to an individual to learn of their illness at an early stage. As a rule, this principle is formulated as the necessity of a treatment option. However, this could also mean adequate counselling and support, which is clearly more beneficial than what would happen if the disorder were not detected in time. The written description of the Population Screening Act cites the example of screening for a progressive, degenerative, untreatable disorder in a young child. Early knowledge that something is amiss could lead to the parents being offered counselling and to less exacting demands being made of the child.

4

The disease in question should have a recognisable latent or early symptomatic stage.

5

There should be an appropriate screening test.

Explanation: The appropriateness of the screening test refers to the sensitivity and specificity of the test in question. A screening programme is not considered acceptable if the screening test misses many cases of the disease or if it too often incorrectly indicates the presence of the disease. As with all medical practice, it must be effective.

6

This test will have to be acceptable to the target group.

Explanation: The test will usually take the form of a medical procedure. This can sometimes involve (slight) risks. From the standpoint of the principle of doing no harm, these risks must be virtually zero. Since, for most participants (fortunately), the programme need not necessarily produce benefits in terms of health, even small risks will be difficult to justify.

Another aspect relates to the rights of the participants on the basis of the treatment agreement. A good screening programme will include measures to ensure that there is as little intrusion as possible into the personal integrity of the participants.

7

There must be adequate knowledge of the natural course of the disorder, and of the progress from latency to disease.

8

It should be apparent (from the values of the test result) whether the individuals concerned should or should not be treated as patients.

Explanation: Both criteria are of relevance from the standpoint of effective prevention and in order to avoid unwanted side effects. If the course of the disorder is insufficiently well understood then it is virtually impossible to evaluate the efficacy of early detection. It is important that indications be clearly defined otherwise either too many or too few people will receive treatment.

9

The costs and benefits of early detection and any subsequent treatment should be weighed against the total costs and benefits to the health service.

Explanation: From the standpoint of justification, it is not acceptable that prevention programmes make such great demands on the budget that this detracts from standard health care. In view of the fact that standard health care (in contrast to prevention) is directed at people who require medical and nursing care, this must not be jeopardised by expensive or labour intensive prevention.

Screening programmes are not always completely cost effective. They can, in fact, lead to an increase in the burden placed on the health service. The costs of such prevention should not take up a disproportionately large part of the entire health service budget.

10

Early detection must be a continuous process rather than a one-off population screening programme.

Explanation: A one-off population screening programme does not usually contribute to a reduction of the incidence of a disease. In addition, it has all the initial problems inherent in the launch stage of a new programme (for example, disorders are often encountered which are at an advanced stage, when they are less easy to treat).

Thus, one-off screening is virtually ineffective and has quite significantly harmful repercussions. This cannot usually be justified on moral grounds.

11

The interval between test and result should be as short as possible, as should the interval between a positive result and follow-up diagnosis or treatment. There must be an adequate structure to offer support with the psychological problems which can arise as a result of (waiting for) the result.

Explanation: A population screening programme can be very burdensome for the participants, particularly if it involves the early detection of a severe disease. Many people will experience anxiety in the interval between test and result. Very rapid results are called for in order to reduce this burden to a minimum.

If the test produces a positive result and follow-up diagnosis is required, an energetic approach is even more important. Perhaps the result is a false positive, so there is relatively little cause for concern? Questions like this must be answered as quickly as possible.

If some participants become so anxious that they start to experience psychological problems, then adequate support is required. In any good screening programme, preparations will have been made for such an eventuality.

12

The call-up system for participation in a screening programme should not cause people to feel that their freedom to decide for themselves (on whether or not to participate) is in any way restricted.

Explanation: Respect for the autonomy of the individual dictates that participation in a population screening programme be voluntary. This in turn means that there should be minimal pressure involved when issuing invitations to potential participants. This relates, for example, to the tone of the letter, the approach used to remind people of the invitation and the person or institute who extends the invitation to the participants.

A wholly neutral message can, however, thwart the aim of reaching disadvantaged groups in particular. If that is indeed the objective, then it is permissible for the invitation to be somewhat more compelling in nature. In extreme cases, key figures in the community concerned may be called upon to assist. Such persuasion should be dominated, however, by the creation of opportunities for a free and premeditated choice with regard to participation.

13

Adequate information must be provided regarding the reasons for participating in a population screening programme, and of the burden involved.

Explanation: Candidate participants should be free to make a well considered choice with regard to participation. Since this does not involve consent for an indicated course of treatment, the provision of relevant information must sometimes go a little further than in the case of treatment. In addition to information about the study itself, about the options and the risks, other issues are also important. Relevant information includes, for example, the severity of the disease and current options regarding treatment. It should also address the matter of whether the test sometimes misses an individual with the disease or, conversely, whether it sometimes incorrectly ‘uncovered’ a case of the disease. In addition, information about the possible drawbacks involved in participation is also important. Such drawbacks include the anxiety experienced while awaiting the result of a test and the repercussions which a positive result may have with regard to obtaining employment or private insurance.

Public information must be aimed at promoting the broad accessibility of the programme for early detection. However, such information should by no means imply moral pressure.

Explanation: It is not fair if only certain sections of the target group participate, since other target groups will not have been reached effectively. Information will therefore have to be attuned to the entire target group.

A high level of participation is usually required in order to ensure the success of the programme. This can lead to an urge to over-accentuate such information, for example by suggesting that failure to participate is not sensible, or even morally wrong. The suggestion that failure to participate is not sensible can only be used if this can be well substantiated at the level of the individual (the fact that a programme is cost effective is insufficient justification in this context). Moral pressure is unacceptable for two reasons. Firstly, a situation should be avoided in which the groups at risk become stigmatised and harmed. Secondly, the freedom to refuse is jeopardised if the impression is created that it is somehow 'wrong' not to take advantage of the offer.

In the case of a population screening programme which (following positive appraisal of its effectiveness and efficiency) has been incorporated into public health policy and which (in the interests of those involved) has been offered to the target group, candidate participants must first give their free and informed consent for personal information to be used for the purposes of research. In such a case, no linkage whatsoever is permitted between participation in the screening programme and consent for personal information to be used for evaluation purposes or for scientific research.

The only exception to this is when the population screening programme is not being carried out primarily for the benefit of the participants. Such a programme would partly or exclusively address the issue of whether the programme is generally suitable enough to be offered to a yet to be defined target group. Here also, evaluation of the object of this study should make as little use as possible of personal information. Instead, consideration should be given to the adequacy of coded data made available for the study. Generally, such a pilot population screening programme must be classified as a medical experiment and will therefore have to meet the appropriate requirements.

Explanation: In a good early detection programme, continuous research is carried out for the purposes of evaluating the screening. Sometime, scientific research will also be carried out into the incidence of the disease, possible risk factors etc. The use of personal information for this purpose can only be sanctioned provided that the express permission of those involved has been obtained. The invitation and the consent for the population screening programme should avoid creating the impression

that this service is only available to those who consent to an evaluation study or any other type of scientific research which are based on personal information.

However, it may be that a population screening programme will still not be included within the framework of the health service until it has been evaluated to see whether it is efficient enough to be incorporated as a service. Under such circumstances, the 'sproetenbus' (a Dutch experiment with a mobile station for the early detection of skin cancer) could serve as a pilot population screening programme. Generally, such a study will also constitute an experiment within the meaning of article 1.1 of the WME. The linkage referred to above is permissible, however, within the context of a pilot study. People must not be pressurised to accept any given condition before they are able to make use of a facility which is beneficial to them. Whether or not such a service is indeed of practical value will be established in the pilot population screening programme itself.

Brief descriptions of clinical pictures

1 **Congenital anatomical abnormalities**

Two to three per cent of births involve children with severe congenital abnormalities other than neural tube defects and Down's syndrome. Congenital abnormalities are responsible for one quarter of all prenatal mortality. Ninety per cent of congenital abnormalities affect the children of parents who had no heightened risk in that regard. Many prenatal disorders can be detected using ultrasonography (more than 200).

Congenital abnormalities can affect various organ systems, such as the cardiovascular system, the central nervous system, the sex organs and urinary ducts, the gastrointestinal system or the skeleton. They may be determined purely by genetics, caused by exogenous factors (infections, medicines) or by combinations of the two. Knowledge of the exact cause also provides information about the chance of prevention or of repetition. Many such abnormalities are lethal.

The sensitivity and specificity of ultrasonographic examination are highly dependent on the type of disorder involved, the quality of the equipment available, the amount of experience of those performing the examination and the amount of time which they have available for this purpose. Where there is a heightened risk and under optimal conditions, screening for congenital heart abnormalities has both high sensitivity (97%) and high specificity (98%). However, when the entire population is screened, sensitivity and specificity are extremely disappointing. With abnormalities of the urinogenital system, the number of incorrect diagnoses can exceed fifty percent.

The latest development is a test in the first trimester of pregnancy, which can reveal numerical chromosome abnormalities. This type of test may form the basis of invasive diagnosis in the future, possibly in combination with other types of risk-evaluation testing.

The early detection of congenital abnormalities can be important for a variety of reasons. In some cases, early detection is important to the development of an optimum prenatal and postnatal policy. In other cases, follow-up testing can lead to an accurate prognosis. In the case of lethal abnormalities, pointless hospital admissions, courses of treatment or surgery can be avoided. It also gives parents the option of electing to terminate the pregnancy.

Aside from the above-mentioned diagnostic uncertainties, another disadvantage is the increasing intrusion of medicine into pregnancy as a result of adopting an overly broad indication.

As the use of ultrasonographic testing clearly demonstrates, methods exist for the detection of congenital abnormalities which involve neither a blood test nor a DNA test but which are nevertheless part of established examination practice.

2 Congenital hypothyroidism

Congenital hypothyroidism (CHT) is caused by a deficiency of thyroxin (T4). The thyroid itself may be defective (primary CHT) or the problem may lie with those organs which stimulate the thyroid to produce thyroxin (congenital thyrotropin deficiency syndrome: CTDS) via thyroid stimulating hormone (TSH). A greatly reduced T4 level can lead to severe mental retardation, behavioural disorders and motor disorders. In the past, it was not usually possible to make a diagnosis until the condition was at a relatively advanced stage (since the symptoms are relatively unspecific and only develop gradually). However, if this disorder is detected in time, treatment with hormone preparations is almost entirely effective in preventing mental retardation. Only in the case of severe T4 deficiency do mild motor disorders occur.

In the Netherlands, the frequency of primary CHT in newborns is 1 in 3,400, while that of CTDS is 1 in 25,000. Diagnosis is made by a paediatrician.

Following initial research in a pilot region, national screening for CHT and CTDS has been in effect in the Netherlands since 1 January 1981. The percentage participation is extremely high (99.5% of all live births). Screening is carried out neonatally by examining the blood of newborns to determine the T4 content and, as a derivative of this, the TSH content. A second 'heel prick' is required in the case of more than 1% of the children. This blood sample should be taken on either the 6th, 7th or 8th day of life. An excessively low hormone level indicates a congenital metabolic disease. From 1981 to 1991 10,165 individuals (0.57% of the population examined)

were referred to a paediatrician for further diagnosis. Of those, 582 were found to have a congenital metabolic disease (529 with CHT and 53 with CTDS). There is a high detection percentage for CHT (99%), while that for CTDS is lower (74%).

Particularly in the case of CHT, screening has achieved its objective (preventing the repercussions of the disorder by timely treatment). The price for improving the detection of patients with CTDS is the referral of greater numbers of individuals for follow-up testing. However, the current total of referrals which are found to have no congenital abnormalities whatsoever is quite high, something which is viewed as a significant disadvantage of screening. Referral not only causes anxiety for the parents in question, it also places a burden on the health service.

3 Down's syndrome

Down's syndrome (trisomy 21) is associated with severe mental handicap and may also be combined with characteristic abnormalities in some organ systems (e.g. the heart and the proximal part of the duodenum). Many patients develop Alzheimer's disease after reaching the age of forty. Most cases of Down's syndrome (96%) involve a separate, extra chromosome 21 (non-hereditary form). In the remaining 4% of cases, a chromosome translocation is involved, with (part of) the extra chromosome 21 being attached to another chromosome. Both abnormalities can be detected by examination of the chromosomes in cellular material taken from the foetus. In 1% of all cases, a balanced chromosome translocation is found in one of the parents (hereditary form). Life expectancy is highly dependent on medical policy with regard to any additional congenital abnormalities.

The frequency of Down's syndrome at birth is established at 1 in 750. In the absence of prenatal screening this would be expected to result in the birth of 270 children with this syndrome each year in the Netherlands. About 25% of such children have mothers who are at least 36 years old, and who constitute an age group with heightened risk. The probability of finding a trisomy 21 in this indication group is dependent upon age, rising from 1 in 300 for mothers aged 36 to 1 in 30 for mothers aged 45. For this reason, with mothers aged 36 and above, age is an indication for carrying out a prenatal chromosome examination. Such tests are also indicated for those pregnancies where one of the parents carried a balanced chromosome translocation (involving chromosome 21). Couples who have previously conceived a child with Down's syndrome are also eligible for prenatal chromosome testing due to a slightly heightened risk of repetition (1 to 2%). Finally, chromosome examination is indicated in cases where ultrasonography has revealed the presence of foetal abnormalities which may correspond to Down's syndrome.

The chromosome examination is highly sensitive and extremely specific (nearly 100%).

The current situation with regard to detection is far from ideal. Three quarters of all patients have mothers who do not fall within the group which is known to have a heightened risk. For this reason, there are those who urge that the target group for diagnostic testing should be established by another means.

The concentration of three marker substances (the triple test) in the mother's blood from the 15th to the 18th week of pregnancy, in combination with the mother's age and the length of the pregnancy (where this has been accurately determined) enable an individual estimate to be made for each pregnant women, regarding her chances of bearing a child with Down's syndrome. If the opportunity for follow-up diagnostic testing is offered to those who have a risk factor equivalent to that of women aged 36 then about 5% of all women examined will be eligible for such follow-up testing. This test consists of an examination of the chromosomes from cells suspended in the amniotic fluid. In 69 out of 70 cases, such follow-up testing indicates that the foetus does not have this disorder. By this means, about 60% of pregnancies involving a child with Down's syndrome can be detected. Sensitivity is dependent upon age.

The triple test also has a number of drawbacks. Around 40% of children with Down's syndrome are still missed. This fact imposes exacting demands on information dealing with the use of the test. The matter of whether people can be made to comprehend an estimation of risk remains highly questionable. Such information must also convey the fact that an amniocentesis (which is vital for follow-up diagnosis where it has been established that there is a heightened risk of Down's syndrome) also carries a risk of miscarriage. The result of the test causes at least temporary anxiety in around 5% of the women examined. Another current drawback is that the test can only be performed during the second trimester of pregnancy.

4 Duchenne and Becker muscular dystrophy

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are sex-linked hereditary diseases with a progressive course, which are associated with mutations of the same gene on the X chromosome. Onset is usually between the ages of two and four years. The earliest symptom is difficulty with walking resulting from weakness in the pelvic girdle and the thigh muscles. The disease gradually spreads to the arm, neck and respiratory muscles. The cardiac musculature is often affected as well. Such children become confined to a wheelchair at around the age of eleven and they ultimately die, aged about 20, from respiratory or cardiac insufficiency. More than one third of such children are also mentally handicapped. One third of cases do not involve a mutation which has been passed down through the family. In these instances,

a de-novo mutation (occurring in the mother in two thirds of cases) is responsible for the disease.

BMD has a somewhat milder course. Both the clinical symptoms (which are also progressive) and the age at which they manifest themselves are more variable than the uniform picture seen with DMD. The disease can simply take the form of muscle cramps, although it can also take the form of pronounced muscular weakness. Here too, the cardiac musculature is often affected, independently of the degree of muscular weakness or of the age of the patient.

DMD occurs in 1 in 3,500 to 4,000 newborn boys. Severe forms of BMD are less frequent (1 in 17,000). There is some doubt regarding the frequency of the milder forms of BMD.

Until recently, a diagnosis of DMD or of BMD was established markedly on the basis of the clinical picture, the course of the disease, the increased activity of the enzyme creatine kinase (CK) and histological findings (using a muscle biopsy). Although these two forms of muscular dystrophy could not previously be distinguished from one another, DNA testing coupled with analysis of the protein involved has now made this possible.

Consideration should be given to the introduction of neonatal screening of all boys for DMD. The reasons for this are the high mutation frequency (whereby one third of cases do not involve a mutation which has been passed down through the family), the occasional late diagnosis (up to age 5 or 6) and the protracted, burdensome pre-diagnostic route for newly appearing cases. A major consideration here is that in two thirds of cases it is the mother who is the carrier of the new mutation, which means that she has a 50% chance of passing this on to any future male child. Furthermore, screening will enable testing to be offered to any other female members of the same family who may also be carrying the gene. Other important factors are the smaller sizes of families and extended families, plus greater mobility. As a result people are less aware of a possible hereditary burden, and even where there is familial transmission, diagnosis may be subject to considerable delays.

The neonatal screening of all male children for DMD can be performed using the blood obtained from a 'heel prick' between the third day and one month after birth. Such samples are analysed in order to determine the activity of the enzyme creatine kinase (CK). If an elevated value is found then the test can be repeated using the same sample, and at the same time it can be established the increase is due to CK which originates from muscle tissue. If a second sample is also found to contain an elevated CK value it almost certainly indicates muscular dystrophy. The parents must be informed about hereditary muscle diseases before medical staff can proceed with further diagnosis. Additional tests are also required. In 0.02% to 0.2% of all children tested, the measurement in the first sample incorrectly indicates an elevated CK value.

These results are not subsequently confirmed by tests on a second sample. Experimental research has not been running long enough to enable reliable information to be given regarding specificity and sensitivity. Nevertheless, using statistics, it can be established that the majority of patients who will go on to develop DMD are indeed being detected. A number of children who will go on to develop a severe form of BMD are also detected.

As yet, there is no treatment for either form of muscular dystrophy. The importance of the test lies in giving the parents a more realistic view of their child's abilities. The test also offers them the option of well-considered family planning, it avoids diagnostic complications and delays and it provides an opportunity to plan the child's care well in advance.

5 Hereditary forms of breast cancer

In the Netherlands, more than 7,000 women are diagnosed with breast cancer each year. Of these, about 20% ultimately die from the effects of this disease. About 350 to 560 of the 7,000 patients who develop breast cancer each year have a genetic predisposition to the disease.

At the close of 1991 it was discovered that two different genes each play a part in the development of breast cancer. One of these genes (p53) is mutated in families with the Li-Fraumeni syndrome (quite a rare disorder). Of greater importance is the BRCA-1 gene on the long arm of chromosome 17. This gene is involved in about 45% of families with a high incidence of carcinoma of the breast and in virtually 100% of families with a high incidence of carcinoma of the breast and carcinoma of the ovary. Mutations in this gene are transmitted as autosomal dominants. Female carriers of the gene have an 85% chance of developing breast cancer at some point in their life. According to American estimates about 1 woman in 200 carries such a mutation. Shortly before this report was published the location of a third gene involved in the hereditary form of breast cancer was discovered. This gene, which has been named BRCA-2, is located on chromosome 13 (Woo94).

It appears that, within 1 to 2 years, a DNA test will be available to many families with hereditary breast cancer. This will provide individuals with information about the genetic risk involved. In principle, it will then be possible to perform genetic screening for a much larger part of the population, to detect mutations in the BRCA-1 and BRCA-2 genes. Although it is now too soon to make statements about such test characteristics as sensitivity and specificity, it can be said that such early detection will only apply to a small percentage of breast cancer cases. However, given that breast cancer is so common, the absolute number of women involved will be considerable. According to data from the Central Bureau of Statistics (CBS), on 1 January 1993 more

than 2.8 million women in the Netherlands aged between 25 and 50. More than 14,000 of these will be carriers of the high risk forms of the BRCA-1 or BRCA-2 genes. Such women will be eligible for genetic counselling and further treatment. Several courses of action are open to those who are identified as carriers.

The most radical preventive treatment is bilateral mastectomy, possibly combined with bilateral ovariectomy in women from families in which carcinoma of the ovary occurs. The efficacy of such radical surgery has by no means been established (Dur93) and it can create a great psychological burden, particularly in younger women.

However, intensive on-going screening using mammography is also perceived as burdensome, partly because of the woman's continuing uncertainty about her chances of going on to develop a tumour. The provisional results of such screening show that it has had a beneficial effect on survival in several Dutch families (Vas94).

Hormonal chemoprevention is a third option, but few data are available. However, it has been found that there is a significant reduction in carcinoma of the second breast in patients who had previously developed a carcinoma of the breast.

Early identification of the risk group in combination with preventive or prophylactic measures can be expected to produce a significant reduction in mortality and morbidity in this group. On the down side, however, is the fact that many of the women screened will be found to have no genetic predisposition but will nevertheless go on to develop breast cancer later in life. The reason for this is that genetic predisposition is involved in only a very small number of cases. A screening programme only makes sense if a sufficiently large percentage of the mutations can be detected. It is reasonable to expect that mutations with the most severe effects will be detected first, since the screening programme mainly uses material from families with a clear genetic burden. A third factor is the burden which accompanies the choice of a course of action. The latter have added significance since the screening test for this disease (regardless of sensitivity and specificity) can neither provide a conclusive prediction about whether or not the disease will develop nor can it predict the age at which this will occur. Patients will therefore have to opt for a particular course of action while they are still far from clear about the situation. This will require a considerable amount of unambiguous counselling.

6 Familial hypercholesterolaemia

Hyperlipidaemia (an excessive level of cholesterol or triglycerides in various lipoprotein fractions in the blood) is common within the population and is one of the most important risk factors in relation to cardiovascular diseases. It has been estimated that one third of the population will die from cardiovascular disease. While the genetic background to hyperlipidaemia is still poorly understood, research has indicated that a

large number of genes are involved. It is possible to distinguish between monogenetic and polygenetic forms of the condition. One important monogenetic form is familial hypercholesterolaemia (FH).

FH is caused by a defect in the gene which controls the synthesis of a cell receptor capable of binding a given lipoprotein fraction (LDL). The defect causes this fraction to accumulate in the blood, its levels varying from normal to highly elevated. This causes atherosclerosis, with a greatly heightened chance of myocardial and cerebral infarction.

The defect is autosomal dominant. The frequency of such patients in the Netherlands is 1 in 500, which means that there are about 30,000 in the entire country.

Biochemical methods or molecular genetics can be used to identify people who are at risk. The total amounts of cholesterol and triglycerides can be measured biochemically. If these exceed certain levels then there is a chance that the person involved carries the gene. Molecular genetics techniques (such as linkage studies or the detection of mutations) are used to find out whether or not other members of a patient's family also carry the genetic defect. More than 100 different mutations of the LDL-receptor gene have been described. Since none of these mutations occurs with a clearly greater frequency than the others, it is a far from simple matter to apply mutation analysis outside the framework of affected families. The biochemical test has a relatively low sensitivity and specificity (anomalous values are found which are not associated with LDL-receptor defects, and vice versa). However, within the framework of affected families molecular genetics does have a high sensitivity and specificity.

Early identification of gene carriers is vital if treatment is to be effective. Medicines are available which can reduce cholesterol levels. However the effectiveness of such drugs varies considerably and one regular finds people for whom they are totally ineffective. Treatment continues throughout life. Just following a diet is not enough, in contrast to other forms of hyperlipidaemia. In homozygotes (10 to 20 people in the Netherlands) treatment with drugs is insufficient, they are instead given liver transplants and blood replacement (plasmapheresis).

7 Phenylketonuria

Phenylketonuria (PKU) is a congenital autosomal recessive disorder. The disease is caused by a defective enzyme. If left untreated, the disease will cause irreversible damage to the central nervous system of affected children, and a severe mental handicap. If the disorder is detected on time, a special long-term diet can prevent damage from occurring. The current view in the Netherlands is that this diet should preferably be maintained throughout life.

This disorder has a frequency of 1 in 18,000 for newborns in the Netherlands. Given the rarity of the disorder and the complexity of the treatment, diagnosis is usually made in a university medical centre.

The Netherlands has had national screening for PKU since 1 September 1974. The percentage participation is extremely high (99.5% of all live births). Screening is carried out neonatally by measuring the phenylalanine activity in the blood of newborns. The blood sample should be taken on either the 6th, 7th or 8th day of life. An excessively high activity indicates a congenital metabolic disease. Besides PKU, two other rare diseases (forms of hyperalaninaemia, which are also treatable) can be diagnosed by follow-up testing. Collectively, these three diseases have a low frequency in newborns (1 in 16,000). Nevertheless, the predictive value of detecting an excessively high activity of phenylalanine is good, since 48% of the children detected require treatment. During the first 15 years of screening in the Netherlands, this has resulted in the detection of 158 children with a congenital metabolic disease. Diagnosis was missed in the cases of three children.

The objective of screening - the prevention of mental retardation - has been achieved to a significant extent. Of all PKU patients aged 5 and above, 90% are in the standard education system while 10% are receiving special education. None of the patients indicated are inmates of institutions for the mentally handicapped. Internationally, the value of neonatal screening for PKU is beyond dispute.

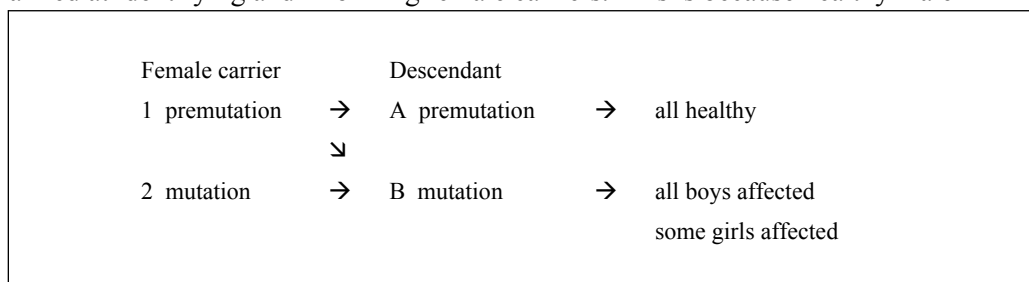
8 Fragile X syndrome

Fragile X syndrome is the most common cause of familial impaired mental development (familial mental retardation). It displays X chromosome transmission with several unusual features: about 35% of the female carriers display mild to moderate mental retardation and it is even possible for a healthy man to transmit the mutation to carrier females. Besides the impaired mental development, there are also physical abnormalities and behavioural problems. Boys with the syndrome generally attend schools for children with extreme learning difficulties. While they generally continue to live at home, they sometimes have to be removed in connection with anxiety attacks or temper tantrums. In adulthood they reside in surrogate family units, other institutions for the mentally handicapped, or with their parents. Some of them attend a sheltered workshop during the day. Women with the syndrome are often less severely mentally handicapped than affected men and, dependent upon their level of disability, they live either independently or in supervised accommodation.

The prevalence of affected men in western societies is estimated at 1 in 1,250, and that of women at 1 in 2,000. Until recently, diagnosis was only possible by an examination of the chromosomes.

The recent identification of the gene which is involved in this syndrome represents a major step forward in terms of diagnosis. There are several different forms of this gene. In the normal form, the nucleotide base sequence 'CGG' is repeated between 6 and 54 times. In patients with fragile X syndrome, this sequence is repeated more than 200 times. In healthy male carriers, it is repeated between 52 and 200 times. This is referred to as a premutation. Direct DNA analysis enables the number of repeated sequences in the gene to be measured. This provides a simple and reliable means of identifying patients and female carriers of premutations or full mutations. The diagram below illustrates the various types of transmission:

When a population screening programme is being considered, this will have to be aimed at identifying and informing female carriers. This is because healthy male



carriers always have healthy children, although their daughters can be carriers. The information relates to the courses of action available to those who want children. A population screening programme can focus either on the situation prior to conception or the prenatal stage. One disadvantage of the prenatal stage is the complexity of the information and the possibility of burdensome repercussions if carrier status is confirmed. However, the target group is more difficult to approach in the stage prior to conception.

9 Infantile spinal muscular atrophy (Werdnig-Hoffmann's disease).

This autosomal recessive disorder is the most dramatic form of a group of disorders of the anterior horn cells in the spinal cord and in part of the brain stem. Muscle weakness and hypotonia are characteristic features of all forms, but they can differ in time of onset and in severity. In the infantile form, these symptoms appear before the child reaches an age of 6 months, and they are sometimes even apparent at birth. This results in an arrest in motor development. The motor milestone of sitting up is never achieved. Besides muscular weakness in the limbs and trunk, swallowing difficulties also occur. Treatment is only aimed at combating the symptoms and most affected children die of pneumonia before the age of two.

The diagnosis is reached on the basis of the classical clinical picture, supplemented with electromyography and the histological examination of muscle tissue.

The frequency of such patients at birth is at least 1 in 20,000. The abnormal genetic trait is transmitted by both parents.

In 1990, the gene responsible for this disease was localised on chromosome 5, although its structure is still unknown. It is estimated that about 5% of the individuals in families in which infantile spinal muscular atrophy occurs have no link with chromosome 5. This indicates that there is genetic heterogeneity. It can be expected that, within the foreseeable future, the gene responsible for this disorder will be identified, as will the various mutations. Since there is, as yet, no direct test for the presence of the mutation, great care must be exercised when making the diagnosis. In 1991, an international convention was reached regarding inclusion and exclusion criteria.

Prenatal diagnosis can be carried out in families with a child that suffers from this disorder, thanks to the presence of highly informative markers on either side of the gene. This even applies if the child has died, provided that some body tissue has been retained. Linkage testing, using chorionic villus biopsies or cells suspended in the amniotic fluid, can achieve accuracies of more than 99%.

10 Cancer of the colon

Within the clinical picture of cancer of the colon, there is a clearly described hereditary disorder called polyposis coli or familial adenomatous polyposis (FAP). This disorder is autosomal dominant.

Polyposis coli is characterised by the presence of numerous polyps in the colon and rectum. These polyps usually develop between the ages of 10 and 14. Without surgery, the chance of one or more polyps deteriorating into a malignancy is virtually 100%. Without treatment, the malignant degeneration of the polyps causes physical signs between the ages of 25 and 30, and ultimately death at around 35. This disorder has a frequency of 1 in 7,500 in the population of the Netherlands.

Because the disease occurs in families, it is quite normal for the immediate blood relatives (aged 10 and above) of a patient to undergo colonic endoscopy once every 2 to 3 years. Any polyps found are removed. Although malignant tumours can develop in the interim periods, this approach has reduced mortality. At the moment, the only form of treatment is removal of the colon before the polyps degenerate into malignancy, i.e. while the patient is still relatively young (about 18 to 20). Regular check-ups are not actually necessary for about half of these individuals since they do not have a genetic predisposition. Now that the gene (APC) has been localised and identified, it is

currently possible (in most affected families) to test immediate blood relatives for the presence of the gene, either by linkage testing or by the direct detection of mutations. These tests can also be carried out when patients are between the ages of 10 and 14. The sensitivity and specificity of such DNA diagnosis exceeds 99% for linkage testing and is almost 100% for the direct detection of mutations. Health service staff in the Netherlands have accumulated considerable experience with this type of screening.

The advantage of screening within families is that endoscopic examination can be restricted to individuals with a genetic predisposition. The need for screening outside affected families is not quite so self-evident. Both the clear familial nature of the disorder and its relatively low frequency would tend to argue against this. However, screening within affected families is not without its problems. Early detection of the presence or absence of the predisposition can impose a heavy psychological burden. This is partly the reason why it is important not to perform these tests on extremely young patients. The disorder need not cause problems with regard to obtaining employment or private insurance. After all, the regular, directed check-ups, possibly combined with other preventive measures, reduce the risk involved.

A second form of hereditary intestinal cancer, which is not related to the formation of polyps, is hereditary non-polyposis coli (HNPPC), which occurs with a similar frequency in the population. Recent research has indicated that this disease can be caused by mutations in at least four different genes, with the two primary instigators contributing about 40% and 30% respectively. It is therefore no simple matter to trace the mutations responsible, and, for the time being, it is only possible to correlate the disease with the gene responsible in sufficiently large families. In the long-term, this situation may be changed by other forms of molecular diagnosis. This will mean that screening can be considered for this disorder, given the various options for therapy.

11 MCAD (a disease involving fatty acid metabolism)

MCAD deficiency (deficiency of the mid-chain acyl co-enzyme A dehydrogenase) is an autosomal recessive disease of fatty acid metabolism. The disorder is linked with a significant chance that metabolism will become disordered, resulting in increasing lethargy (particularly when fasting or feverish) and ultimately in coma and death. This clinical picture is held to be responsible for 2% of all cases of cot death. The symptoms usually develop at an age of 5 to 24 months. The chance of death is highest between the ages of 15 to 26 months.

Prevalence at birth in the United States, Denmark and Britain is 1 in 28,000, 1 in 40,000 and 1 in 19,600 respectively. There are no details concerning prevalence at birth in the Netherlands. However, there are a remarkably large number of patients (55 per

15 million), while in Britain there are 34 per 55 million, in Denmark there are 3 per 5 million and in Germany 17 per 75 million).

Until recently a diagnosis could only be made on the basis of blood and urine tests (where the samples were taken during crisis situations or by means of the 'provocation' test). Following both of these tests, further confirmation of the diagnosis (in the form of enzyme tests) is required. The MCAD gene has already been identified, as have several mutations which are known to be associated with the clinical picture (one in particular being extremely common, occurring in 99% of patients and 90% of the heterozygotes).

If MCAD deficiency is shown to have a high frequency of occurrence in the Netherlands then consideration could be given to the option of screening all newborns for this life-threatening but eminently treatable disease. Screening could be performed using the blood obtained from a 'heel prick'. Such screening would enable 80% of all patients to be traced immediately, and another 19% after supplementary testing.

Once a diagnosis has been made then disease symptoms can be prevented by avoiding extended periods of limited food intake. Adequate amounts of sugar should be consumed during illnesses which are accompanied by fever, the amount of fat in the diet should be limited and extra vitamin B2 and carnitine should be administered.

Besides these benefits, there is also a problem which still has to be solved. Since multiple mutations are associated with the clinical picture some patients will be missed by the screening programme, dependent upon the part of mutations which can be detected by screening. Subsequent testing of individuals in which only a single mutation occurs can further reduce the number of patients who slip through the net. If this testing can be done using the same blood sample (molecular, biochemical) then the problem will be solved. Until then, all those in which a single mutation is found (1 in 40 to 1 in 60) will be approached for further testing. These considerations may affect parents' willing to agree to the 'heel prick', thereby having a negative influence on the detection of phenylketonuria and congenital hypothyroidism.

12 Myotonic dystrophy

This autosomal dominant disorder is the most commonly occurring muscular dystrophy in adults. Besides muscular dystrophy there may also be abnormalities in various other organs. Those carrying the genetic abnormality are certain to develop the disease. There is great variation in terms of severity and time of onset. With the congenital or infantile form, the symptoms of muscular weakness following birth are often so severe that the child dies within a few days. This form only occurs when the abnormal gene is inherited via the mother. If the onset of the disease occurs during childhood there is some muscular weakness, although the clinical picture is predominantly one of mental retardation. With the adult type, the initial symptoms of the disease manifest

themselves between the ages of 12 and 50. In general, muscle weakness is gradually progressive. Affected men in whom disease onset occurs during early adulthood are generally sterile. Life expectancy is determined by the occurrence of acute cardiac arrest and respiratory disorders, usually as a complication during general anaesthesia. The late onset type usually begins during late middle age (above age 50) and often manifests itself primarily in the form of cataracts.

In the general population, the disease affects 1 in 20,000 people, while 1 in 8,000 newborns has the genetic predisposition.

The mutation which is responsible for myotonic dystrophy is located on chromosome 19 and consists of an abnormally frequent repetition of a sequence of three nucleotides (CTG). Diagnosis is made on the basis of the classical clinical picture, possibly supplemented with electromyographic and ophthalmic tests. In this way, carriers of the gene mutation who are free of physical signs can be identified with 92% certainty. DNA testing boosts this certainty to 100%. Such testing is only carried out in families with a genetic burden.

It has, however, been established that most mutations develop slowly (over many generations) into an unstable preliminary stage of 50 to 80 CTG triplets, after which the clinical picture manifests itself in the family within one or two generations. This information gives rise to the question of whether, in certain areas where the disease has a high frequency of occurrence, carriers of an unstable gene should perhaps be actively sought out. The argument in favour is that this is a severe disorder and that it often occurs in previously unaffected branches of the family, since the premutation remains unnoticed for a long time. However, the counter arguments are that it is not possible to distinguish conclusively between normal and unstable genes, and that the possible courses of action are currently limited to family planning. At present, the prospects for therapy consist of nothing more than symptomatic and supportive measures.

13 Neural tube defects

Disruption of the closure of the neural tube during embryonic development can lead to anencephaly or spina bifida, dependent upon the location of the closure defect.

Anencephaly is a lethal abnormality which results in death either before or soon after birth. In 1988, the total number of new cases of anencephaly in the Netherlands was estimated to be 75 per annum (GR88).

The severity of *spina bifida* is dependent upon the magnitude of the closure disorder. Surgical closure of the defect is often required in order to ensure that the patient does not acquire a lethal infection in the first few weeks of life. The disease is accompanied by symptoms of neurological injury which generally lead to paralysis of both legs and to permanent incontinence. If the spinal cord is involved in the closure

defect (myelocoele) then hydrocephaly is an extremely frequent complication, one which usually necessitates a series of neurosurgical operations.

Neural tube defects exhibit multifactorial transmission. This means that more than one gene is thought to be involved, in combination with environmental factors. Recent research has shown that adequate amounts of folic acid in the diet during the period surrounding conception reduce the risk of neural tube defects.

Couples who have previously had a child with one of these disorders, or who have siblings who were born with the disorder or who include a partner who was born with the disorder have a heightened chance of having a child with the disorder. Some anti-epileptic drugs also increase the chances of having a child with spina bifida in particular.

Since both clinical pictures involve anatomical abnormalities, diagnosis can be made using ultrasonography. When experienced staff are involved, sensitivity is around 90% to 100%, and specificity between 92% and 99.8%. Measurements of the amount of alphafoetoprotein (AFP) in the amniotic fluid can be an extremely reliable indication of an open neural tube defect. In addition, measurement of alphafoetoprotein in the mother's blood is used as a screening method. Sensitivity is between 80% and 90% for open defects.

If ultrasonography is carried out solely on the basis of the above-mentioned indications, in centres with good equipment and experienced operators, then it is more likely to soothe anxiety than to cause it. Unfocused, large-scale testing will inevitably give rise to incorrect indications of heightened risk and to false positives. This will have an unfavourable effect on the balance between benefits and drawbacks.

The courses of action are limited. There is no therapy at all for anencephaly. Open spina bifida requires surgery in order to limit the repercussions of the disorder. A prenatal diagnosis can lead to a decision to terminate the pregnancy.

14 Cystic fibrosis

Cystic fibrosis is an autosomal recessive disease which results in damage to the respiratory system and to digestive functions. The clinical picture usually manifests itself at a very early age. About 3% of the population of the Netherlands carry a harmful mutation in the gene which is involved in this disease. The frequency of patients at birth is 1 in 3,600. Such individuals receive an abnormal genetic trait from both parents. Although the severity of the disease can vary, it often leads to frequent hospital admissions and periods of treatment. Generally it is a serious handicap which forms a great burden for the parents and family. Thanks to intensive therapy and support, the average life expectancy of such patients (dependent upon when they were

born) has gradually increased from 25 to 40. Thus 50% of such patients will have died before attaining that age.

The gene which codes for the protein involved in cystic fibrosis was identified in 1989. More than 400 different mutations of this gene have now been identified. Mutations of this gene can be reliably identified by means of DNA testing, which makes it possible to screen for carrier status. Screening is mainly directed at people wishing to have children. One particular mutation is by far the most common, even though its frequency varies between different population groups. In the population of the Netherlands, this particular mutation is found in 75% of carriers of the disease gene. Screening for the most frequent mutations in the Netherlands can lead to the identification of 85% to 90% of the carriers of a CF mutation. This in turn would lead to the detection of 72% to 81% of those couples who have a 1 in 4 chance of having a child with cystic fibrosis.

The partial nature of such identification imposes special requirements of the information provided about the screening. Comprehensive information is required, since if both expectant parents are shown to be carriers, the severity of the disease in any future offspring cannot be determined with any precision. The information which is given to couples where only one partner is identified as a carrier is even more complex. It is not possible to be 100% certain whether the other partner is not a carrier. They then may become anxious, having an average chance of 1 in 800 of producing a child which will suffer from cystic fibrosis. This is greater than the 1 in 3,600 which applies to all couples in general. In view of the potential size of the population to be tested, a study must be made of the facilities required to provide these couples with genetic counselling.

On the other hand, couples in which both partners have been shown to be carriers of a mutation can be informed of the possible courses of action. Should they decide to have children of their own, then tests on the foetus will reliably indicate whether or not it will suffer from cystic fibrosis, since both the mutations involved are then known.

15 Thalassaemia

The name thalassaemia covers several autosomal recessive clinical pictures, which involve faulty synthesis of the red blood pigment, haemoglobin. Haemoglobin is the protein which is responsible for the take-up and release of oxygen by red blood cells. It is constructed from two pairs of protein chains, namely two alpha chains and two beta chains. Foetal haemoglobin has a different structure, being constructed from two alpha and two gamma chains. The gradual production of adult haemoglobin commences even during foetal development. The major shift from one form of haemoglobin to the other occurs during the first few months of life. Some forms of thalassaemia can be

extremely severe. In the case of alpha thalassaemia major, the alpha chains cannot be synthesised, thereby preventing the production either of foetal or adult haemoglobin. This leads to the death of the child during pregnancy or shortly thereafter. It can also lead to severe pregnancy-related complications for the mother. With beta thalassaemia major the defect blocks the production of the beta chains. At birth, the child has normal levels of haemoglobin but an extremely severe anaemia develops soon after birth (the production of gamma chains stops naturally, but no beta chains can be produced).

The treatment of thalassaemia either involves numerous blood transfusions (and removal of the resultant excess of iron) or bone marrow transplantation. Although these therapeutic techniques can greatly improve and extend the lives of such patients, the side effects should not be underestimated.

Alpha and beta thalassaemia occur frequently in South East Asia, West Africa and the Mediterranean region. The frequency of carrier status varies greatly between different population groups. In Sardinia, for example, this is as high as 17% for mutations associated with beta thalassaemia. It is now possible for diagnoses to be made in good time and for carriers of the mutations associated with this disease to be identified by means of blood tests and DNA diagnosis. The detection techniques used have a sensitivity and specificity of around 100%. In many areas where there is a high frequency of patients among the newborn, screening programmes have been initiated in order to identify carriers. Participation in the programme is particularly high in Sardinia and Cyprus, partly because people there are familiar with the disease and fear it. The early detection of carriers, together with genetic counselling provides carriers with courses of action which will enable them to have children who will not suffer from the disease.

If introduced in the Netherlands, screening for carriers of beta thalassaemia would involve a special consideration. Significant frequencies of carriers of the mutations concerned occur only within certain minority groups within the population (immigrants). For this reason, screening for thalassaemia requires that extra consideration be devoted to determining whether there is sufficient basis for such testing within the population groups concerned and within the population as a whole. The aim of this is to avoid various problems, such as discrimination, developing as a result of the screening programme.

16 Alzheimer's disease

Dementia, which is characterised by progressive memory disorders, deterioration of cognitive functions and (often) personality changes, leads to the disruption of patients' ability to function. As a result, during the course of their illness, patients become gradually more dependent on others to take care of them. Dementia is not a disease of

the brain in the strict sense of the word, but rather a syndrome. Alzheimer's disease is one of the most important causes of dementia syndrome in elderly people. In the Netherlands more than 100,000 people suffer from dementia, with another 10,000 new cases being added each year. Down's syndrome patients frequently develop Alzheimer's disease in later life.

A diagnosis of Alzheimer's disease cannot be made with any certainty during life without recourse to a cerebral biopsy. Supplementary tests are also required in order to eliminate other possible causes of dementia. The neuropathological changes in the brain which accompany Alzheimer's disease consist of neurofibrillar degeneration and of senile plaques composed mainly of amyloid. The chance of developing the disease is strongly dependent on the presence of a particular allele (E4) of the apoprotein E (ApoE) gene on chromosome 19. The ApoE protein, which is involved in the transport of lipids in the blood, is found in the senile plaques (and elsewhere) and may be implicated in the precipitation of amyloid.

Although this disorder usually occurs in isolation, there is also a familial form of the disease. Molecular genetic research into this rare form of Alzheimer's disease (which is transmitted as autosomal dominant) has indicated a number of gene locations. Of particular importance are the point mutations in the amyloid precursor protein (APP) gene on chromosome 21 which can cause a change in the composition of APP. APP gives rise to the β A4 protein fragment which, in turn, leads to the production of the highly insoluble amyloid fibrils.

At the moment, early detection of the disorder does not present any options regarding the course of action to be taken.

17 Huntington's disease

Huntington's disease, which is transmitted as autosomal dominant, is associated with degeneration of the nervous system. The disorder usually becomes manifest during adult life, although some cases occur earlier and some later. Following the appearance of the first symptoms, the disease progresses gradually for 15 to 25 years with the loss of mental and physical functions as well as personality changes until the patient finally dies. All carriers of the abnormal gene have an almost 100% chance of developing the disease before they reach old age. By the time the disease makes its appearance, patients have usually had children, and have thereby passed the disease on. The disease is incurable. Carriers of the abnormal gene occur with a frequency of 1 in 5,000 among the general population. There are about 1,000 such patients in the Netherlands.

The use of linkage-testing in family studies has meant that, in recent years, it has been possible to offer a predictive test with a reliability factor of 96-99% to about 95% of all possible carriers. For psychological reasons, only a small fraction of those at risk

(about 10%) chose to take advantage of this offer. The molecular-genetic abnormality which accompanies the clinical picture has now been identified. This consists of an abnormal repetition of a nucleotide sequence (CAG) in the gene concerned. Having identified the mutation associated with the clinical picture, it is now possible to test for the genetic predisposition, outside the context of the family and with a reliability factor of almost 100%. Now that the test carries such certainty, more people are taking advantage of it. However, it is still too soon to be able to quote reliable figures, nor there has been an abrupt surge in requests.

The significance of the test for the members of families in which the disease occurs is that it provides an opportunity for elective family planning. For such individuals, the advantage of the test (besides its extreme reliability) is that it is no longer necessary to test other members of the family.

However, considerable psychosocial problems are connected with the performance of the test. The disease is almost exclusively restricted to families with a known genetic burden. Accordingly, it is not sensible to offer the test to individuals outside such families nor is this being considered. The confirmation of carrier status or of non-carrier status for the gene abnormality can bring relief on the one hand and psychological problems on the other. Proof of carrier status can have repercussions for obtaining employment or private insurance cover, both for the person being tested and for other members of the family.

18 Tay-Sachs disease

Tay-Sachs disease is an autosomal recessive disorder in which the enzyme hexosaminidase A is absent. This results in a disruption in the breakdown of fatty substances (gangliosides) and accumulation of these substances in the brain cells. The clinical picture is characterised by disrupted development of brain and muscle functions. Children with Tay-Sachs disease initially show normal development, but the disease manifests itself at around the age of 6 months. Children with the disease usually do not live beyond the age of four. In some cases the initial symptoms only occur at around the second to the third year of life. Such children usually survive longer, until the fifth to the tenth year of life. The disease process, which causes severe mental handicap, deafness and blindness, is untreatable.

The mutation which causes the enzyme defect occurs with a high frequency in Ashkenazi Jews. In this population group, about 1 in 30 individuals is affected and, without screening, 1 in every 3,600 live births will be a Tay-Sachs patient. In the non-Jewish population, about 1 in 150 individuals is a carrier of the mutation concerned. This means that 1 in 90,000 live births is a child with Tay-Sachs disease.

Carriers of the mutation can be easily identified with a simple test which involves measuring the activity of the enzyme hexosaminidase A in the blood. If necessary, such activity can also be determined in white blood cells. In this way 99% of the carriers in an Ashkenazi population can be identified, while the chance of missing a carrier is less than 1 in 30,000.

Within the Ashkenazi Jewish population in the United States, screening for the genetic predisposition to Tay-Sachs disease has been introduced with the support of the population group concerned and their religious leaders. Participation in screening varies from region to region. Some special circumstances such as the often high degree of participation and acceptance of the opportunities offered by prenatal diagnosis have meant that, in the population group concerned, the numbers of Tay-Sachs patients being born have been significantly reduced. In order to improve the accuracy of carrier testing in a number of cases, DNA testing is being introduced. Due to the extremely cautious manner of its introduction, this screening programme serves as a model for screening in minority groups

Concepts and abbreviations

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- *allele*
one of the various forms of a gene
 - *alphafoetoprotein*
a protein which is produced by the foetus
 - *autosomal dominant*
mode of inheritance in which the allele of a gene which is situated on one of the autosomes is fully expressed both in the heterozygous situation and in the homozygous situation
 - *autosomal recessive*
mode of inheritance in which the allele of a gene which is situated on one of the autosomes is fully expressed only in the homozygous situation
 - *autosome*
see chromosomes
 - *BIG*
Individual Health Care Professions Act
 - *carrier status*
the presence, within the genetic material, of one mutated and one normal allele of a gene associated with a recessively inherited disease
 - *chorionic villus biopsies*
pieces of tissue from the placenta
 - *chromosomes*
structures which can be seen, with the aid of a microscope, in the cell nucleus and
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- which contain DNA; a distinction is drawn between sex chromosomes (X and Y) and the 22 non-sex chromosomes (autosomes)
- *DNA*
chemical compound whose structure is such that it is capable of storing genetic information
 - *effectiveness*
the degree to which the procedure has the desired outcome in everyday practice
 - *efficiency*
this is the yield produced by a procedure set against the financial cost, manpower and resources required and the time factor
 - *expression of an allele*
the information is read from the DNA and expressed as a genetic trait
 - *gene*
the portion of a DNA strand within a chromosome which contains the genetic information for a single trait
 - *heterozygote*
the two alleles for a given gene (on both chromosomes where the gene is located) differ from one another
 - *homozygote*
the two alleles for a given gene (on both chromosomes where the gene is located) are identical to one another
 - *in-vitro fertilisation*
artificial fertilisation under laboratory conditions
 - *monogenetic*
associated with a single gene
 - *multifactorial*
associated with a number of factors (genetic or environmental)
 - *mutation*
an abnormality in the structure of a gene or chromosome, or in the number of chromosomes, or the process by which such abnormalities arise
 - *neonatal*
the period shortly after birth (until a few weeks of age)
 - *order in council*
items of subordinate legislation to be published in the Government Gazette
 - *penetrance*
the percentage of those individuals possessing a given genetic predisposition in which that predisposition is actually expressed
 - *predictive value*
a characteristic of a test indicating what fraction of the positive test results are
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- correct (positive predictive value) and what fraction of the negative test results are correct (negative predictive value)
- *prenatal*
the time between the start of a pregnancy and birth
 - *prevalence*
the frequency with which a given trait occurs within a given group
 - *sensitivity*
a characteristic of a test for a particular trait, namely the chance that a person who possesses the trait in question will obtain a positive test result
 - *sex-linked transmission*
transmission of genetic information which is located on the X chromosome
 - *specificity*
a characteristic of a test for a particular trait, namely the chance that a person who does not possess the trait in question will obtain a negative test result
 - *stage prior to conception*
the period between contemplation of a pregnancy and the actual start of pregnancy
 - *ultrasonography*
test which uses images created by means of ultrasound
 - *WBO*
Population Screening Act
 - *WGBO*
Medical Treatment Agreements Act
 - *WME*
Medical Experiments Bill
 - *WPR*
Data Protection Act
 - *WZV*
Hospital Provisions Act
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