

HEREDITY: SCIENCE AND SOCIETY

On the possibilities and limits of genetic testing and
gene therapy

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gene therapy

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Report issued by a Committee of the Health Council of
The Netherlands

submitted to

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the Minister and State secretary of Health, Welfare
and Cultural Affairs

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No 89/31, The Hague, 29 December, 1989

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SUMMARY

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1 Introduction

This report was prepared by our committee on request of the government, as stated in a letter of February 11th, 1988. The report covers the current state of knowledge and the social, ethical and legal implications of genetic testing and gene therapy. We looked into various issues, considering their consequences for individuals as well as for society as a whole and for groups within it.

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Congenital and hereditary abnormalities are a major cause of human illness and death; in the first year of life, they are the main cause of death. An estimated 4 to 6 per cent, of full-term babies have a congenital or hereditary disorder. Some of these are so minor that they present no problems, while others can be remedied by appropriate treatment. Most, however, cannot be helped.

Heredity also plays a role in illness and death in later life. The susceptibility of predisposition to cardiovascular disease and cancer, the main causes of death in older people, have been shown to be influenced by hereditary factors.

The scale of the problem of congenital and hereditary abnormalities justifies an increased emphasis on research in this field. Our rapidly-accumulating knowledge of the structure and function of the human genetic material will also improve our understanding of the causes of congenital and hereditary disorders.

In the following sections, we review briefly the

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different topics which will be addressed in the report.

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2 Genetic testing and genetic counselling

There are currently eight centres for clinical genetics in The Netherlands, closely linked with teaching hospitals and university laboratories. These centres carry out genetic testing, including pre- and post-natal chromosome analysis, biochemical testing and DNA typing, as well as providing genetic counselling and support following the testing.

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Genetic counselling.

Our committee would like to emphasize that the main purpose of genetic counselling must be to provide clients with information, especially concerning reproductive matters. This information must enable individuals to make choices acceptable to themselves, in their own situation, in accordance with their own beliefs. The information provided must also be neutral; it is not for the counsellor to give unasked-for advice.

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Role of the State

The role of the State with respect to genetic testing and counselling includes at least the promotion of the right to choose for oneself, and therefore the freedom of the individual to decide for him/herself. This also implies support for the provision of information to the public, for guarantees of accessibility to services and for quality control of these services.

We do not condone any coercion on the part of the state to induce individuals to undergo genetic testing nor to take preventive measures. Such action would be in contradiction to fundamental principles of law and of human rights.

Concerning access to prenatal chromosome analysis, our committee does not find that there are sufficient grounds for reducing the present age limit in The Netherlands (36 years).

We would also oppose any restriction of access to such testing, for example by limiting it to women who are willing to agree in advance to terminate the pregnancy if an abnormality is found in the foetus. The arguments sometimes proposed in favour of such a policy, for example that the facilities for this service are few and costly, cannot justify its implementation. Moreover, prenatal diagnosis is not meant to be aimed at termination; its purpose is to provide pregnant women and their partners with information. Restricting access to this information would give rise to inequalities in human rights.

Many objections can be raised to the uncritical use of cost-benefit analyses to solve the problem of distribution of the scarce resources for genetic testing and screening. Neither the costs nor the benefits can be established with any certainty, and the contribution to human welfare cannot be expressed in positive or negative figures.

Our committee considers the present standards of quality and of quality control to be satisfactory. We do, however, recommend that DNA analysis using simplified technology (DNA test kits) be restricted to laboratories in centres for clinical genetics. Only these centres possess the necessary expertise, not the least of which is their ability to provide the support needed because of the far-reaching consequences of some test results for those involved.

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Ethics and law in genetic testing.

Among the many ethical and legal aspects of genetic diagnosis, our committee has concentrated in this report on the client's right to information, his/her right not to be informed, the right to confidentiality, protection of privacy, and provision of information to family members.

We find that the principle of an obligation to provide information must be fully respected. Exceptions are permissible only if and to the extent that the client is likely to suffer serious harm, or where the professional obligation of secrecy towards a third party takes precedence.

Similarly, the right not to know may be infringed upon only in extreme situations.

The question of confidentiality with respect to family members brings certain dilemmas to light, for example, when the need to approach family members for information infringes on their privacy, or when a family member refuses to agree to give information which is relevant for the client (using his/her own right to confidentiality).

In general, our committee urges extreme caution in revealing information about the client and in disclosing such information to relatives. The privacy of the relatives must also be closely guarded. We would accept an infringement of these various rights only in exceptional circumstances, and then using a 'conflict of duties' approach, in which case there must be a reasonable certainty that the breaching of confidentiality is necessary to prevent or to minimize serious harm to a third party.

The possible legal liabilities of the professionals involved do not, in our view, raise problems fundamentally different from those affecting other kinds of professional assistance.

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3 Genetic registries

Genetic registries and the use thereof must be limited to the strictly necessary. Persons appearing in such records are protected by the rights spelled out in present and future laws on this subject. In particular, it is important that the recording and storage of genetic information only be done with the permission of the individual involved. Our committee also stresses the importance of the right to have information deleted from records, or to have it stored anonymously.

We recommend the development of provisions to protect the rights of family members appearing in genetic registries, to avoid problems with their rights (Data Protection Act). Detailed regulations governing the storage of especially sensitive data, as envisaged in the Act, will provide a framework suitable for the protection of personal genetic data

in general, both within and outside the health care system.

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4 Cell banks

The rights of the 'donor' of body tissues or cellular material must of course be respected. This does not mean, however, that unnecessary barriers should be erected to the use of such material for the benefit of other persons, or for research. We propose that a code of conduct be drawn up, in which the rights of donors would be specified. How these rights are to be put into effect should be covered by a written agreement at the time the material is obtained. The agreement must specify such aspects as the storage and use of the material, and the considerations of confidentiality and privacy.

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5 Mass screening

Certain inherited metabolic disorders can be detected by neonatal screening. Newborn babies in The Netherlands are presently screened for phenylketonuria (PKU) and congenital hypothyroidism (CHT); for both disorders, effective treatment is available. Screening for other conditions, discussed in this report, could lead to timely genetic counselling and improvements in treatment prospects. Our committee opposes, however, neonatal screening for untreatable, late-onset conditions because this would only burden the child with distressing information. Similarly, screening for disorders that present during childhood is not recommended when diagnosis is unreliable and effective treatment unavailable.

Although it would already be technically possible to carry out large-scale screening of adults to identify carriers and genetic defects, there are important limitations to this approach. These include genetic heterogeneity, and the lack of sufficiently reliable and practical methods of detection. Our committee feels that the application of large-scale screening requires careful deliberation, especially to ensure that the benefits outweigh the disadvantages.

Within a few years it will probably become possible,

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by means of mass screening, to reliably identify carriers of cystic fibrosis, a recessive hereditary disease affecting 1 in 3,600 newborns in The Netherlands. (The present tests are not reliable for mass use.) An estimated 1 in 30 persons may be carriers. When both partners in a couple are carriers, they should be informed of the probability (25%) that their child will be affected by cystic fibrosis, and of the possibilities for prenatal diagnosis.

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6 Genetic testing outside the health-care system

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Insurance

We have formulated, in this report, measures related to genetic testing in the context of access to life and disability insurance and to personal pension schemes. To avoid unacceptable consequences for insurance clients while minimizing the risks to insurers of 'self-selection' among clients, we advocate a ban on genetic testing in this situation, as well as restrictions on the requirement to disclose information from previous genetic tests. Further investigation of the European legal context is necessary.

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Employment.

Our committee rejects, in general, the use of tests of genetic predisposition in selection of employees. Exceptions to this rule should only be considered, if in the future sufficiently reliable tests are developed, where the health interests of the individual concerned, or of a third party or parties, are demonstrated to be at risk. Such genetic testing in employee selection was also considered unacceptable by the Interdepartmental Working Group on Employment Medical Examination. The criteria drawn up by the Working Group in 1989 should be reinforced and supplemented by the addition of a general requirement that testing must not result in unfair distinction between or discrimination against groups within the society. If the Working Group's recommendations, thus amended, are not implemented in the near future through

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self-regulation, we believe that legislation is required.

In principle, genetic screening and monitoring in the place of employment could enable detection of increased genetic susceptibility to disease, and diagnosis of damage to genetic material due to environmental/occupational factors. This information could lead to preventive measures. The methods available for such research, however, are not yet sensitive enough for large-scale application.

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7 Looking ahead

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Pre-implantation testing

The views of the committee members differ as to the permissibility of experimentation on pre-implantation embryos for development of pre-implantation diagnostic techniques, one of the issues involved being the question of the intrinsic value accorded the pre-embryo (and thus its need for protection).

Were such experimentation to be permitted, the question would arise whether only surplus pre-embryos from in vitro fertilization (IVF) programmes may be used, or whether pre-embryos may be created for the purpose of research. On this point the opinions of the members of our committee also differ, even among those who agree that such research is permissible in principle. Leaving aside the latter question, the majority of the committee regards such experiments as permissible in the context of specific requests by a couple for assistance, providing strict conditions are applied. Caution is, however, urged in this matter.

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Gene therapy

Correction of genetic abnormalities at the DNA level is still in the laboratory research stage. Nonetheless, the first clinical trials of somatic-cell gene therapy are expected to start within the next few years.* Germ-line gene

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* Note added in the translation: the first trials have started in the mean time.

therapy, in contrast, is at this time no more than a theoretical possibility.

Although somatic-cell therapy is still in an experimental stage, we judge that when that stage has been passed, this type of therapy does not differ essentially from other forms of medical treatment, such as organ and tissue transplantation. Since development is still experimental, our committee will, in this report, formulate certain substantive and procedural conditions.

Germ-line gene therapy involves such uncertainties about the risks to human beings that we consider a moratorium on such research necessary.

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1 RECOMMENDATIONS

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1.1 Main points from the report.

In this report, our committee has discussed the main problems and issues associated with genetic testing and gene therapy. Over the last ten years, an effective network of Centres for Clinical Genetics has been set up in The Netherlands. We feel that their work has contributed to the sound basis of development of genetic research and testing in this country.

In this report, we draw conclusions and make recommendations; they are summarized, according to topic, below.

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- 1** Knowledge of congenital and hereditary disorders
- Our committee finds that it is important to increase our knowledge and understanding of these disorders, and of the methods for diagnosis and treatment of these within the health-care system.
 - The Centres for Clinical Genetics can occasionally provide referring general practitioners with information which will enable them to deal effectively with requests for advice.
 - Training and refresher courses (also for psychotherapists and social workers) on congenital and hereditary disorders can contribute to effective and timely use of clinical genetics facilities.
 - Education of the public about the principles of heredity and the possibilities for diagnosis and prevention of congenital and hereditary disorders also

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plays an important role, and should be promoted in primary and secondary schools, by the Health Education Service, and through the mass media.

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2 Access to services

- Our committee urges introduction of safeguards to assure equal access to clinical genetic testing and counselling services, regardless of income and without prior conditions or pressure to influence the clients' personal choices. The government should seek to remove any obstacles to free and equal access to such services for all for whom testing is indicated.
- If policies were to develop which would restrict access to genetic counselling services, by setting conditions on the possible decision in the case that an abnormality should be detected, then the government should introduce legal guarantees for access without conditions.
- We do not see any grounds at present for altering the age limit of 36 years for prenatal chromosome analysis (by chorionic villus sampling or amniocentesis).
- We recommend that the professionals involved in prenatal testing keep abreast of the developments in the area of the indications for it, but feel that it is not necessary to compile a detailed list of indications.
- Our committee does recommend retaining the current restrictive policy on foetal sex determination, under which it is done strictly for medical reasons.

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3 Quality of genetic testing

- We feel that the present arrangements for quality control in clinical genetic testing, through self-regulation, are satisfactory; government intervention is not needed at this time. In particular, to maintain quality control, we suggest that the diagnosis of hereditary diseases using DNA

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analysis kits (simplified testing techniques) should be restricted to the laboratories in the Centres for Clinical Genetics, even if such kits attain very high accuracy. They should not be made freely available.

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4 Clients' legal position

- Our committee does not favour the formulation of special legal regulations to govern the legal positions of clients and their families. The general regulations which already cover health care should apply.
- Genetic counsellors should give the client complete information, except when the client does not want to be (completely) informed.
- Information may be withheld from clients only when disclosing it could be expected to cause serious harm,
- Information about a client should not be disclosed to any relatives who may be involved in testing, unless either the client has given permission for this, or the disclosure of such information will prevent serious harm to the relatives themselves.
- The relatives' right to privacy and confidentiality must be respected as far as possible.
- We urge that any dilemmas which arise in connection with any of the above be resolved using the 'conflict of duties' approach; a number of stipulations have been formulated to guide this process. Adequate information provided to the clients in advance can greatly decrease the likelihood that such conflicts will develop.

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5 Genetic registries and privacy

- Records of genetic test results must meet the requirements of the Data Protection Act, and the proposed legislation on contracts for medical treatment.
- In addition to the rights conferred (or to be

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conferred) by this legislation, such as the requirement that data may be included in records or disclosed to third parties only with the express permission of the subject, the client should also have the right to have data destroyed, or made anonymous. Regulations governing genetic registries must make allowance for this right.

- We recommend that provision be made under the Data Protection Act to deal with possible problems concerning the rights of relatives whose data are included in records. The Act requires that when data on a relative which could identify him/her are included in a file, he/she must be notified when that data is first taken into the file; the relative could then be confronted with unwanted information. The proposed arrangement could be introduced as part of a further provision, envisaged in Section 7 of the Act, governing records of sensitive information.
- Our committee urges that before any information on a client is filed, the client be asked to give specific written authorization for the use of the data, for example, to help relatives, or for research purposes.
- Proposed legislation on contracts for medical treatment would permit disclosure to third parties of data which could be used to identify a person, for example for research purposes, without the permission of the subject. This provision should be interpreted and applied very restrictively, certainly for genetic information.
- Although current and proposed legislation would not limit the use of information which could not identify individuals, we believe that vigilance is needed to prevent uncontrolled use of the data released. This need is the more pressing because of the growing power of data processing systems, and the possible uses of genetic data outside the health-care system.
- Privacy provisions in the regulations governing

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genetic records should include safeguards to ensure compliance with the principle that results of genetic testing may only be used for the purpose for which the testing was done.

- Given the sensitive nature of genetic data and the growing tendency to want to use such information for various purposes, we favour the setting-up of committees to supervise compliance with the privacy provisions for genetic records.
- As long as self-regulation continues to provide adequate safeguards for the protection of privacy, the storage period for data, the use of data and the supervision of record-keeping, our committee does not see a need for statutory regulations beyond the provisions of the Data Protection Act.
- Should self-regulation prove inadequate in the future, further statutory regulation should be introduced.
- We encourage close collaboration with the patients' organizations in the process of self-regulation. This is already a practice at a number of the Centres for Clinical Genetics.

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6 Legal position of the 'donor' of body tissues/materials

- Cells and tissues obtained from clients and/or their relatives will need to be stored in cell banks, often for long periods, to be used later in diagnostic tests, for counselling clients or relatives, or for research.
- Our committee feels that a code of conduct is needed, which would respect the rights of the donor while ensuring that no unnecessary barriers are created to the use of the material for the benefit of persons other than the donor, or for research. Specific written agreements should be made at the time the samples are taken.
- The specific rights of the 'donor' include:
 - specific permission with respect to the storage and

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- use of material;
- observation of rules for information, confidentiality and privacy;
- the principle that the 'donor' can withdraw consent given previously for the use of body material (as far as it is still identifiable), such as its use for later diagnostic tests, for counselling of relatives or for research;
- the right to request destruction of material still traceable to him/her;
- the right to change his/her mind about a previously expressed wish to receive, or not to receive, any new information obtained from stored material.
- The relevant patients' organizations should be included in the preparation of the code of conduct.
- We find that it is in the first instance the duty of the cell-bank operators to provide the necessary safeguards through self-regulation. Should this prove unsatisfactory, consideration must be given to legislation.

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- 7** Mass screening
- We recommend the strict application of the criteria developed for mass health screening, to any potential genetic screening programmes.
 - An evaluation project should be built into every screening programme. The proposed legislation covering mass screening now before the Lower House provides a suitable framework for the management of genetic screening.
 - We do not consider it acceptable to screen newborns for untreatable disorders that will develop later in life.
 - Our committee urges caution in the systematic application of tests for early detection of genetic predispositions.
 - Screening of (young) adults may be considered only

when the advantages clearly outweigh the disadvantages, and when a certain number of stipulations formulated by the committee have been met. This may be the case, for example, for testing to identify carriers of certain haemoglobinopathies, or cystic fibrosis.

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Genetic testing and insurance

- Access to basic health insurance and the social security system in general must remain open to all.
- Our committee finds that further consultation with the insurers is needed to consider the complex issues involved, which extend beyond the field of genetic testing.
- We recommend prohibition of the use of genetic testing in connection with access to life and disability insurance and to personal pension schemes.
- Similarly, we urge restriction of the rights of insurers to require disclosure of known genetic information; when the coverage applied for is in keeping with the applicant's real needs, there should be no obligation to reveal the results of genetic testing done on the applicants themselves, or their relatives.
- Our committee expects that the implementation of its recommendations with respect to insurance will require new legislation.
- In relation to the provisions envisaged in Section 7 of the Data Protection Act governing the registration of sensitive data, the private sector should also be required to establish regulations governing genetic registries. In the meantime, self-regulation should continue.

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Genetic testing and employment

- We reject the use of tests of genetic predisposition as part of job-selection procedures, such as to check

for genetically determined sensitivity to toxic substances in the place of work, or the possibility of developing hereditary disorders later in life.

- If sufficiently reliable tests become available in the future, their use should be considered only in special situations, where the health interests of the person concerned, or of a third party or parties, can be demonstrated to be at stake.
- The general criteria formulated in 1989 by the Interdepartmental Working Group on Employment Medical Examination should be strengthened and supplemented by the addition of a requirement that testing may not result in unfair distinction between or discrimination against groups within the society.
- If the Working Group's recommendations, thus amended, are not implemented through self-regulation, then legislation should be introduced in the future.
- Genetic information obtained in the course of selection for employment must be stored in compliance with the Data Protection Act.
- Genetic information kept by the health officer must be filed separately from other personnel records.
- The requirement that genetic data may be included in files only with the express permission of the subject, and that they must be destroyed if the subject requests it, should be embedded in the framework of the Data Protection Act (further provision governing the registration of sensitive data in personal files). In the mean time, self-regulation should continue.
- We endorse the view of the Interdepartmental Working Group on Employment Medical Examination, that medical examinations at the time of joining collective pension and disability schemes are unnecessary and unproductive; swift action on that group's recommendations is urged.

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10 Recent developments

- The majority of the members of our committee, while urging caution in the matter, consider that experimentation on pre-implantation embryos is acceptable, subject to certain conditions.
- We have drawn up a number of substantive and procedural stipulations, which such testing should meet:
 - a pre-embryo should not be grown for any longer than is needed to answer the experimental question as formulated in the protocol, to a maximum of fourteen days after fertilization (excluding any period during which its development is halted);
 - the information to be gained by these experiments must be unobtainable by other means;
 - pre-embryos used for experimental purposes must not be implanted;
 - the opinions of a medical ethics committee and of the Central Committee on the Ethics of Medical Research of the Health Council must be sought.
- We consider that, once it has passed the experimental stage, somatic-cell gene therapy will not differ essentially from other types of medical treatment.
- As long as somatic-cell gene therapy is experimental, a number of substantive and procedural conditions should apply to its use; our committee has listed a number of these.
- We urge a moratorium on research on germ-line gene therapy as applied to human beings.

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11 Further research

Recommendations for further research are mentioned in this report; they include the following.

- Further research is needed into the psychosocial and other benefits and drawbacks of early testing for late-onset hereditary disorders, especially those for

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which no treatment is available.

- Developments in neonatal screening for Duchenne's muscular dystrophy must be followed, particularly with the expectation that treatment may become available.
- Consideration must be given to the possible need to extend neonatal screening for treatable conditions.
- Advances relevant to the screening of (young) adults, for example to detect carriers of certain haemoglobinopathies or cystic fibrosis, must be closely monitored.
- We recommend revision and updating of the Health Council's 1981 report on mutagenicity.
- The usefulness of blood-testing all, or large groups of, pregnant women to detect increased risk of neural-tube defects or chromosome abnormalities in the foetus merits further evaluation.
- Further developments in the mapping of genetic information could increase our understanding of the interactions between hereditary and non-hereditary factors leading in turn to improved methods for prevention of disease. Epidemiological studies (the execution of which must preserve the rights of the individuals studied) can make a contribution to this topic. Such studies must be monitored by medical ethics committees.
- The privacy safeguards governing genetic registries now provided by self-regulation require further examination and evaluation. Further research and discussion are needed on the use of predictive medical data in a more general sense in relation to the provision of social welfare. The measures proposed here, for insurance policies, will have to be examined in relation to the implications of growing European unity.
- We find the notion of 'individual' genetic passports unrealistic; nevertheless, further investigation of the possibilities of mass screening for carriers using

DNA techniques is recommended.

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1.2 Answering the Government's questions

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Prenatal and postnatal testing in the context of genetic counselling.

Questions related to the present position and indications for testing are covered in section 3.2.

Our committee makes fundamental objections to basing policies on the result of cost-effectiveness analyses of genetic testing and screening (section 4.2.1).

With regard to the information needed to plan future services, reference is made to the data provided in section 3.2 and the Health Council's Annual Report and Recommendations for 1990.

As to the statutory framework for quality control, we find the present situation satisfactory, and does not, therefore, propose additional measures in this area. Special focus is advocated, however, for the role of the genetic counsellor, discussed in section 4.1.1.

The psychosocial, ethical, legal and other social implications of genetic testing are covered in detail in chapter 4.

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The detection of genetically-determined late-onset disorders is referred to in sections 3.3.2, 4.1.1 and 4.3, among others.

2 GENERAL

2.1 Text of the governmental letter requesting the report. The Minister of State for Welfare, Health and Cultural Affairs requested, in a letter of 11th February, 1988, to the President of the Health Council, that an advisory report be prepared on genetic testing and gene therapy. The text of this request is reproduced below.

- Since 1977, the Health Council has issued four reports concerning clinical genetics and genetic counselling:
- Genetic Counselling (1977)
- Screening for Congenital Metabolic Disorders (1979)
- Cytogenetic Laboratories (1979)
- Genetic Counselling (1980).

These reports looked at the current state of development in these areas, and pointed out the ethical implications of application of the prenatal and postnatal diagnostic techniques then available, in the context of genetic counselling.

Postnatal chromosome analysis and prenatal testing were brought under the planning and licensing system covered by Section 18 of the Hospital Provision Act in 1984, partly on the basis of the recommendations of the Health Council. The related planning decree, outlining the need for services in this field up to 1990, and suggesting how the need could be met, came into force in 1987. The decree was only able to consider the use of pre- and postnatal chromosome analysis and postnatal biochemical and DNA testing. For the prenatal tests of the latter two types, the lack of relevant information meant that only a very rough assessment of needs was possible.

As predicted by the Health Council, recent years have witnessed major advances in clinical genetics and genetic counselling, advances which could have been considered minimally or not at all in the previous reports. In particular, further investigation is required on developments in the field of genetically determined disorders in order to determine the appropriate government policy.

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Great advances have been made in the ability to detect genetic abnormalities, including the risks of genetically-determined disorders that manifest themselves later in life. Such disorders include serious diseases of the neuromuscular system (such as Huntington's chorea) and of the kidneys (polycystic kidney disease). In the near future, genetic markers may well be identified for such common conditions as cardiovascular disease and certain forms of diabetes.

Genetic testing will not, in the future, be limited to reproductive issues, such as the risk that a couple will have a child suffering from a serious, genetically-determined condition, or the diagnosis of abnormalities in the foetus or neonate. Tests will increasingly be able to focus on each individual's risk of developing a genetically-determined condition later in life. In some cases, the condition in question will lend itself to preventive management (as in cardiovascular disease) but in others, it will be one for which, at least for the affected individual, neither preventive nor therapeutic measures are yet available (Huntington's chorea). Once genetic markers have been identified for common diseases, the question as to the value of mass screening, involving entire populations or large groups within the population, will also arise.

Finally, the development of DNA-level laboratory testing has, in principle, opened up the possibility of gene therapy - the correction of inherited abnormalities at the level of the gene - in somatic cells. Attempts are being made, for example, to introduce a 'healthy' gene into the bone-marrow cells of patients suffering from a hereditary disease of those cells (thalassaemia). Since this form of gene therapy does not alter the genetic constitution of the germ cells, it has no urgent ethical or legal implications.

The same cannot be said of germ-cell gene therapy, or the correction of genetic defects in a fertilized ovum. Although this type of therapy is still only a theoretical possibility, it may well be wise to begin to address the ethical and legal aspects of laboratory experimentation in this field. Guidelines on this have been developed in the United States and other countries.

This general summary should make it clear that developments especially in the areas of detection and prediction of genetically-determined disorders may have major social, ethical and legal consequences. One important issue concerns the use of the new techniques outside the field of individual health care, especially the extent to which information on a person's genetic constitution should be allowed to play a role in connection with his/her employment or insurance.

I should be grateful for your recommendations on this matter, and specifically for your answers to the following questions:

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- I Prenatal and postnatal testing in the context of genetic counselling.
- 1.a Which types of prenatal and postnatal testing are in current use in The Netherlands or may be used in the foreseeable future?
 - b What stage of development will be reached in such tests, in the period up to 1995 (experimental applications, development of clinical applications, routine clinical use)?
 - c What are the indications now being used, or which should be used, for the application of such testing?
 - d Does a lack of effective treatment for many genetically-determined conditions influence the indications for the use of such tests?
 - e To what extent is the use of such tests likely to be cost-effective?
 - 2.a What will be the need for prenatal and postnatal testing in the period up to 1995 (number of tests per year)?
 - b Can this need be met by the existing centres for such testing?
 - 3 For which forms of pre- and postnatal testing, on which grounds and for what period, would it be advisable to formulate a statutory regulatory framework (such as Section 18 of the Hospital Provision Act)?
 - 4 What special precautions are needed in connection with the possible adverse psychological consequences of testing on family members tested? What are the social, ethical and legal implications of these new developments, and what measures are needed to avoid undesirable effects?
- II Detection of (predisposition to) late-onset genetically-determined conditions.
- 1 Which developments now under way in the area of genetic screening may find practical application in The Netherlands in the foreseeable future?
 - 2 What is the Council's opinion on the application of these techniques, from the point of view of public health?
 - 3 What could be the eventual extent of the use in The Netherlands of predictive testing considered by the Council to be desirable?
 - 4 What are the social, legal and ethical implications of these developments, and which measures does the Council see as necessary to avoid undesirable effects of them, most notably their use outside the area of individual health care (for example, in connection with insurance or employment)?
- III Gene therapy
- 1 Which forms of somatic-cell gene therapy may find application in The Netherlands in the foreseeable future, and on what scale?

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- 2 Which special conditions should be applied in the use of such treatments?
- 3 Is it likely that in the foreseeable future, laboratory experimentation in the field of human germ line cell gene therapy will take place in The Netherlands? To what restrictions should such research be subject?
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2.2 The committee

This report was prepared by a committee created by the Vice-President of the Health Council on October 30th, 1987. At the time of completion of the report, the membership of the committee was as follows:

- Mrs HOC Roscam Abbing, Chair.
professor of health law, Maastricht
- JH van Bommel
professor of medical informatics, Rotterdam
- D Bootsma
professor of genetics, Rotterdam
- JKM Gevers
professor of health law, Amsterdam
- BCJ Hamel
clinical geneticist, Nijmegen
- WLAM de Kort
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3 HEALTH CARE AND SCIENCE

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3.1 Introduction

Congenital and hereditary abnormalities are a major source of disease and death in human beings (GR77, Sa86, GR88a, Ga89). Among infants in the first year of life, these are the main causes of death in the Western world, where the traditional causes of infant mortality - malnutrition and infectious diseases - have largely been eliminated. Heredity also plays a part in morbidity and mortality at later ages: inherited factors, in the form of susceptibility or predisposition, have been identified in the aetiology of cardiovascular diseases and cancer, the main causes of death in older people.

At least 32% of deaths among babies in The Netherlands in their first year are due to congenital and hereditary conditions. This is probably even a conservative estimate, since by no means all abnormalities which are present in babies who have died will be detected and recorded. In the age group 1-15 years, 13% of all deaths are a result of congenital and hereditary conditions.

Equally important is the impact of chronic physical or mental handicaps. Studies in Britain have shown that by about the age of seven years, just over one in twenty children display developmental delay or another handicap, and that no less than 85% of these are due to a congenital abnormality.

Four to 6% of full-term newborns display a congenital or hereditary abnormality; given the current Dutch birth rate, this translates into 7 to 10 thousand infants each year. Some of the abnormalities are very minor and cause no problems;

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others can be remedied by suitable treatment, but the majority cannot. For the last group, the consequences depend largely on the nature of the abnormality. It may result in serious disease, the patient gradually deteriorating and finally dying, or in a handicap with a limited effect on life expectancy but requiring intensive care for that individual.

Heredity can also play a role in the aetiology of the diseases of later life, including certain cardiovascular conditions, some forms of cancer, and diseases of the nervous system such as Huntington's chorea and Alzheimer's presenile dementia. In some cases heredity may play a central role, while in others it may be only a contributing factor. Each person has genetically determined susceptibilities to particular diseases, at different stages of life; advances in scientific research are providing more and more information on such susceptibilities.

All of the above factors justify the continuing growth of interest in congenital and hereditary conditions. During the last few decades, scientific research has given us an ever greater understanding of the nature of the different types of abnormalities. This understanding, and the advances in diagnostic techniques, have greatly increased the scope of application of genetic testing.

Congenital and hereditary conditions can be classified according to cause or background as follows (see also Appendix 1):

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- Conditions arising as a result of harmful external influences on the developing embryo

External influences may include diseases afflicting the pregnant woman, infections, exposure to ionizing radiation or to certain chemicals, and the use of medicines. This category probably accounts for no more than a few per cent, of all birth abnormalities. Prevention is generally possible through provision of adequate information, and with support

during subsequent pregnancies.

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- Chromosomal abnormalities

Chromosome abnormalities usually arise during the formation of the germ cells, or during the early divisions of the fertilized ovum. The likelihood of their appearance increases with maternal age; it is also augmented by exposure to external factors such as radiation or certain substances. At least half of all spontaneous abortions result from abnormalities of the embryo, but despite this natural selection, still one in 200 newborns - about 900 babies each year in The Netherlands - has a chromosomal abnormality. These usually result in multiple congenital malformations, mental handicaps or disorders of sexual development or function. A small fraction of chromosomal abnormalities is inherited from one of the parents, who is thus a healthy carrier. The risk that a subsequent child will be similarly affected depends very much on the nature of the abnormality.

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- Genetic mutations

Genetic mutations, which can produce hereditary metabolic and other disorders, involve molecular 'errors' in the DNA, which have arisen during the formation of germ cells, or during human evolution. Recessive mutations (see also Appendix 1) can be passed unnoticed from one generation to another; the abnormality will manifest itself only when two carriers of the same mutation produce offspring. Then there is a 25% chance that their child will suffer from the hereditary disorder. In contrast, dominant mutations nearly always produce disease symptoms, although not always before the individuals concerned have produced children. Patients have a 50% chance of transmitting the mutation, and the disorder, to their children. The number of disorders known to be caused by genetic mutations has now reached more than four thousand, affecting between 0.5 and 1.5% of all live births (McK88). Some of these disorders appear only in later life. In The Netherlands, about 1,750 patients are affected by such

disorders every year.

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- Interactions between often unknown external factors and genetic predisposition

Abnormalities in this category affect 2.5-4% of all newborns, familiar examples including spina bifida, congenital heart defects and clubfoot. when one child has been born with such a malformation, there is an increased probability that future children will be similarly affected. As noted above, interactions between external factors and genetic predisposition are thought to play an important role in the aetiology of several diseases arising later in life.

Table 1 shows the incidence and the risk of recurrence of the best-known congenital and hereditary conditions.

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3.2 Genetic testing in Centres for Clinical Genetics

In this section, the various methods for diagnosis of congenital and hereditary disorders before and after birth are discussed, including the indications for using the tests, the types of tests, and the counselling and support practices customary in this country. The Foundations for Clinical Genetics are important in this system; they operate eight centres in The Netherlands. Appendix 2 describes the centres' origins and activities, and their arrangements for cooperation,

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3.2.1 Postnatal chromosome analysis

Chromosomal abnormalities can be detected by the examination of cell chromosome patterns under a light microscope; this testing is done after birth, on children or adults. Usually a blood sample is taken, from which certain of the cells (the lymphocytes) are incubated in a culture medium, in which they will divide. After a brief period of culture, it is possible to analyze the chromosome patterns of the cells. This testing is used to obtain early diagnosis of abnormalities in often very young patients, so that they can be given the best care, and to avoid unnecessary testing

Table 1. Incidence and risk of recurrence of congenital and hereditary disorders (international data)

	Incidence live births	Risk of recurrence
CHROMOSOME ABNORMALITIES		
- sex chromosomes - males	1: 400)	
- sex chromosomes - females	1: 700)	1-2%
- autosomal trisomies	1: 700)	
- balanced translocations (carriers)	1: 500) }	5-100%
- unbalanced and structural abnormalities (patients)	1: 2 500) }	
DISORDERS OF METABOLISM		
<u>dominant</u>		
- familial hypercholesterolemia	1: 500)	
- Huntington disease	1: 5 000)	50%
- Marfan syndrome	1:20 000)	
<u>autosomal recessive</u>		
- cystic fibrosis	1: 2 500)	
- phenylketonuria	1: 5 000)	25%
- mucopolysaccharidosis	1:25 000)	
<u>X-linked</u>		
- Duchenne muscular dystrophy	1: 7 000)	25%
- hemophilia	1:10 000)	(sons 50%)
MULTIFACTORIAL MALFORMATIONS		
- spina bifida	1-4: 1 000	1-6%
- anencephaly	0,5 - 4: 1 000	1-5%
- congenital heart defects	6-8: 1 000	1-4%
club foot	1-6: 1 000	2-8%
cleft lip/palate	0,5-1,5: 1 000	3-6%

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later. In addition, the parents and other family members can be advised as to the risk of recurrence in a subsequent pregnancy. Particularly important is the early identification, through family studies, of carriers of 'balanced' chromosomal abnormalities (see Table 1), which do not produce signs of disease in the carrier. This information can help couples to reach decisions even before there is a question of a first pregnancy.

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The indications for postnatal chromosome analysis are the following:

- repeated spontaneous abortion or premature birth - in which case, both father and mother should be tested to determine whether they are carriers of a chromosomal abnormality;
- the presence of malformations in a neonate, whether or not it was born alive;
- the presence of combinations of abnormalities, as in Down's syndrome, which suggest a chromosome abnormality;
- abnormal sexual development;
- suspicion that the individual may be a carrier, based on the presence among the family or relatives of a patient with a possible chromosome abnormality;
- suspicion of an X-linked mental retardation; about one-ninth of all cases of mental handicaps among males are associated with a fragile region on the X chromosome. Often the mother is a carrier, in which case, sons have a nearly 50% chance of mental retardation, and daughters have a 50% chance of being carriers. Some of the female carriers also have a slight to moderate mental handicap. Family studies aimed at identifying carriers are therefore of great importance if this cause of mental retardation has been detected in a family;
- suspicion of a hereditary disease in which chromosomal breakage is common.

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Besides these tests, cytogenetic analysis of bone-marrow blood cells is done in connection with the diagnosis and treatment of patients suffering from leukaemia and other myeloproliferative conditions.

The results of the postnatal chromosome analyses carried out in The Netherlands in 1986 are shown in Table 2. A comparison of results from the different centres reveals that the total percentage of chromosomal abnormalities detected varied little, between 20 and 30%. Because screening procedures have demonstrated that one in 200 neonates has a chromosome abnormality, the number of new patients and carriers found each year should be about 900, but as can be seen in Table 2, there were 1,150 in 1986 (excluding bone-marrow analyses). This discrepancy can be explained by a catching-up effect, in which previously unidentified chromosomal abnormalities in handicapped persons in institutions are detected; this added number is likely to decrease rapidly.

In recent years, the number of requests for chromosome analysis has stabilized; the total is unlikely to rise above 6-7,000. Thanks to the availability of laboratory facilities, and to the close cooperation between the Centres for Clinical Genetics and doctors working in other areas (paediatricians, general practitioners, doctors for youth and for the handicapped), most of the patients and many of the carriers in this country have been identified. This facilitates the provision of genetic counselling in good time.

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3.2.2 Biochemical tests

Diagnosis of a hereditary condition due to a single-gene defect requires different techniques than for chromosome analysis. Certain of these conditions consist of deficiencies in one of the proteins called enzymes, which play a vital role in metabolic processes. Diagnosis may then be by metabolic testing, or determination of the level of the

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products of those metabolic processes, which in the case of deficiency may be low or absent.

Alternatively, the tests may determine whether the enzyme itself is present. Both types of test have been reimbursed by the health insurers for the past ten years. The indications for their use in children are unexplained developmental delay, or any symptoms suggesting a hereditary metabolic or other disorder. Most of the laboratories doing these tests are attached to paediatric teaching hospitals; they test blood, urine, or in some cases other body substances, for abnormal metabolic products; this is usually by chromatographic and electrophoretic separation. More complex analytical techniques, such as mass spectrometry, can provide more detailed information on the molecular nature of an abnormal metabolite. On the order of 7,000 new cases - mainly children - are tested each year (that is, up to 1000 in each of the eight centres). Additional testing is done on patients in whom a hereditary metabolic disorder has already been detected; when they are being treated with diets or drugs, follow-up testing is needed to ascertain whether the treatment regime needs adjustment. Checking treatment success by awaiting the reappearance of symptoms would be dangerous, since delay can lead to irreparable damage in the form of physical or mental handicaps.

As is shown in Table 2, the eight centres together carried out metabolic tests on 4,000 people in 1986; hereditary disorders were detected in about 5%, and non-hereditary metabolic disturbances in about 20% of the cases. The latter were usually associated with nutritional deficiencies or an infectious disease and disappeared either spontaneously or after treatment.

More than 4,000 hereditary disorders are already known, most of them rare, and caused by a single-gene defect. Approximately one hundred of these can be diagnosed by tests which detect characteristic abnormalities in the blood or urine.

For a more precise diagnosis, it is necessary to demonstrate, in addition to the effect of the abnormal gene, that this is due to the specific genetic defect, in the form of the abnormal enzyme (protein). Enzyme testing is now possible for about 350 hereditary disorders; these analyses require specific expertise which is available only in certain university laboratories (since 1985, there is also a specified fee structure for these tests). This kind of biochemical testing usually involves the spectrophotometric, fluorometric or radiometric analysis of red or white blood cells, samples of tissue (organ biopsies) or cultured skin cells (fibroblasts). In some cases, not only patients affected with a hereditary disorder but also healthy carriers can be detected with these methods. The data in Table 2 show that in 1986, the eight centres tested nearly 1,000 cases, and identified a genetically-determined enzyme deficiency in slightly more than 200 of them. Several hundred carriers of an abnormal gene were also found (recessive mutations).

Early diagnosis is vital in the case of these hereditary metabolic disorders. Offspring of carriers have a 25% or 50% chance of being affected, and parents with one affected child are at risk for having more children with the same disorder. Early diagnosis offers them the possibility of avoiding having affected children, if that is their preference.

It is not possible, at this point in time, to express exactly the capacity in this country for early diagnosis of inherited metabolic disorders. The state of development is less advanced than in the case of chromosome analysis, although there has been more progress in The Netherlands than in most other countries. This is due not only to the laboratory expertise and facilities that have been developed, but also to the interest in metabolic disorders on the part of paediatricians. It appears that the knowledge of other medical specialists on this subject, and on the scope for early diagnosis, is not yet optimal.

Table 2 Results of the work in the Foundations for Clinical Genetics (1986)

	number of persons tested	number of abnormalities found	number of births prevented*
TESTING OF INDEX PATIENTS AND CARRIERS			
- chromosome analysis	5800	1150 (20%)	50-100
- metabolite studies	4000	220 (5%)	55-110
- enzyme tests**	940	210 (22%)	50-100
COUNSELLING (complex issues)	2260	1/4 no increased risk 1/2 risk 1-15% 1/4 risk 15-50%	175-350
PRENATAL TESTING	5150	180 (3,5%)	180-360

* By deciding to have no (further) children or by abortion

** Excluding the University Hospital in Nijmegen

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3.2.3 Prenatal testing

Prenatal testing - amniocentesis, chorionic-villous sampling (CVS), and tests on foetal blood from the umbilical cord - can be used to determine the sex of a foetus, or to detect chromosomal abnormalities or an increasing number of metabolic disorders (see also RCP89). Amniocentesis is done at about the sixteenth week of pregnancy, CVS at the tenth week; umbilical-cord puncture is not possible until after the seventeenth week, and demands considerable skill and experience.

The main indications for prenatal testing are:

- pregnancy in older women (since 1985, tests have been offered in this country to all pregnant women over the age of 35);
- a previous child with a chromosomal abnormality;
- the father or mother carries a balanced chromosome rearrangement;
- the mother carries a sex-linked hereditary disease (such as X-linked mental retardation);
- an increased risk in the foetus of a neural-tube defect (e.g. spina bifida or anencephaly); that is, when a previous child or the mother or father has the condition, or when there are one or more patients among close relatives. This abnormality can only be detected by determining the concentration of alpha-foetoprotein in the amniotic fluid in the 16th week of pregnancy;
- an increased risk in the foetus of a hereditary metabolic disorder detectable in amniotic fluid cells; that is, when a previous child has the disorder, or either parent has been identified as a carrier;
- an increased risk in the foetus of a hereditary disorder detectable by DNA analysis (e.g. cystic fibrosis, Duchenne's muscular dystrophy, haemophilia); that is, when the disease occurs in other members of the family;

- use by the mother of medicine which may damage the foetus;
- a high probability of a chromosomal abnormality in the foetus based on structural abnormalities detected ultrasonographically.

The results in Table 2 show that of the more than 5,000 tests on pregnant women done in the Centres for Clinical Genetics in 1986, foetal abnormalities were found in nearly 4%. In most cases, the prospective parents chose to terminate the pregnancy. In the other 96%, the test was able to allay the parents' fears. In the following sections, we review the types of genetic testing used in this context.

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Prenatal chromosome analysis

Chromosomal anomalies can be identified in the foetus by analyzing the chromosome patterns of cells from the amniotic fluid or the chorionic villi; all eight Centres for Clinical Genetics in The Netherlands carry out such tests. It is not precisely known how many of the women for whom such testing would be appropriate actually undergo it, but it is estimated that about one-half of all pregnant women over the age of 35 request testing. Were specific advice to be provided, the proportion might well rise to 85%.

Chorionic villus sampling, which can be done earlier in pregnancy than amniocentesis, has increased the acceptability of prenatal testing for some people. At the beginning of the 1970s Russian, Scandinavian and Chinese scientists proposed chromosome analysis on chorionic villi, which involves removing a sample of tissue from the developing placenta between the 8th and the 10th week of pregnancy. A few years ago, the Italian researchers Brambati and Simoni demonstrated the safety and reliability of the technique (Br86). Since then, a growing number of centres world-wide has built up considerable experience of the method. The advantage of using cells from the chorionic villi is that their rate of division is rapid, which permits chromosome analysis without

time-consuming culture procedures. The result is usually available within a few days to a week, at most two weeks from the time of sampling. When an abnormality is found, the pregnancy can be terminated, if the parents decide on this, by suction curettage. This can be done at an outpatient clinic, and is not only medically less radical but also, often, emotionally less stressful for the patient than a later termination (for example, following amniocentesis). There may also be an advantage in the fact that other people, including family and friends, need not come to know of the pregnancy.

From the 12th week of pregnancy, it is also possible to sample placental tissue for the purpose of chromosome analysis, through a puncture of the abdominal wall. The results of such a 'late villus testing' are also available within a few days.

Both types of villus testing have the advantage over amniocentesis of providing results quickly. Not only is the latter performed later (in the 16th week), but a further two or three weeks are needed to culture the cells and to complete the chromosome analysis.

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Prenatal biochemical analysis

Many inherited metabolic disorders, and diseases due to defects in structural proteins, such as haemoglobinopathies, are detectable before birth by amniocentesis, chorionic-villus sampling (CVS) or foetal blood testing.

The potential of CVS has been greatly expanded by the advances made in DNA analysis (see below); all conditions which can be identified through 'informative' DNA studies in a family (see Table 4) can now be diagnosed in the foetus by CVS. Amniocentesis is now really only necessary for the determination of alpha-foetoprotein (AFP) levels, supplemented when necessary by acetylcholinesterase typing, in the diagnosis of neural tube defects.

Continuing research is identifying the molecular defects responsible for more and more hereditary diseases. The

vast majority of the cases involve diagnosis by detection of a genetically-determined enzyme deficiency, through comparison of the biochemistry of cultured amniotic cells with normal control cells, and with skin cells (fibroblasts) from one or more patients and carriers. The cellular material needed for comparison must be available at the time of prenatal testing, which necessitates the maintenance of a cell bank. Prenatal testing for hereditary metabolic disorders in The Netherlands is centralized in Rotterdam, where a cell bank comprising several thousand cell lines collected over the years is stored in liquid nitrogen. Detection of disease by DNA analysis requires cellular or DNA material from the patient, the parents, and in some cases from other relatives.

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Prenatal ultrasonic detection of malformations in the foetus

(Relevant here is a Health Council report, issued in 1990, on the application of invasive diagnostic and therapeutic techniques to the unborn child; this topic is covered only briefly here.)

Various malformations, some of them severe, can be detected with chromosomal, biochemical or DNA analysis of chorionic villus samples or amniotic fluid cells; they are also associated with raised AFP levels in maternal blood serum and in amniotic fluid. It is estimated that between 1 and 2% of newborns are affected by structural abnormalities of the brain (e.g. hydrocephalus), face, heart, urinary tract, digestive tract, skeleton or limbs. Early detection of some of these abnormalities has been made possible by the greatly improved resolution offered by ultrasonography and the general availability of the technique. The primary reason to use ultrasonography is failure of the pregnancy to progress normally, in the absence of previous indications for that; for example, when the uterus is growing too slowly or too fast, or when there is bleeding or other complications. Ultrasonographic detection of a structural abnormality may provide grounds for further testing (checks for abnormalities

in other organs, chromosome analysis) to help clarify diagnosis and prognosis. Ultrasound scans may also be offered to pregnant women already known to be at risk of carrying a child with a structural abnormality (for example, after the birth of a previous child with such a condition).

Ultrasound scans generally reveal structural abnormalities between the 16th and 24th weeks of pregnancy, and sometimes later; detection of an abnormality at such a late stage can create serious problems with respect to termination. Transvaginal scanning, now being introduced (EUR89), may make it possible to detect malformations earlier in the pregnancy.

The early detection of structural abnormalities in the foetus using ultrasonography requires special expertise which in The Netherlands is available in only a few centres. Effective cooperation between the general practitioner and a range of medical specialists is therefore necessary. Ultrasound scanning in the case of increased risk of congenital malformations is not yet covered by the compulsory health insurance scheme.

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3.2.4 Genetic counselling

In recent years, considerable progress has been made in the area of genetic counselling and support in The Netherlands. Since 1985, 'complex' genetic counselling (that is, requiring the expertise available in the Centres for Clinical Genetics) has been available under the health insurance schemes.

A Health Council report issued in 1977 estimated the number of people in The Netherlands for whom genetic counselling would be appropriate at between 15 and 20 thousand per year (GR77). Counselling is mostly requested by parents who already have a handicapped child, or couples who fear that their children may be at risk because of the presence in the family of congenital or hereditary disorders or handicaps. Adults who are themselves affected with a congenital or hereditary condition, and who want to have children, may also

request counselling, as do many couples who fear that they may be at risk of having a handicapped child on other grounds (consanguinity, exposure to environmental hazards, use of medicines, etc.) In general the questions asked can be answered by a general practitioner, or by a specialist in the field encompassing the condition.

A doctor treating a child with a congenital or hereditary condition has an obligation, in addition to caring for the patient in question, of informing the parents as to their possibly increased risk in a subsequent pregnancy, and of possible preventive measures. In practice, however, many doctors do not yet know enough about patterns of inheritance, risks (including the risk of recurrence) and preventive measures. Moreover, they often lack the time needed for a full discussion of what are often, for the parents, complex and emotionally-charged problems.

One of the functions of the Centres for Clinical Genetics is to provide general practitioners and specialists with the information they need to respond to requests for guidance. In some cases, those enquiring may need to be referred to a Centre for Clinical Genetics; a preliminary estimate suggests that this may apply to about 20% of the queries received by doctors, i.e. 3-4,000 each year. Referral to a centre is indicated when complex genetic testing is needed (in the case of conditions with multiple or variable symptoms), for calculations of probability, for complex biochemical or DNA analyses and for pedigree studies. Sensitive support is also needed for those facing difficult choices and dealing with difficult problems; most of the Centres employ social workers or clinical psychologists for such situations. The eight Centres currently handle 2-3,000 enquiries of a complex nature every year (see Table 2). Approximately half of those seeking advice are referred by medical specialists, and about one third by general practitioners. A limited number of people approach the Centres without having been referred, because they have not been able to obtain answers to their questions through the normal

channels. Research has shown that such persons have about the same risk of having a handicapped child as do those referred by a doctor.

The reasons people give for seeking genetic counselling are summarized in Table 3. The most important are that a previous child was affected by a congenital or hereditary condition, or that one or more relatives are affected. The diagnosis in more than 30% of the index patients (those giving rise to concern in others) is mental impairment, or another mental or neurological condition. Combinations of abnormalities (syndromes) based on a chromosomal anomaly, and disorders of the skeleton or connective tissue are other frequently-encountered diagnoses in the index patients.

Accurate diagnosis is the main basis for sound genetic counselling. Supplementary tests on family members or extensive pedigree studies may also be needed. Once all the data have been collected, the significance of the diagnosis, the pattern of inheritance and the risk of occurrence/recurrence are discussed with the client, usually in two interviews. Attention is also given to the possibility of preventing the birth of a child with the abnormality in question. In some cases, the clients are given psychosocial guidance while the data are still being collected; in others, this is not necessary until choices have to be or have been made. The decisions involved here are often extremely important and difficult ones: not to have children of one's own, for example, or the choice between adoption and artificial procreation using donor sperm or ova. Other possibilities are the acceptance of the increased risk of a handicapped child, or natural pregnancy with the option of testing and, if desired, abortion. Many factors influence these choices, including the seriousness of the condition in question, whether or not the couple already have one or more healthy children, the size of the risk of abnormality in the

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Table 3 Reasons for requesting genetic information (data from the Centres for Clinical Genetics in The Netherlands, collected by Dr. BGA ter Haar) (1981)

Parents already have a child with a congenital or hereditary disorder	37%
One or more family members have the disorder in question	35%
One of the parents-to-be has the disorder in question	19%
Partners are relatives	2%
Others reasons	7%

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offspring, the parents' age and social circumstances, and of course their religious and moral beliefs.

Although there has been little research following up the effects of genetic counselling in The Netherlands, both national and foreign data show that a large proportion of couples at risk opt not to have children. This choice is made by between 50 and 85% of those facing a relatively high probability (such as 25%) of having a child with a serious abnormality; even when the risk is smaller (of the order of 3-10%) an impact can clearly be seen on decisions about reproduction. The decision not to have children is nevertheless a very difficult one for many people, as is evident from the large proportion (83%) of at-risk parents who choose to go ahead with a further pregnancy when prenatal diagnostic tests are possible. When there is no prenatal test, thus eliminating this option, fewer parents decide to take a chance with a further pregnancy (52%).

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3.3 Recent advances in genetic testing.

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3.3.1 DNA analysis

Since the mid-1970s, recombinant DNA technology has given a new dimension to genetic testing (Be85, Ho86, Ca87, Ge87a, Ge87b, OTA88, GR88a). Methods have been developed to determine the DNA code of genes, and it has become possible to identify pathological mutations in a code using specially-developed DNA tests. These are, however, as yet available for only a limited number of inherited conditions, including certain of the haemoglobinopathies (e.g. sickle-cell anaemia, rare in this country), haemophilia, alpha-1-antitrypsin deficiency, and recently, Duchenne's muscular dystrophy (Ko87). The gene responsible for cystic fibrosis has also recently been identified, thus making it possible to diagnose this relatively common disease by direct detection of the DNA mutation (albeit not yet in all cases). The discovery of this gene may also open up the possibility of mass screening for carriers (see also section 3.3.3).

In the case of some hereditary diseases for which the responsible gene has not yet been identified, it has been possible to find characteristic DNA variations in the immediate vicinity of the abnormal gene (generally on either side). These regions can serve as markers for the presence or absence of the gene in a family. The technique to find such markers, known as restriction-fragment length polymorphism (RFLP) analysis (Sh86, Do87), is currently used in the diagnosis of such disorders as polycystic kidney disease, Huntington's chorea and muscular dystrophy (a disease of the muscles). This procedure is only useful within a family. The first step is to determine the markers associated with the abnormal gene, and this preliminary testing must include family members both with and without the hereditary condition. Such an analysis depends on the cooperation of those concerned; often cell or tissue samples from several people are required for the extensive testing. If no cell or tissue material was retained after the death of the only collaborating patient, the procedure can no longer be used. Continuing collaboration sometimes entails a considerable emotional burden on the family members, both healthy and affected. It is, however, expected that it will eventually be possible to pinpoint the defective genes responsible for many of the conditions currently diagnosed using this method; then the extensive testing of relatives would no longer be necessary.

The hereditary conditions which can at present be detected by DNA analysis are listed in Table 4. The number is likely to grow rapidly over the next few years, thanks to progress in the mapping of the entire human genome (all of the genes together) (Sh86, Do87). There are already maps with markers for each chromosome, which makes it easier to locate as yet unknown abnormal genes. The analysis of separate genes has been improved since it has been possible to study relatively large fragments of DNA, because of new separation techniques and new methods of inserting these fragments into yeast cells. Once these have been cultured, accurate analysis

Table 4 Inherited disorders detectable by DNA analysis*

Acatalasemia
 Adenosine deaminase deficiency
 Adrenoleukodystrophy
 Adult-onset polycystic kidney disease
 Agammaglobulinemia, X-linked
 Amyloid polyneuropathy (familial)
 Antithrombin III deficiency
 Alpha-1-antitrypsin deficiency
 Alzheimer disease
 Apolipoprotein deficiency (A1, B, C3)
 Becker muscular dystrophy
 Charcot-Marie-Tooth polyneuropathy
 Choroideremia
 Chronic granulomatous disease
 Congenital adrenal hyperplasia, 21-hydroxylase deficiency
 Cystic fibrosis
 Duchenne muscular dystrophy
 Ehlers-Danlos syndrome
 Familial hypercholesterolemia
 Fragile X syndrome
 Gonadal dysgenesis, Y chromosome deletion type
 Hemochromatosis
 Hemophilia A and B
 Huntington chorea
 Hypohydrotic ectodermal dysplasia, X-linked
 Inherited growth hormone deficiency
 Lesch-Nyhan syndrome
 Lymphoproliferative disease, X-linked
 Myotonic dystrophy
 Neurofibromatosis
 Norrie disease
 Oculocerebrorenal syndrome of Lowe
 Ornithine decarboxylase deficiency
 Ornithine carbamoyltransferase deficiency
 Osteogenesis imperfecta (type I)
 Phenylketonuria
 Porphyria
 Retinitis pigmentosa, X-linked
 Retinoblastoma
 Retinoschisis
 Severe combined immunodeficiency disease, X-linked
 Sickle cell anemia and other hemoglobinopathies
 Thalassemia, alpha and beta
 Von Willebrand disease
 Wilms tumor aniridia complex

* This list is not exhaustive. Adapted from Os88

can be done. Computers are also used to determine the specific sequences of the DNA bases - 'building blocks' of the genes.

Another major technical advance in the field of DNA analysis is the polymerase chain reaction (PCR) (Sa85, Ed88), with which specific DNA fragments (or messenger RNA transcribed from them) can quickly and accurately be detected. This technique is based on the replication of the DNA or RNA fragment during several steps in a chain reaction; amplification by a factor of over a million is possible.

These technical advances will rapidly expand our knowledge of the organization and function of genetic material, the loci of disease genes and transmission within families. The early detection of new genetic anomalies (spontaneous mutations), for example using chorionic-villus sampling during pregnancy, is, however, not likely, since it would require the charting of the structure of all 100,000 of the foetus' separate genes - an impossible task.

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3.3.2 Predictive testing for late-onset hereditary disorders

Advances in the field of DNA analysis also offer the possibility of detecting genes which will produce (serious) disease symptoms or death only in middle or old age. Such presymptomatic diagnosis, which could be done before or after birth, was until recently virtually impossible, with the exception of assessing cholesterol levels when there was evidence of familial hypercholesterolaemia.

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Untreatable disorders

The knowledge that one is going to develop a serious and untreatable disorder at some future time would no doubt be a great emotional burden. While some people may opt for the certainty of knowing, in the case of some conditions, many families may prefer not to use the new diagnostic techniques. Effective psychosocial support for those at risk, considering the wishes of those seeking advice both during and after

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predictive diagnosis, must be a required condition for the implementation of such DNA testing. For example, a person with a 50% chance of becoming afflicted with a dominantly-inherited disease (such as Huntington's chorea) may not wish to know his/her own prognosis, while nevertheless wanting to exclude any risk to an unborn child through the use of DNA analysis. If the unborn child is found to share a chromosome with a grandparent who has suffered or is suffering from the disease, then the child has a 50% chance of developing the disease as well. If the prospective parents are unwilling to accept this uncertainty, they can opt for termination (Qu87).

Psychosocial problems also arise in connection with hereditary conditions such as Alzheimer's disease, which severely impair mental function in old age. It is now known that the form of the condition which arises in middle life (after the age of 45) is often due to a dominant abnormal gene, probably located on chromosome 21. Were it possible to identify a diagnostically useful marker gene within a family, the probability that family members or potential offspring would inherit the condition could be calculated.

For the time being, the localization of the gene for Alzheimer's does not offer a reliable means of prenatal diagnosis for prediction, but it is expected that a reliable technique will be developed in the future.

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Treatable disorders

It is possible, in the case of some dominantly inherited forms of cancer, to use DNA analysis to distinguish between carriers and non-carriers of the abnormal dominant (or X-linked recessive) gene. This is to the benefit of carriers, who can then be examined regularly and if necessary, given preventive treatment. Carriers can also transmit the condition to their children.

Even when treatment is available, the application of such DNA analysis must be preceded by a careful assessment of the psychosocial advantages and disadvantages. Although knowing in advance that one will contract a disease may be

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emotionally stressful, DNA analysis also offers the possibility of early reassurance that one is not going to be affected by that condition. This would also eliminate the need for regular testing over a period of many years. A good example of this is the case of polyposis coli, a dominantly-inherited form of bowel cancer: those at risk, between the ages of 15 and 50, must undergo full examination of the large intestine (coloscopy) every one or two years. Increased life expectancy thanks to early treatment is an important motive for participating in a DNA analysis programme, although there are as yet only a few hereditary forms of cancer (tumour syndromes) for which early diagnosis and treatment can greatly improve life expectancy.

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3.3.3 Mass screening for carriers

There may be some value in screening the general population for a limited number of abnormal genes which cause common diseases. A good example of a disorder for which screening might be appropriate in this country is cystic fibrosis (CF), mentioned in section 3.3.1. An estimated one in 36,000 people in the Netherlands suffers from CF, and one in 30 carries the gene (Ka75, Ga89). A screening programme for carriers would identify couples in which both are carriers. Their children would have a one-in-four chance of being affected with CF, so that the woman would be a candidate for prenatal testing during pregnancy.

Mass screening must meet high technical and organizational standards, especially in the case of screening for hereditary conditions, given the potentially far-reaching social consequences (see Chapter 4).

The technical conditions which must be met before any programme of mass screening for carriers can be considered are as follows:

- The abnormal gene(s) in question must be detectable using relatively simple but reliable techniques.
- It is preferable that the detection method

demonstrates the presence of the abnormal gene directly, rather than via markers. Although marker-based approaches are suitable for testing within families with one or more patients, they do not lend themselves to mass screening. In the general population, it is at best possible to determine statistically and approximately which DNA markers might be associated with a disorder, or an abnormal gene.

- The tests must produce reliable results suitable for use in genetic counselling of individuals.

Finally, the tests must be done and supervised within an organization which has all of the necessary expertise in both genetics and individual genetic counselling. The obvious course would be to restrict the application of such tests to the Centres for Clinical Genetics.

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3.4 Looking ahead

In this section, we examine developments in genetics which have been receiving increasing attention because of their potential impact on the practice of medicine, as well as their far-reaching social and ethical implications.

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3.4.1 Gene passport and gene map

The much-discussed notion that we might soon have individual 'gene passports' (We89a), containing information on all of our genes, has no basis in reality; it is not technically feasible and it would serve no useful purpose. Work is in progress in several countries on the mapping of the entire human genome (Sh86, Do87), which is distinct from the preparation of individual genetic charts. Proponents of the exercise argue that this will facilitate the localization of genes responsible for presently unclear genetic conditions, thus advancing our understanding (and perhaps the prospects for treatment) of these diseases (GR88a). Most of the DNA in the genome does not code for hereditary traits; the

approximately 100,000 genes which human beings are known to have are estimated to account for only 5 to 10% of human DNA, the function of the remainder being as yet unknown. Elucidation of the letter code of this remainder will no doubt reveal astonishing information (GR88a).

Should we believe or fear that gene maps might make it possible in the future to manipulate human characteristics such as behaviour, intelligence or musicality? The answer is no, because such traits are determined not only by genetic make-up but also by upbringing and environment; knowing the loci of human genes which merely code for particular proteins will contribute little to our understanding of this complex interplay. Mapping the human genome could well help to identify pathogenic changes in the genetic code, however, and this information could then be applied in response to individual requests for information (see also section 3.2.4.).

Thus far, only approximately one-tenth of the human genome and a quarter of one per cent, of all human genes have been identified and described. Even in the case of the most intensively-studied chromosome, the X-chromosome, little more than one per cent, of the DNA has been mapped.

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3.4.2 Diagnostic tests on the pre-embryo.

In section 3.3, the new techniques of prenatal testing, such as the application of DNA analysis to the foetus, were discussed. Another form of testing, which is the object of much attention recently, is the direct diagnostic investigation of the pre-embryo, outside the uterus (Ku83, GR86, Le86, Mc87, Br89, Ha89, We89b, We89c). (The term 'pre-embryo' is here used to denote approximately the first fourteen days of embryonic development, i.e., the period before implantation in the womb.) This technique has been under development for some time; it may, in the future, enable the checking of pre-embryos for hereditary abnormalities, so that only those free of them are implanted in the womb (selective implantation). Theoretically, such a procedure could also be followed for the purpose of gene therapy in the

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pre-embryo, or in the ovum or sperm cell. This possibility, which is still purely theoretical, is considered again in section 3.4.3.

A possible advantage of pre-implantation diagnosis is that some women may find selective implantation emotionally or morally more acceptable than the current practice of implantation followed by prenatal testing, possibly followed by termination. Were pre-implantation testing to become possible, prospective parents otherwise seriously at risk of having a handicapped child could be offered the certainty of eliminating this risk from the beginning of the pregnancy.

The main technical drawback to pre-implantation testing is that it is, at least at present, restricted to in vitro fertilization (IVF). (In theory, it would be possible to test embryos produced by in vivo fertilization, then removed from the womb by lavage. But since this procedure can lead to serious complications, notably ectopic pregnancy, it will not be considered further.) The link with IVF means, among other things, that the woman must undergo hormone treatment to ensure that sufficient ova are produced. Moreover, the probability that an IVF pre-embryo will develop into a child is still relatively low, not more than about ten per cent. Pre-implantation diagnosis, even if it were a safe and reliable procedure in itself, would therefore only be a safe alternative to current types of prenatal testing if the chance of a successful pregnancy following selective implantation were to improve considerably.

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Research

Pre-implantation diagnosis is still at a very early stage of development. The first publications in this field appeared only last year; they demonstrated the possibility of DNA testing for inherited abnormalities in the pre-embryo, using the PCR (polymerase chain reaction) technique (see section 3.3.1).

Interest is currently focused on two diagnostic approaches in particular. The first involves taking one or

more cells from the very early pre-embryo (at the four-, eight-, or sixteen-cell stage) and allowing it/them to develop further. Because these cells are totipotent (i.e. can give rise to cells of all types), this effectively means the production of a second, genetically-identical, pre-embryo. The process is known as embryo-splitting. Diagnostic tests are then carried out on one of the two. The second method involves testing the cells of the trophoblast of a slightly more advanced pre-embryo (the trophoblast will give rise to the tissues external to the embryo, such as the placenta). It is not yet known whether the removal of groups of cells damages the pre-embryo, reducing the chance of implantation in the uterus, or increasing the chance of spontaneous abortion or the development of a child with a congenital abnormality.

Research is needed to develop accurate pre-implantation test methods and to determine their safety and reliability. Such research is going on in a number of centres all over the world, making use in the first instance of experimental animal embryos. Research is also under way on human pre-embryos, using spare embryos obtained from couples making use of IVF (the procedure often results in more fertilized ova than are needed for implantation).

The development of reliable pre-implantation tests will probably also require examination of pre-embryos from couples who are genetically at risk. In principle, such testing could form a regular part of the treatment offered in response to specific requests for assistance. In the early stages, it will clearly not be possible to give a definitive answer with respect to the presence or absence of a genetic abnormality. Given the purpose of pre-implantation testing, the pre-embryo examined in this way would no longer be regarded as suitable for implantation.

Evidence on the safety of the technique, as to whether removal of cells from the pre-embryo can cause abnormalities, will probably need to be obtained mainly from animal experiments. It is not clear, at this point in time, to what extent it will be necessary to produce human pre-embryos in

order to ascertain the safety of the technique; the possibility that this will be the case cannot be excluded.

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3.4.3 Gene therapy

The growing understanding of the structure and function of genes, and the laboratory techniques developed for their isolation, replication and transfer to other cells, have prompted speculation about the possibility of correcting inherited abnormalities (Fr87, He87, Le87a,b). Treatment for a hereditary condition could then include the addition of a 'healthy' gene or genes to the patient's cells or tissues.

A distinction must be made between two types of gene therapy:

- somatic-cell therapy, in which correction is done in somatic (non-germline) cells, including those of the bone marrow (involved in blood production), liver or skin, and
- germline-cell therapy, in which correction is done in cells of the germ-line, i.e. egg or sperm cells, or the totipotent cells of the embryo.

In somatic-cell gene therapy, the correction in the genetic material affects only the patient, and is not passed on to his or her progeny, while in germ-line cell gene therapy, the correction would be passed on to later generations.

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Somatic-cell gene therapy

Extensive research has already been done in this field. The necessary intermediate steps have been tested in the laboratory, and although the therapy has yet to be tried on patients, both American and European safety protocols have already been drawn up for this purpose (EMRC88).

The purpose of somatic-cell gene therapy is to improve the functioning of cells in one or more of the patient's tissues, by introducing one or more 'healthy' copies of the abnormal gene. This form of therapy is applicable only to

recessively-inherited disorders. (Correction of dominantly-inherited disorders is possible only by eliminating or otherwise 'switching off' the dominant disease-producing gene.) For technical reasons, the introduction of the 'healthy' gene has to be done outside the patient's body, in the laboratory; the treated cells are then re-introduced. The application of such therapy is thus limited to cells and tissues which can be maintained in culture, such as bone marrow, skin and perhaps liver cells. There must also be a reasonable probability that the protein(s) produced by the corrected cells will indeed relieve the symptoms of disease. Such a protein must, for example, be able to reach the tissues where it will be effective, perhaps being transported through the blood.

Molecular geneticists have developed a range of techniques for gene transfer which may be suitable for use in gene therapy. To ensure that the introduced gene has a good chance of producing its effect, experiments are under way using special carriers known as 'expression vectors'. In the vector, the gene to be transferred is provided with characteristic sequences of DNA whose job in the cell is to ensure that the gene can be 'read', so that the protein will be produced in the appropriate cells and tissues. Viruses are often used for this purpose, especially retroviruses (Eg88), whose ability to penetrate cells enables the transfer of genetic material to a large number of cells. Retrovirus genetic material consists of RNA; once this has been copied into DNA it can be incorporated into cellular DNA. The viruses thus function as transport units, carrying new genes into the cell. The particular retroviruses used are 'disabled', that is, they are modified to ensure that they cannot produce viral proteins or oncogene products (substances which may, *inter alia*, play a role in the formation of malignant tumours).

Although modest successes have been achieved in the laboratory (corrected genes, for example, have been shown to function in bone marrow cells), there are still a number of technical obstacles to the introduction of somatic-cell gene

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therapy:

- the number of gene copies per cell that is introduced cannot be calculated in advance
- the site at which the gene is inserted cannot yet be selected with any precision, so that there is a risk of disturbing the function of other important genes through the transfer
- the regulation of the inserted gene is not always predictable.

Major advances have been made recently thanks to the development of techniques for homologous recombination, or an exchange between the introduced DNA and the corresponding abnormal gene already present in the cell (Man88). This makes it theoretically possible to correct a mutation in a gene by replacing it with the proper DNA sequence, or to neutralize a dominant abnormal gene by replacing it with harmless DNA sequences, thus abrogating its function.

At the present time, somatic-cell gene therapy could in theory usefully be applied to certain very rare conditions, such as adenosine deaminase deficiency, and to a few more common diseases such as sickle-cell anaemia and thalassaemia (two blood disorders involving structural defects in the protein haemoglobin).

Initially, research was directed primarily at gene therapy in or through bone-marrow cells (and the production of enzymes by these cells), but current efforts focus on other types of cells as well, including liver and connective-tissue cells. For example, techniques have already been devised to introduce a normal gene into hepatocytes to cure the congenital metabolic disorder phenylketonuria (PKU).

The blood-brain barrier forms an obstacle for the use of gene therapy in the case of diseases which are manifested largely in the brain. Experiments in animals, in which gene therapy via bone marrow cells has been applied to correct lysosomal accumulation diseases (enzyme deficiencies, often associated in human beings with serious mental impairment),

have yet to demonstrate convincingly that the enzyme production induced in the bone marrow can remedy the accumulation of metabolic products in nerve tissue. This lack of success is attributed to blockage by the blood-brain barrier.

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Germline-cell gene therapy

Germline-cell gene therapy involves the correction of one or more genes in cells which form part of the germ line, that is, egg and sperm cells, and the totipotent cells of the pre-embryo.

Gene therapy in egg or sperm cells is virtually unimaginable for technical reasons: identification of an abnormality in an individual germ cell would inevitably involve the sacrifice of that cell. In mice, it has proved possible to insert genes (e.g. human genes) into a 1-8 cell embryo, by micro-injection or using disabled retroviruses. Furthermore, embryonic stem cells from mice into which genes have been transferred, have been inserted into mouse embryos at an early stage of development (Ma88). This results in the development of chimeric animals: only that part of their tissues which developed from the genetically-manipulated stem cells will include the introduced gene. If the chimerism extends to the germ cells, the introduced gene can be passed on to the animal's progeny. Over the past five years, this 'transgenic-animal' technology has greatly increased our knowledge of gene regulation (Ja88), including such matters as tissue-specific expression, the operation of oncogenes, the phenomenon of cell differentiation (the specialization and maturation of cells) and the functioning of the immune system. Transgenic-animal technology theoretically would make it possible to study human hereditary disorders in animals.

Recently, an Italian research team appeared to have succeeded in introducing DNA fragments into murine sperm cells (Ia89); the fertilization of ova with these genetically-manipulated sperm cells produced large numbers of transgenic mice. This result has, however, yet to be replicated by other

researchers.

As has been mentioned, *it* has been possible to make specific changes in an abnormal gene through homologous recombination (Ma88). The fact that this is also possible in cultured embryonic mouse cells could theoretically pave the way for germline-cell gene therapy in the future. For many reasons, however, such therapy is far from becoming feasible in human beings. For example, the introduction of 'new' genetic material may induce mutations, producing structural abnormalities in the offspring (as has been shown to occur in mouse embryos). Moreover, there are immense practical obstacles to ascertaining the safety of the technique in human beings, because this would require demonstrating not only that the 'diseased' locus in the DNA has been made 'healthy' (or at least 'healthier'), but also that the treatment has not caused any damage which might eventually result in cancer, mental or physical handicaps, or other problems. Finally, the changes in the genetic material induced by germline-cell gene therapy can be transmitted from one generation to another, and will therefore be maintained unless countermeasures are taken. In the light of all of these risks, it would be irresponsible to do experiments on germline-cell gene therapy in human beings.

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4 SOCIETY, ETHICS AND LAW

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4.1 Introduction

As was shown in the previous chapter, rapid advances are being made in the diagnosis of congenital and hereditary abnormalities in human beings. Thanks to the development of DNA analysis and of new techniques for obtaining foetal material (such as chorionic-villus sampling), it is now possible to make accurate diagnoses during pregnancy of more anomalies than was the case only a few years ago. The introduction of DNA analysis into traditional genetic research (family studies, pedigree analysis) is also making a contribution to our understanding of the patterns of inheritance of increasing numbers of hereditary disorders.

The growing knowledge of the patterns of human heredity is prompting growing concern about the uses to which this knowledge may be put (GR88a). Unrealistic expectations regarding the prospects for deliberate intervention in human genetic material also play a role in this discussion. With increasing frequency, concern is voiced in society, as people wonder where these developments are leading (GR88a). Will doctors, and with them, health and life insurers and employers, acquire an even tighter hold on people's lives? Will the freedom to decide whether and when to have children, irrespective of the question of hereditary disorder, be threatened? Will access to certain jobs be limited by employers willing to hire only workers with the 'right' genetic predisposition? And more along the same lines.

Popular fears about the undesirable consequences of advances in genetic science are fed by the complex and

wide-ranging nature of the subject. Many find it difficult to follow what geneticists are actually doing, within the laboratory and outside of it; one could guess that there are exaggerated notions in society about what is now or will become possible. The lack of adequate knowledge and understanding gives rise to unfounded expectations and predictions about the extent of future possibilities to control disease, or to manipulate the hereditary factors in intelligence and behaviour (GR88a).

The scientific developments outlined in the previous chapter are likely to have major social, ethical and legal consequences. The most important of these will be discussed in this chapter, as will the measures that may need to be taken to counter any undesirable effects of these developments.

In Appendix 3, a number of Health Council and other reports on various aspects of genetics issued over the last ten years are summarized. These documents (GR77, GR79, GR80, GR86, WVC87, GR88b, STG88, WVC89) contain views on various social aspects also covered in this report: the place and purpose of genetic counselling, the definition of the job of the counsellor, and the implications of diagnosis of untreatable conditions. Both the Health Council reports, and those of the Steering Group on Future Scenarios in Health Care (STG88) rightly give great importance to the individual's right to decide for her/himself. The documents issued by the Secretary of State for Welfare, Health and Cultural Affairs (TK87, WVC87) state the policies on the prevention of congenital anomalies, without elaborating on the social and ethical implications.

As the scope for genetic testing widens, there is an evident need for public debate, sound information, and more broadly well-thought-out and forward-looking policies acceptable to the society.

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4.1.1 Content and quality of genetic counselling.

There is a number of different definitions for the term 'genetic counselling'. That which is now almost

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universally accepted, and which is here endorsed, was formulated in an earlier Health Council report (GR80):

Genetic counselling is a communication process which deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family. This process involves an attempt by one or more appropriately-trained persons to help the individual or family to 1) comprehend the medical facts, including the diagnosis, probable course of the disorder, and the available management; 2) appreciate the way in which heredity contributes to the disorder, and the risk of recurrence in specified relatives; 3) understand the alternatives for dealing with the risk of recurrence; 4) choose the course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards, and to act in accordance with that decision and 5) make the best possible adjustment to the disorder in the affected family member, and/or to the risk of recurrence of the disorder.

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According to this definition, the purpose of genetic counselling is not to maintain or to improve general standards of health, but to assist individuals who are seeking advice (Ha82, We88b). This is a task for the counsellor. In the following section, this task will be examined more closely, with respect to three aspects: information, advice and support.

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Information

The main purpose of genetic counselling is to provide clients with the information they need to make the choices appropriate to their beliefs and circumstances. Clients usually ask questions related to their potential offspring; the information they receive covers a wide range. This may include the diagnosis of the condition about which guidance is sought, the prognosis, the risk that a child - whether a first or subsequent - will be handicapped, the treatment available for particular conditions, and the options open to the client. The options generally are:

- to accept the risk (or perhaps certainty) that a child will be born with a handicap;
- to seek abortion, if prenatal testing reveals an abnormality;
- to opt for artificial procreation (insemination using

donor sperm, or in vitro fertilization using a donor egg);

- to decide not to have (more) children, and perhaps to adopt.

To provide information effectively on these options takes time. Information must be made understandable to the client and it is the job of the counsellor to ensure that it is understood. The details must be written down in comprehensible language, and the document given to the client for future reference. The provision of a written document is also important for others providing assistance to the client, and for informing other family members.

In some cases the clients contact the genetic counsellor directly, but usually they first approach their general practitioner, paediatrician or gynaecologist. When these doctors have the necessary information, they can themselves offer counselling (perhaps after consultation with colleagues), but since they are not normally familiar with the entire field of genetics, and the developments going on in that field, referral to a Centre for Clinical Genetics is usually desirable. The referring doctor can then give assistance to those who have received genetic counselling, helping them to digest and to act upon the information they have received.

The provision of information by genetic counsellors is bound by ethical and legal considerations regarding the scope and limits of their duty to supply information, professional confidentiality and civil liability. These issues are considered in section 4.2.

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The role of the counsellor.

Effective genetic counselling enables clients to make choices appropriate to their own beliefs and circumstances; this essential aim is endorsed by all of the Centres for Clinical Genetics. In practice, clients respond in very different ways to approximately equal risks of having a

handicapped child; whether or not a given risk, handicap or form of prevention is deemed acceptable depends on a range of often very personal factors.

Respect for the clients' religious and moral convictions and their right to decide for themselves requires that counsellors adopt a neutral approach, giving clients every opportunity to make their own decisions about the consequences which follow from the information they are given. Counsellors must never impose their own views. But however hard they may try to achieve this goal, complete impartiality is unattainable in practice, and counsellors may unintentionally reveal their own preferences, perhaps by a gesture, or by repeated mention of a particular option. Counsellors may find themselves guiding clients out of a concern that they may not have fully understood the information given to them. Realizing that subtle forms of influence can slip into the communication between counsellor and client can help the former to approach neutrality as closely as possible. For this reason, if not for others, it is vital that counsellors also be trained in oral communication techniques.

Counsellors and doctors are often asked what they would do if they were in the client's position. This question usually means that the client still has difficulty in reaching a decision, and needs more time or more information (or that the information already provided was not sufficiently clear). Should a counsellor recommend a particular option in such circumstances? Some members of our committee felt that any notion of 'recommendations upon request' should be rejected, that the counsellor is not in a position to determine the course of action most appropriate to the client's beliefs and circumstances. Counsellors cannot and must not put themselves in the client's position. Others in the committee felt that there may be exceptional situations in which a 'recommendation upon request' might be acceptable, provided that the counsellor makes it clear that it is a personal opinion that is being given, and that the client still has to make the

final choice. When a client has difficulty in reaching a decision, or in dealing with information received, a frequent practice at the Centres for Clinical Genetics is to consider, with the client, whether the involvement of a mediator (for example a legal adviser, member of the clergy or family doctor) might help to resolve the issue. Most of the Centres employ a social worker or clinical psychologist.

Our committee believes that counsellors should never recommend a particular course of action unasked; this would contradict the accepted definition of the purpose of genetic counselling. Moreover, all of those who seek advice have their own views, which must be respected, on the risks, handicaps and choices they find acceptable; counsellors who impose their own value judgements are exceeding the bounds of their own function. The principle that counsellors may not promote their own moral convictions does not, however, mean that they must comply with every request made by a client; they are, for example, bound by the code of conduct of their profession.

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Support.

Being informed about genetic abnormalities has a profound effect on many people, and often results in powerful emotional reactions. Factors which play a role in this process include the following:

- clients are generally unfamiliar with the concepts and terminology of medical genetics, and may not understand the implications of what they have been told;
- genetic counselling may reopen old wounds, for example in relation to a deceased child;
- the realization that one is a carrier of a hereditary abnormality can give rise to a needless sense of guilt or inferiority;
- serious crises of conscience can occur when clients are asked to consider telling relatives that they may be genetically at risk; the existence of taboos about hereditary conditions can form an additional obstacle

to informing relatives;

- clients are often faced with a choice from a limited number of childbearing options and may be unable to resolve the dilemmas involved;
- partners may reach different conclusions following the genetic counselling.

It is important to stress that genetic counselling is more than just the provision of medical and technical information. When personal (or inter-personal) emotional problems arise, help must be offered to deal with the information. It would be cruel to leave the clients to struggle with their problems alone; counsellors must be able to notice the need for support and to try to ensure that it is met. Professional support can often be given by the social worker or clinical psychologist attached to a Centre for Clinical Genetics; general practitioners can also play an important role. In other cases, social workers in the clients' own areas may be involved, while contact with other people in a similar situation (for example through parents' or patients' organizations) can also be a source of comfort.

Support may be needed before genetic testing begins (Cr86, La87). The consequences of the testing must be discussed with the subjects in advance, especially when it may provide information about their own or their children's future health. For example, in presymptomatic testing for serious hereditary disorders that appear only relatively late in life, such as Huntington's chorea, it is vital that the counsellor recognizes the sense of hopelessness and the potential for suicide which can arise in those found to have the condition. As to members of families in which there are affected individuals, the uncertainty as to whether they themselves will develop the disease can be a torment. Some will opt for certainty, however difficult it may be to deal with the knowledge that one is affected; they can take this knowledge into account in planning their lives, and in deciding whether or not to have children. The counsellor must, if necessary,

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encourage intensive discussions to determine whether the client really prefers knowledge to ignorance, and whether he or she is aware of the psychological and social consequences of being found to have the condition. The counsellor must also try to determine whether the client's decision to request testing has been freely made; coercion would be unacceptable. Skilled support must of course also be available during and after predictive testing of this type. International guidelines specify that such tests may only be done in centres which have, in addition to their technical facilities, expertise in identifying and dealing with psychosocial problems. The committee endorses this approach.

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4.1.2 The role of the government

Against this background of advances in clinical genetics, the question arises of the proper role for government. Our committee finds that it should comprise at least the following duties and responsibilities:

- The government policy should centre on the individual's right to make his/her own decisions; there is no place for official eugenics. The government also has the duty to protect individuals from social pressures which might erode their freedom to reach their own decisions.
- The government should promote public education in the principles of heredity and the scope for diagnosis and prevention of congenital and hereditary conditions.
- The government should ensure that everyone has access, financially and otherwise, to clinical genetics services.
- The government must ensure that such services are functioning at a consistently high standard.

Various aspects of this issue are dealt with in the following.

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Coercion or pressure?

Genetic counselling helps clients to make well-considered choices about the risks to their own and to their (potential) children's health. Prospective parents will not be indifferent about the health of their offspring; those who are at risk of having a seriously handicapped child must be able to weigh their desire for a family against the interests of the possible children. They take into account such factors as the size of the risk, the nature of the condition, the treatment available and the child's chances of having a reasonable quality of life. In practice, different people will reach different conclusions, for example as to the best interests of the child, because of differences in their religious or moral beliefs.

In The Netherlands, it is generally accepted that the individual must decide whether to undergo genetic testing, and if a risk is identified, whether to take preventive measures. The inviolability of the person, based on the right to self-determination, is laid down in Article 11 of the Constitution; were the government to consider requiring genetic testing - an unlikely prospect in this country - it would be in conflict with this provision in the Constitution. Only very weighty arguments, based on other statutes, could justify the infringement of the inviolability of the human body. Such a requirement might also constitute an infringement of the right to family life (Article 12 of the European Convention on Human Rights).

Our committee unequivocally rejects any possibility of compelling individuals to undergo genetic testing, or to take preventive measures. There can be no legal grounds for such compulsion. The State must recognize freedom of procreation just as it recognizes the individual's freedom to choose a partner. (It is recognized that exceptions to the latter exist under current law; for example, Article 41 of the Civil Code prohibits marriage between close relatives.) We wish to emphasize our position on this point, partly because of the

suggestion which is sometimes made in the literature - mainly originating in the United States of America - that freedom of procreation should be restricted (Fl88). This suggestion is based on several different lines of reasoning.

One of these is economic and may be summarized as follows: the care of the handicapped places a heavy burden on health care budgets; the government therefore has a right to compel citizens to undergo genetic testing and to take preventive measures, when this would result in significant savings. This argument is based on the idea that the State may prohibit highly personal choices for the sake of economic advantages. If such a principle were to be applied consistently, it would result in a grave invasions of privacy. In addition, this line of reasoning assumes, wrongly, that the interests of society would best be served by cost control. We feel that the concept of social value must include the idea of the amount of freedom enjoyed by the members of the society. It is, moreover, a mistake to assume that preventive measures could, in the short term, greatly reduce the number of handicapped individuals in the society. Most handicaps are a result of spontaneous mutations in the genetic material, and are therefore not predictable. There will always be disabled people, and society must bear the cost of caring for them.

A second argument which is sometimes advanced in favour of compulsory testing is that the State has a duty to reduce the number of pathological or lethal genes, thereby reducing the number of people who will suffer in future generations. This idea is often compared to the case of control of communicable diseases: just as the State may limit individual freedom in some cases, to counter the spread of infectious disease, so too may it force people to make choices that would limit the transmission of hereditary abnormalities. This argument, too, is ill-founded, because hereditary conditions are transmitted in a very different way from infectious diseases. Measures to prevent transmission of infectious diseases are aimed at the prevention of epidemics which could threaten the health of many people. These measures

are, moreover, temporary in nature, and therefore far less radical than measures aimed at limiting hereditary risks to future generations would be.

Underlying this argument is the assumption that abnormal genes can be eliminated by preventing reproduction in the people who carry them, so that they are not passed on to the following generation. Technically, the possibilities for selecting particular genes and eliminating them from the population is very limited (Hi76). Any attempt to reduce the gene frequencies of recessive conditions by preventing carriers from producing children is doomed to failure: every person carries perhaps three to eight lethal recessive mutations (i.e., abnormal genes which could produce a fatal condition if inherited from both parents) (Hi76). A programme to eliminate such genes would require such extensive restrictions on procreation that the continued existence of the human species would be threatened. In the case of some dominantly-inherited conditions, affected persons do not survive to have children and the genes are thus not passed on at all. In other cases, of dominantly-inherited conditions which do not interfere with procreation (such as Huntington's chorea), selecting out the gene is theoretically possible. If every patient and all of those at risk could be induced to refrain from having children, then in one generation the gene frequency for the condition would be reduced to that of spontaneously-occurring mutations. We feel however, that such a policy would be in contradiction to fundamental principles of law and human rights.

Finally, there are those who seek to justify the regulation of reproduction by the State by referring to the interests of the future child (Fl88). Just as the State may restrict the freedom of some individuals in the interests of preventing harm to others, so too might it intervene when individuals would cause serious harm to a severely handicapped child by bringing it into the world. In this connection, reference has been made to the child's right to be born with a healthy physical and mental constitution. Again, we would

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dispute this line of reasoning; there can be no 'right' to be born healthy, simply because the health of the foetus or child is to a large extent determined by factors over which human beings have no control. It must also be remembered that an acceptable quality of life is also possible for handicapped people, depending partly, of course, on the efforts made by others in the interest of their welfare.

In summary, we reject any and all forms of compulsion as a matter of principle. Such policies would not only infringe on fundamental principles of law and human rights, but also place a stigma on the persons concerned, which would have a number of social consequences.

There is, however, a real danger of pressure - indirect compulsion - of various kinds. First, subtle pressure may come from the social environment. Increasing numbers of people are likely to make use of the facilities in the field of clinical genetics and the possibilities for prevention appear to be very attractive to them. People may begin to wonder why anyone who runs a high risk of having a handicapped child should do so, if it could be prevented. Individual choices could give rise to new social norms, which could greatly limit personal freedom. In that case, individual genetic counselling could unintentionally lead to the spread of a new reproductive morality, in which the duty of prevention could play a central role. The danger of such social pressure is a further reason for the advocacy of a neutral approach by genetic counsellors; the choices made by their clients must be personal ones.

A second form of social pressure is economic pressure. The economic advantages of prevention could be a reason to restrict the freedom to choose whether to have children. For example, the health insurance schemes could be amended to shift the costs of caring for and treating handicapped children onto the parents, who, whether or not they were aware of the risks, had failed to prevent their birth. We

emphatically reject any such policy, firstly because the main victims would, quite unjustly, be the handicapped children themselves. Secondly, such a policy would restrict freedom to procreate, because it would imply enforced genetic testing; this is unacceptable. Our committee finds it the duty of the government to create a climate in which genetic counselling can continue to be offered on the basis of free choice.

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Promoting public information

The number of consultations at the Centres for Clinical Genetics in The Netherlands has ranged between 2,000 and 3,000 per year for a long time. This is a much lower figure than might be expected on the basis of genetic data. There are general practitioners and specialists outside these centres who also provide information to parents and prospective parents about conditions with patterns of heredity known to them. It is nevertheless striking that only a minority of those who could benefit from the centres' services actually make use of them. One reason for this discrepancy is that the general public knows little or nothing about the principles of human heredity and many are unaware of the existence of the Centres for Clinical Genetics. We therefore attach great importance to informing the public. Well-informed people can ask specific questions about the possible hereditary component of conditions that appear in their families, and are more likely to understand what they are told by genetic counsellors. The general public's understanding of heredity can be promoted by devoting more attention to the subject in primary and secondary schools. In addition, the health education programmes should be strengthened, and greater use made of the media for this purpose.

Specific training for general practitioners, obstetricians and providers of psychosocial care would undoubtedly lead to an increase in the use made of the Centres for Clinical Genetics, which development is to be applauded.

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Access to services

Prenatal testing is often done on the grounds of the age of the expectant mother, or another specific indication. Of particular relevance to the issue of how extensive the indications should be are the following questions:

- Should the age threshold for access to prenatal chromosome analysis be lowered, or abandoned?
- Should a detailed list be compiled of the indications for prenatal testing?
- Is there a case for restricting access to prenatal testing to those women who indicate in advance that they will opt for termination if the foetus proves to be abnormal?

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Age threshold for prenatal chromosome analysis

At the present time, tests to detect chromosomal abnormalities such as in Down's syndrome are available in The Netherlands only to women considered to be at risk of having such a child. The main indication is age, and the threshold is set at 36 years (see also section 3.2.3). The age threshold implies that some women who may be at risk are ineligible for testing, and casts some doubt on the justification of this policy (E187), because the risk of foetal abnormality *in* women over the age of 35 *is* not much greater than in younger women. (There is, however, a clearly increased risk after the age of 36: the risk of 1 in 384 at age 35 rises to 1 in 30 in 45-year-olds.) Moreover, most (about 70%) of the children born with chromosomal abnormalities are born to women younger than 36; although the risk for each individual may be smaller than for the older group, as a group they bear by far the most children. All this considered, it is not surprising that there is some demand for the abolition, or at least the reduction, of this age threshold.

Our committee, however, would not regard the abandoning of the age threshold as desirable, whether as a general rule or at the request of individual women. Such a

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move would probably lead to large-scale and costly testing, with a relatively low probability of finding abnormalities (the risk of having a child with Down's syndrome is only 1 in 1,500 in women under the age of 25). In addition, the risk of miscarriage associated with amniocentesis and chorionic-villus sampling, while low (about one-half of one per cent.), is nevertheless a real one. So for this reason as well, it would not be advisable to lower the age threshold for chromosome analysis.

We believe that an effective programme of information for women over the age of 35, and for younger women for whom testing is medically indicated on other grounds, is more important than lowering the age threshold for chromosome analysis.

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A list of indications?

Until recently, prenatal testing was only done on women known to be at risk for having a severely-handicapped baby. Thanks in part to the introduction of DNA technology, however, it is increasingly possible to identify genetic abnormalities in the foetus that would give rise to late-onset diseases (such as Huntington's chorea and neurofibromatosis) or that are expressed only in combination with certain external factors. One can, for example, be tested for a genetically-determined predisposition to cardiovascular disease.

With the growth of the range in diagnostic tests, there has been a call for a list of the conditions for which prenatal testing should be permitted (i.e., covered by health insurance) (LI89). Although there is currently no evidence that prenatal testing is being done for trivial reasons in this country, our committee feels that the professionals involved should carefully consider the limits of the application of indications. The compilation of a restrictive list of indications would not, however, solve the problem. The assessment of the severity of a given condition by a woman and her partner depends on personal factors, including religious

and moral beliefs and the composition of the family. Limiting the availability of prenatal testing to items on a list would not make adequate allowance for this. In addition, such a list would be constantly outdated due to the rapid advances in diagnostic techniques.

Finally, we note that the Centres for Clinical Genetics do prenatal testing to determine the sex of a foetus only when there is known to be a risk of a sex-linked hereditary condition. Our committee endorses this restriction; prenatal sex determination in the absence of a heredity-related indication (i.e. for non-medical reasons) has nothing to do with genetic counselling.

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Willingness to undergo abortion as a precondition?

Should prenatal testing be offered only to women who are willing to undergo an abortion if the foetus *is* found to be abnormal? Some would give an affirmative answer to this question (Ha72), primarily because such testing is expensive and facilities are scarce, so that priority for their use should be given to women who agree to accept the consequences of the diagnosis of an abnormality. A second argument is that being informed that the foetus is abnormal will be a heavy burden for those who do not accept abortion. Thirdly, as has been noted above, the tests themselves are not risk-free; even when done in a specialized centre, amniocentesis results in miscarriage in 0.5% of the cases.

Our committee finds these arguments for limiting access to prenatal testing unconvincing, and endorses the position formulated in an earlier report of the Health Council (GR80):

"When parents request a prenatal test in the hope of a reassuring result but are as yet unwilling or unable to decide whether they would opt for termination in the opposite case, their request should still be granted whenever possible. Indeed, testing should be available to parents who are resolved not to request termination, but who nevertheless wish to be informed of a possible abnormality before the birth of their child. In such cases, there should be extra emphasis on information and support, considering the emotional burden of a positive result from a diagnostic test."

Moreover, the purpose of genetic testing is not the termination of pregnancy when abnormalities are found (see also Po79), but the provision of information to pregnant women and their partners. For some couples, this information is important in reaching a decision on whether or not to let the pregnancy continue, but for others (between one and two per cent.), the test is requested to allow them to prepare themselves for the birth of a handicapped child, if necessary. Both of these motives are legitimate. Any exclusion from prenatal testing of women who will not consider termination would create a situation of inequality before the law, and could lead to unacceptable pressure on individual women. There is also the practical argument that such a restriction could still fail in its purpose, since there is no way to stop people changing their minds.

A particular problem may arise when a woman or a couple requests prenatal testing for a late-onset untreatable condition, but will not consider termination. If the result is a positive diagnosis, the child will later be confronted with highly distressing information it never asked for. This could then violate the child's right not to know of its future risks. On the other hand, prospective parents may want prenatal testing even when they are not prepared to consider abortion, because if the foetus is found not to be affected, their minds can be set at rest. The conflict between the parents' interest in and right to information, and the future child's interest in and right to ignorance, is thus unresolvable.

As was previously noted, it has been suggested on occasion that health insurers might in the future decide to cover the costs of prenatal testing only when the diagnosis of abnormality is followed by termination. We regard such a policy as quite unacceptable. It is unlikely that any question of this will arise in The Netherlands, but should insurers seek to apply conditions to reimbursement for prenatal testing, the access to this aspect of health care should be guaranteed by law.

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Quality control

The Centres for Clinical Genetics consult nationally and regularly on the subject of maintaining standards in clinical genetic testing. Certain of the centres have also arranged a sort of registration in collaboration with the Health Care Information Centre. These quality-control activities are the subject of Appendix 2. Our committee finds the present self-regulation functions satisfactorily, and we do not feel that government measures are needed at the present time.

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DNA kits and self-testing

There is a recent development which could threaten the standards of genetic testing. The widely available techniques for processing DNA (cutting, recombining and replicating it) have simplified DNA analysis and a number of firms are currently marketing (or considering marketing) relatively easy-to-use DNA test kits, even self-test kits. Such kits contain a combination of enzymes and test substances (probes) with which, for example, DNA tests for cystic fibrosis within families can be carried out.

We believe that the use of these simplified techniques to test for hereditary conditions should be limited to the laboratories in the Centres for Clinical Genetics, because of the need for:

- skills and facilities in the area of family and pedigree studies. A great deal of DNA analysis is based on comparisons of DNA marker patterns in family members with and without the condition in question;
- skill in carrying out the DNA analysis. Even with 'simple' tests, using commercially-available kits, experience is necessary for the interpretation of the results (which also requires an appreciation of the nature and limitations of the test itself);
- facilities for statistical analysis, particularly in the area of genetic linkage studies;

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- provision for reliability in the final evaluation of results;
 - skills in the area of genetic counselling.

In the near future, simple tests may be used to detect specific gene abnormalities (mutations) involved in disorders common to particular population groups (such as sickle-cell disease, or cystic fibrosis). Tests are also becoming possible for late-onset (autosomal dominant) hereditary diseases such as neurofibromatosis. We recommend that such tests not be made generally available, but that their use be restricted to the Centres for Clinical Genetics. This restriction should also apply to tests which may in themselves be sufficiently accurate.

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~~Costs~~ Costs

There is a growing interest, within the health care sector, in the determination of the efficiency of care and treatment, for example through cost-benefit or cost-effectiveness studies. The issue is mentioned in the letter of request for this report. This type of analysis, which is to a certain extent helpful in clarifying issues in the distribution of scarce resources, has also been done for the field of clinical genetics (Co88, RCP89). The analyses show that genetic testing and mass screening programmes often reduce spending, when considerable sums can be saved for example by preventing the birth of children with genetic abnormalities, or by treating genetically deficient newborns to prevent disease.

It is necessary to emphasize, however, that the application of costing studies to health care, and to genetic testing as well, has its limitations. The costs of genetic testing and counselling and of subsequent termination of pregnancy can be set against the 'benefits' achieved, which may include a reduction in the costs of caring for the handicapped, if fewer handicapped children are born. Appendix 4 gives an idea of the costs and benefits as illustrated by a

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particularly severe hereditary condition. For neonatal screening, the costs of testing and prevention (e.g. by diet) can be compared with the savings achieved by reducing the need for paediatric care. The essential purposes of genetic studies, however, - the prevention of human suffering and grief, and facilitation of decisions affecting one's life and one's choice about having children - cannot easily be expressed in financial terms, and therefore tend to get ignored in any economic analysis.

Our committee urges the government to assess new forms of genetic testing (both individual and mass screening tests) primarily according to their potential contribution to human welfare, rather than their economic yield. Putting a disproportionate emphasis on the economic advantages of genetic testing is extremely offensive to handicapped children and their parents; it could create a climate in which the handicapped are seen simply as expense which could be avoided.

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4.2 Ethical and legal issues surrounding genetic testing and counselling

Every year, genetic testing and counselling help thousands of couples find answers to questions about the causes of a handicap in a child, one of the parents or in another family member, and about the chances of its recurrence. The main function of the Centres for Clinical Genetics is to provide clients with the information they need in order to make free, independent and well-thought out choices. Ethical and legal issues may arise in relation to these activities, and although the issues are not new, the rapid advances made in genetics and the growing range of genetic tests available mean that such questions arise with increasing frequency. They include the following:

- What are the limits on the counsellor's duty to inform?
- What are the implications of the clients right not to know?
- How can the principles of confidentiality be applied, along with the requirement for consent prior to

approaching relatives?

- Do relatives have a right to information on genetic risks?
- May professional confidentiality be violated when moral dilemmas arise?

In the following sections, these and other questions are considered, first focusing on the right of the client to information (section 4.2.1.) and to confidentiality (4.2.2.); in this context, the issue of informing relatives is also considered. Then the protection of privacy in a broader sense will be dealt with, in relation to genetic records (4.2.3.), followed by a consideration of cell and DNA banks (4.2.4.) and of epidemiological research (4.2.5.). Finally, the counsellor's civil liability in connection with genetic testing will be examined (section 4.2.6.).

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4.2.1 The client's right to be informed

The right of the patient to be informed plays an essential role in the relationship between doctor and patient (Le88); such information forms the basis for the patient's consent or refusal to undergo a certain test. Generalized norms have been developed in case law and in the academic literature (Le88), which say, briefly, that the doctor is required in principle to provide the patient with full information, even when this *is* not expressly requested, on all issues and results which may be relevant to the patient. This requirement is not, however, absolute: doctors do have some freedom - the 'therapeutic exception'¹ - to determine how much to tell and when, depending on the risk of harm to the patient. A doctor may decide to withhold certain information in order to prevent harm to the patient. This exception is, however, expressly limited to the obligation to provide information, and does not affect the patient's right to look through their own medical records.

In the context of clinical genetics, the client's right to information obliges the counsellor to ensure, before

any testing is done, that the client is fully acquainted with the nature and purpose of the proposed test (Gev87). This must include the possibility that relatives may need to become involved, and that samples of body tissues may have to be taken and possibly stored. The counsellor must also make clear to the client that the results of the testing could be unexpected or distressing. The counsellor must also point out that there may be social consequences of testing, for example problems with job applications or in obtaining insurance. When such information is given in advance, it can help the client to decide whether to go ahead with testing. When testing is to be done, the counsellor's obligation to provide information also extends to the results of the testing.

The right to be informed and the therapeutic exception have been recognized for a long time. More recently, the right of a patient not to receive information has also been recognized (Gev87). This right not to know may imply that a client decides not to proceed with testing, and that, if testing is done, the client may choose to remain ignorant of the results.

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Limits on the obligation to inform

In an earlier report (GR80), the Health Council formulated the principle that a client is entitled to all of the information relevant to him or her that the counsellor can provide, unless the latter decides to withhold particular facts in clearly defined cases. The committee supports this position.

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Relevance of information

In the above, reference has been made to 'all information relevant to the client'; genetic testing can produce information which is not medically relevant (as in some cases, the sex of the foetus, although in others this is medically relevant). Should counsellors disclose such information, and if yes, should they do so of their own accord or only upon request? Our committee feels that all medically

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relevant information should be given spontaneously, while non-relevant information should only be provided on request. In this example, the sex of the foetus should be revealed by the counsellor if asked. If there is doubt as to the relevance of the information, the facts ought to be disclosed spontaneously, so that clients can reach their own conclusions. Withholding information would mean that the counsellor is making decisions on behalf of the clients, which would contravene the obligation to be neutral.

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The therapeutic exception

In practice, situations may arise in which exceptions to the primary rule of complete openness are justified. The information being handled in the genetic counselling might, for example, relate to an individual's chances of developing an untreatable disease. In such a case, full disclosure could blight the lives of the person concerned and his or her family. Counsellors would then face a dilemma: with incomplete information, a decision can not be well thought-out, while complete information may cause suffering. We find that the greater weight must be given to the right to complete information, and that counsellors are justified in withholding facts only in exceptional cases in which their relevance and importance is eclipsed by the potential harm. The counsellor must then be able to justify this decision, perhaps in a court of law. When a counsellor in such a difficult situation opts for full disclosure, the client(s) must of course be provided with tactful support.

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Right to information versus obligation of confidentiality

The counsellors' obligation to provide information might confront them with another dilemma: to give complete information to a client might entail infringement of the obligation of confidentiality with respect to a third party. For example, this could occur if the information includes the evidence that the supposed father of a child is not its true

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father. In such cases, great importance should be attached to professional confidentiality, and the decision reached should be balanced, well-founded and defensible. The right to confidentiality of a third party, however, cannot fully override the right to information of the person tested (see also section 4.2.2.).

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The right not to know

A third kind of limit on the obligation to provide information can be set by the patient's wish not to receive certain information (Le88).

There are positive aspects to ignorance; the knowledge that one will develop a disease, particularly one with no prospect of prevention nor treatment, can greatly decrease the quality of life for an individual. This is illustrated by the high suicide rate among persons carrying the gene for Huntington's chorea.

Another reason for preferring ignorance may be the effect of genetic information on an individual's chances of gaining employment or access to insurance or pension schemes.

The counsellor's obligation to provide information is derived from the client's right to receive information, which right the client may choose to waive. Moreover, everyone has the right to organize his or her life as he or she wishes; this freedom is protected by a constitutional guarantee of respect for the private sphere. Obliging a client to receive information would be incompatible with this constitutional right, so when a client wishes to remain ignorant, this wish must be respected by the counsellor.

In the case of genetic counselling, it is reasonable to assume that the client will wish to receive at least that information necessary for making well-considered decisions. The desire not to receive certain information, once one has decided to undergo testing, will most likely relate to adventitious findings, unexpected discoveries. This possibility must be explained to the clients in advance, and

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they must be asked whether they wish to be told, should the need arise. The counsellor must make clear that the desire not to know will mean, in certain cases, that the client is refusing knowledge which may be of great import to him or her. When clients state that they do not want to be given unrequested information, counsellors should not give it. In addition, information should also be withheld if clients, after testing, state that they no longer wish to be given information which they originally sought.

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The right not to know is not absolute

In practice, cases may arise in which it is difficult to respect the wish not to know. In the course of testing, counsellors may receive information which they regard as so important to the client that they feel conscience-bound to reveal it. Also, the right of clients not to know may conflict with the right of their relatives to know.

The latter situation can arise when tests need to be done in the whole family in order to establish which members, if any, will develop a disorder which is treatable if diagnosed in time. This dilemma could also arise in the case of untreatable diseases. If the child of someone who has opted for not knowing wants to be told, the parent may then have the unwanted knowledge forced on him or her. Such dilemmas are likely to arise with increasing frequency. Although there may be special circumstances in which the counsellor may be convinced that the client's right to remain uninformed must be ignored, we wish to stress the importance of the right not to know. Infringement of that right is justifiable only in extreme cases, when a counsellor, after full deliberation, concludes that certain family members must be told, even if this means that someone will receive information contrary to his or her wishes. In such situations, the counsellor must apply the 'conflict of duties' approach (see below).

Summarizing, the obligation to provide information must be honoured fully. Exceptions are permissible only when

complete revelation may cause the client serious harm, when there is an overriding duty of confidentiality towards a third party, or when the client does not want to be (fully) informed. The right not to know may be infringed upon only in extreme cases.

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4.2.2 The clients' right to confidentiality

Information obtained through genetic testing, like other medical information, is covered by the obligation of professional confidentiality (Ka76, Br88). The client has a right to confidentiality and the counsellor has a duty not to disclose information to third parties without the prior permission of the client, except when there is a legal obligation to do so.

This duty not to disclose information is not only a corollary of the right to confidentiality of the individual patient, but also serves a wider social purpose. The fear that information might be revealed to and used by third parties could discourage people from seeking medical assistance.

The primary rule that confidentiality must be maintained except in cases of consent or of legal obligations could lead to problems with genetic testing, if a counsellor wishes to involve other family members in order to help the client, or to inform them of hereditary risks they may have to confront.

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Approaching relatives for information

In order to make a diagnosis, counsellors often need information on the incidence of similar abnormalities among the relatives of their client (Gev87, Le88, Gi88). The normal practice of having the clients themselves ask their relatives' permission to disclose such information is to be preferred, but some people may find it difficult to approach relatives on this subject. Their lack of experience in asking such questions increases the chances of arousing unnecessary concern and fear in the family. Some clients, therefore, ask the counsellors to approach the relatives.

This creates two problems: first, such an approach clashes with the relatives' right to privacy, and secondly, it may conflict with the client's right to confidentiality. Being approached tells the relatives that they are part of a family in which there may be a hereditary abnormality, and disclosure of such information to persons with whom the counsellor has no (contractual) relationship is a violation of their privacy. This may be compensated by the fact that indirect disclosure of a possible hereditary risk may benefit the relatives involved, who can then use the information, for example to decide whether to have children. This aspect gains in importance when the relatives are approached not only to obtain information from them, but also to provide them with information, if they wish, about a risk which has emerged from genetic testing (see below).

The essential problem is that the relatives have no opportunity to express whether or not they want to receive the information about a possible hereditary risk. Counsellors cannot ask them in advance whether they want to know about a risk without alerting them to its existence. The committee finds that due importance should be attached to the relatives' right to privacy. They may be approached, with the consent of the client, if the information to be obtained or transmitted is relevant to them, and cannot be expected to cause harm, i.e. if it is reasonable to assume that, faced with the choice, they would wish to receive the information.

The second problem is that in practice, approaching relatives often means that information about the client must be made known to the family. When it is possible to approach relatives for information without revealing for whom it is, this should be done. When this is not possible, the client's right to confidentiality is at stake, so the client must decide whether and to what extent personal facts should be revealed to the relatives. If the client insists on full confidentiality with respect to the family, the relatives should not be approached.

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Family members' rights to confidentiality

When it has proved possible to approach the relatives, the next step is for their own doctor to ask their permission to provide information about them. This is necessary because doctors are not allowed to disclose information to anyone other than the subject of it. When this permission has been given, the doctor may then provide the details requested to the counsellor involved. When permission cannot be obtained because the relative in question has died, the data can only be released if it can reasonably be assumed that the subject would have agreed to this, had he or she still been alive. When a relative chooses to withhold information the doctor must also withhold information.

In some cases, the relative's doctor and the client's counsellor may agree that failure to obtain the facts in question will harm the vital interests of the client. This represents a conflict to be resolved, between the interests of the client, in receiving information about a possible hereditary condition or susceptibility, and the right of the relative to confidentiality. The doctor may decide that the interests of the counsellor's patient should override the interests of his or her own patient. This issue will be returned to later.

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Testing relatives for the benefit of clients

When information about the relatives of a client is needed to reach a diagnosis or to determine a risk, the data already in the possession of their doctor may not be sufficient. It may be necessary for some of the relatives to undergo testing, and this situation can be expected to arise with increasing frequency because of the developments in DNA technology. Family members must of course give free and informed consent for any such testing. The counsellor must explain fully the nature and purpose of the tests, and must ask whether the subject wishes to be informed of the results. This requirement causes difficulties when no consent can be given, for example in the case of young children, or of adults

who are incapable of giving informed consent. Under the proposed legislation on medical treatment contracts (section 1653q), the relative's power of decision then passes to his or her legal representative, attorney or other legally-designated person. This power does not, however, extend beyond what is necessary for the health of the person concerned. It is therefore not clear whether genetic testing could be done on persons incapable of giving informed consent only for the benefit of a third party. In almost all cases, however, the test would also serve the interests of the individual concerned, since it would provide information which may be relevant to his or her treatment or *care*; in such a situation, it would be acceptable to have parents or other legal representatives give consent. If the test to be done is solely in the interests of the original patient, however, consent of parents or legal guardians would not be sufficient, unless the original patient's interests were to be considered very important indeed, and could not be served in any other manner.

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.Informing family members of genetic risks

As was noted earlier, approaching relatives often entails, in practice, the disclosure of information about the original enquirer, and this person's right to confidentiality means that his or her consent must be obtained before any such approach is made. Another issue which arises in connection with contact with relatives is their right, if any, to be told of any possible hereditary risks revealed by genetic testing. Are counsellors under any obligation to notify the relatives of their clients? There are, for example, cases in which information on a genetic risk identified in a client may be relevant to the decision of his or her relatives as to whether they will have children. Or a hereditary condition may be diagnosed in a family at a point at which it is still amenable to treatment, so that early notification of relatives could prevent serious suffering.

There is no legal basis for a general obligation to inform family members. Although we committee feel that

everyone has a moral obligation - within certain limits - to protect others from misfortune, and to prevent suffering, there cannot be a general obligation for counsellors to inform their clients' relatives of possible genetic risks. Any such obligation would be in conflict with both the clients' and the relatives' rights to privacy and would disregard the counsellor's obligation to maintain confidentiality. It might happen, however, that the need to record genetic information on relatives, which has been gained from tests on clients, would create the obligation to notify the relatives in advance (see section 4.2.3).

Even when there may be no legal obligation to inform relatives, there may be a moral duty to break professional confidentiality, depending on the severity of the (possible) abnormality, the degree of risk, and the availability of supplementary diagnostic tests and preventive measures. If, for example, a counsellor finds out that the brothers and sisters of a client have a 50% chance of a serious intestinal disorder which can be treated effectively if caught in time, this serious harm to the siblings' health could be prevented by informing them.

Our committee favours proceeding such that the rights to privacy and confidentiality are maintained; if it is clearly in the interests of the family to receive the information in question, the counsellor must first appeal to the client's sense of responsibility towards the relatives. This will be after the counsellor has judged the information important enough to warrant invading the privacy of the family. The most obvious person to inform the family is the client, who may, however, ask the counsellor to do it for him or her; the counsellor must accede to such a request. If the client remains passive, the counsellor must take the initiative in asking permission to inform the family. Asking permission is necessary because of the client's right to confidentiality; notifying the family inevitably means disclosure of information about the client.

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Conflict of duties

Clients may refuse to give this permission, perhaps because they do not want relatives to know they have a genetic abnormality, or because they have no contact with the family (Gev87). A counsellor will often be able to persuade the client to give permission, but some will still refuse, leaving the counsellor with a dilemma. As has been noted above, the counsellor will then face a conflict of duties: professional confidentiality requires silence to be maintained, while there is a moral obligation to prevent suffering, and therefore to speak out. There is no legal obligation to give the information - on the contrary, a breach of confidentiality can incur liability - but in exceptional cases, such as the example above, allowance made be made under the law for counsellors to do what they are not properly entitled to do, that is, to give out the information. There may, thus, be circumstances in a particular case which justify a breach of confidentiality.

Because of the great import attached to professional confidentiality, counsellors can find themselves faced with a difficult decision, and in a vulnerable position. The decisions in Dutch courts on cases of breach of confidentiality have become more rigorous in the recent past. While the balance between the interests is still crucial in individual cases, guidelines can be given. The following conditions apply to the decision as to whether a counsellor might be justified in violating confidence:

- everything possible must have been done to persuade the client to give permission;
- the counsellor must face a real moral dilemma if he or she continues to maintain confidentiality;
- the breach of confidence must be the only way to solve the problem;
- not breaching the confidence must be likely to cause serious harm and serious suffering;
- it must be nearly certain that the family will make

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use of information, so that harm will be prevented or minimized;

- no more information must be disclosed than what is strictly necessary to prevent harm and suffering;
- the infringement on privacy must be minimized.

A counsellor who, when faced with a conflict of duties, decides to violate confidence, must be able to justify that decision before a court or disciplinary tribunal, where it will be decided whether the decision was a reasonable one.

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Avoiding conflicts of duty

In the context of the growing demand for genetic testing, various suggestions have been made for avoiding such conflicts of duties (Gev87, Le88). An earlier Health Council report (GR80) suggested that a solution might be found in the legal regulation of the conditions under which counsellors may break confidentiality. The committee rejects such an approach: conflicts of duty cannot be reduced to rules and regulations; formalization is accompanied by the danger that exceptions become the rule. Legal regulation is not even necessary, because if the situation should come to court, a doctor could always plead a conflict of duties.

Another solution might be in avoiding the conflict by requiring clients who seek testing to consent in advance to certain results being disclosed to relatives. We reject this proposal. Firstly, it makes the offer of help to clients conditional on their willingness to help others, and secondly, a client can withdraw previously-given consent, which would bring back the conflict of duties for the counsellor. Finally, such a policy might be counterproductive, scaring off potential clients, which would result in the genetic counsellors in the end helping fewer instead of more people.

A third proposal to assist counsellors with a conflict of duties is to waive the traditional rules of confidentiality for genetic testing. Because the information acquired from genetic tests relates not only to the individual tested but

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also to the family, it could be seen as family property, which would imply its free availability to members of the family. This approach deprives the individual of the right to prevent the free flow of genetic information within the family. Our committee regards this solution as undesirable, because it would require everyone to tolerate breaches of medical confidentiality for the benefit of others. The fact that the other people in question belong to the same family *is* not sufficient justification; indeed, genetic information can be a very sensitive matter especially within families. Moreover, removing genetic data from confidentiality could jeopardize the confidentiality of other medical information within the family, and this could carry the risk of its becoming known outside the family. Such considerations could discourage individuals from seeking genetic testing.

We observe that the dilemma discussed above is inherent in the comprehensive function of the genetic counsellor. Caution *is* advised in giving information to relatives when the individual client refuses to inform the family.

The situation in which counsellors are encouraged by fear of liability to play safe and to inform relatives even when their interest in the information is debatable, must be avoided. The frequency with which such conflicts arise may be limited by ensuring that clients appreciate the interests of other family members in being informed.

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4.2.3 Genetic registries and the protection of privacy

Everyone has a right to privacy. Recording, storing and using personal data carries the risk of violating that right (GR78, Be88, Ge88a, Ro88, WRR88), because there is a chance that information may be accessed by persons not authorized by the subject to have it, or that it may be used for purposes other than those for which it was collected. This is true for any collection of personal data, but genetic information is particularly risky because it must be held for

long periods of time, and the need to use it for testing and research is great. In addition, those outside the health care system may have an interest in genetic information. Our committee urges, therefore, that the establishment and operation of genetic registries must guarantee fully the privacy of the subjects in it.

Information obtained in the course of genetic testing is recorded and stored in databanks of various types and sizes. Individual general practitioners file information on their patients, each Centre for Clinical Genetics maintains a local system, and there are regional registries. A national register is presently under consideration.

The uses made of this data are also varied. They are needed to respond to individual queries, but also for research and in analyses done for policy purposes, all of which are within the sphere of health care. We feel that the protection of privacy demands that information collected in order to help individuals should not be used for other purposes without the consent of the subject. The information may also not be used for other purposes than health care, without express permission.

Privacy with respect to the information in files kept by individual counsellors is largely safeguarded by professional confidentiality, and the forthcoming legislation on medical treatment contracts also includes regulations governing medical files. Whenever collections of data are accessible as systems, they are also covered by the Data Protection Act.

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Forthcoming legislation on medical treatment contracts

This legislation will apply to medical data recorded in the context of individual care. Sections 1653 i-m will regulate the recording, storage and disclosure of medical data by the person giving medical care, who is required to keep those records of patient information relevant to treatment and care for at least ten years. At the end of that period, or earlier at the patient's request, the data must be destroyed,

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unless very important considerations in the interest of the patient, the person treating him or her, a third party or public health necessitate their being retained, or if the patient and the practitioner agree to retain them. Practitioners must allow patients to look into copies of the recorded information, except when this would violate the privacy of a third person.

According to the draft law, practitioners may not disclose information to third parties without the consent of the patient, unless under a legal obligation to do so. This is also forbidden if disclosure would threaten the privacy of the third party in question. The permission of the patient is not required when information will be used for scientific or statistical research in the area of health care, providing all of the following conditions are met:

- there is no reasonable possibility of asking permission;
- the research serves the public interest;
- the research cannot be done without the information in question;
- the privacy of the subject will not be disturbed to an unreasonable degree.

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Genetic registries in The Netherlands

Besides the files kept by those involved in individual care, there are currently three types of genetic registries: the local databanks held by the Centres for Clinical Genetics, the databank of the Institute for the Detection of Hereditary Tumours and the Eurocat databank. There are in addition a number of medical record systems only partially concerned with genetic data. The largest system is in the Centres for Clinical Genetics, each of which has its own file. This information is used primarily for individual care, but also for scientific research and for development of government policy; none of the personal data is used for the latter purpose.

In addition to the local files, consideration *is* presently being given to the establishment of a national register, which would include a very limited selection of the data from the individual centres. This centralized system would comprise two national directories, one listing the names of those who had been helped, at which centre and with which services (for example, chromosome analysis, genetic counselling, etc.) and the other recording the diagnoses reached at the various centres, dissociated from the personal data. Clinical geneticists are currently debating the usefulness of such national lists; the reservations of this committee on the topic are expressed later in this report.

The Institute for the Detection of Hereditary Tumours maintains a register in which personal data obtained from examinations by the subjects' own physicians are recorded and stored, for the purpose of coordinating and supporting the activities of the doctors involved, and for facilitation of research.

Another register is that maintained by Eurocat, a European collaborative project for the recording of data on congenital anomalies and multiple births. This system contains data stored anonymously but traceable to the individual; it presently covers the provinces of Groningen and Drenthe but is being extended to include a new trial area, the south-west of The Netherlands. This system is directed solely to research and statistics; it is intended to provide an idea of the nature and scale of the anomalies concerned.

There is also a national Neonatal Register which is in preparation, after trials carried out in 1986. This system will include data on all disorders (including genetic ones) afflicting babies admitted to paediatric units within 28 weeks of birth. The information will be anonymous, but traceable to the individual.

Obstetricians and midwives in The Netherlands register all spontaneous abortions and all births taking place in or after the sixteenth week of pregnancy. A record is also kept of all hospital deliveries conducted by gynaecologists. Data

recorded cover the period up to and including the date of the spontaneous abortion or birth, including those on genetic abnormalities. Again, the data are held anonymously but are traceable to the individuals.

Genetic information is also recorded in the context of artificial procreation. The Health Council's report on the subject (GR86) stated:

"Genetic data and certain general information concerning the donor should be coded and recorded, so that they can be recalled separately from details specific to individuals; they should be accessible to the receiving parents and to the child. Specific features of the donor should not be recorded."

All of the systems so far mentioned are concerned with health care. There may also be collection and recording of genetic data in other contexts, for example in the files and other databanks of life, disability, accident and health insurance organizations.

Various guidelines for the protection of privacy have been developed with respect to genetic registries. Since 1983, for example, the Centres for Clinical Genetics have been directed by guidelines approved by the Minister of Welfare, Health and Cultural Affairs (KGC83); these were developed in consultation with parents' and patients' organizations.

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Data Protection Act

The Data Protection Act, which was passed by the Upper House on December 27, 1988 and came into force on July 1, 1989, sets the standards which must be met by personal files and regulates the rights of the subjects. It also provides for the introduction at a later date of stricter regulations covering sensitive data. Personal genetic files are expected to be covered by the Act's more restricted rules, which means that those holding such data will be required to set up a regulatory framework for their work. Such files may be compiled only when this is essential to the proper performance of the function of the holder, and may contain only data which were lawfully acquired.

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On the first occasion that data on an individual are recorded, the holder of the file must notify the subject, except when the latter is already aware, or can reasonably be assumed to know that the information is being recorded. This obligation may be overridden by significant interests other than those of the one holding the file (see below). The length of time that information may be kept is subject only to a general legal limit. Files may contain only that information needed for the purpose for which they are kept; if this purpose ceases to be valid, or the information ceases to be necessary for it, the file must be closed and the information destroyed.

Data may be used only for the purpose for which the file containing them is kept. Disclosure of data to persons outside the organization holding them is permitted when it serves the stated purpose; otherwise, disclosure is permissible only with the consent of the subject or on the basis of a legal requirement. Personal information may also be released to others for research or statistical purposes, provided there is no excessive violation of the subject's privacy. Finally, data may be released to persons or agencies performing an official public function, when the data are needed for that function. Again, this may not result in unreasonable violation of the individual's privacy. Disclosure is not permitted when the one holding the file is bound by rules of confidentiality associated with his or her profession.

Any person on whom a file is kept must be given full information as to its contents, and the sources of the information, within one month of applying for it. The file holder may reject such an application on the grounds of significant interests of persons other than the applicant, which may include the holder of the file. The subject can also ask the holder of the file to correct errors, fill gaps or remove irrelevant material from it.

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Privacy and the recording of genetic data

The main registries of genetic data have been

described, and the relevant legal provisions summarized. Whenever personal data are recorded, there is a risk of their being misused. We therefore urge that their recording of genetic data be limited to what is strictly necessary for the purpose, and that subjects be given the greatest possible say in what is done with the data.

When the above factors are taken into account, our committee has reservations about the establishment, presently under consideration, of a national register of persons who have undergone some form of genetic testing. Such a list would be intended to prevent duplication and to ensure that information would be quickly accessible when required. But we believe that the benefits of a national register of personal data must be weighed against the inherent threat to privacy. Even if the national records contained no substantial genetic data, the fact that a person's name appeared there would in itself constitute a possible invasion of privacy. We are not convinced of the rationale for such a list. Under the Data Protection Act this file would have to meet the criterion stated in Section 18.1: "Files may be compiled only when this is essential to the proper performance of the functions of the holder of it."

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Subject's rights

Granting wider rights to clients is desirable. We endorse the view taken by an earlier Health Council report (GR80) that: "The centralized recording of data on named persons is acceptable only with the consent of the subject." Although this general position is now supported by legislation, our committee still feels concerned about certain points. There is a difference between the recording of information in the context of individual care, and the storage of data traceable to individuals in a more general register. Although the latter generally includes much less information than is held in a medical file, we find that the subjects' consent is still necessary before data can be stored;

otherwise their privacy will be violated.

This committee feels that the requirement for consent must take effect immediately upon the establishment of any system of records, whether it be a local, regional or national databank. The necessity for consent comes from the increase in accessibility and availability of data that systematic storage implies. The proposed national system discussed above is intended to further just such aspects. We feel that the client's consent must always be obtained before any information about them is recorded in files other than their own medical files. The need for consent is also implied by the requirement in the Data Protection Act that data be acquired lawfully, in that the provision of information to third parties is involved, and consent is required for that.

Our committee also believes that the subjects must have the right to have data deleted from a file, or stored anonymously. Even if the data in question may be of great value to persons other than the subject, for example his or her family, the right to ask for deletion must still be allowed. The Data Protection Act makes no such provision, but there is no reason that those holding files could not adopt self-regulation. A right to deletion could also be included in the regulatory frameworks governing the activities of those holding files (such as the Centres of Clinical Genetics); this has in some cases already been done.

The exercise of these rights requires that patients know in advance that their data will be included in a register with a wider purpose than just a medical file. Those keeping such registers are responsible for notifying the subjects and for obtaining their consent.

With regard to the right of subjects to inspect 'their' data, the following point is important. When a counsellor is informing a person, there is some scope for withholding some of the information at a given moment; this possibility does not exist in the case of access to personal files. Subjects are entitled to direct access to all information held on them, provided that there is no violation

of privacy of a third person; information on third parties is thus excluded from the right of total access. Genetic registries will often contain information on third persons, and will need to be organized such that access is facilitated. Subjects must also be able to request the correction of errors, filling of gaps and removal of irrelevant material, and the regulations governing clinical genetics files provide for this. Many potential requests for access are in fact forestalled, because the Centres for Clinical Genetics generally offer clients a written summary of their test results.

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Rights of relatives included in registries

The question must now be addressed as to the extent to which the above rights - of notification of proposed inclusion in a file, of withholding of consent to inclusion, of deletion of data, or conversion of data to anonymity, inspection and correction - should apply to relatives of clients. The Data Protection Act refers, in this connection, to "any person concerning whom personal data are held in a file": the criterion is thus the traceability of the data to an individual, rather than the status of the individual as a client or a relative. Under the Act, the above-mentioned rights are extended to family members for whom there are data, in a form which could permit tracing, in a genetic register. When the information is kept in a form which would not permit tracing the individual, family members do not have rights as to its inclusion in a file. A detail in the form of a designation (e.g. 'paternal grandmother') is theoretically traceable; the family member in question would then be entitled to direct notification by the holder of the file at the time that the information is first included (unless one of the exceptions detailed in Section 28 of the Act applies).

In practice, there have been few problems so far. In general, everyone on whom personal data are held in a system of clinical genetic records has been asked to give consent. Information on relatives included in the medical file (for

example, obtained from the family medical history) is not transferred. We would recommend, nevertheless, that the General Administrative Order made under Section 7 of the Data Protection Act regulate the recording of medical data in such a way as to obviate potential problems involving the rights of relatives noted in files.

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Uses of genetic data

Three uses of genetic data have been distinguished above, namely, in the context of individual care, of scientific and statistical research, and of official policy-making. As to the first, the use of personal data should normally be restricted to the purpose for which they have been collected and recorded. In the discussion on confidentiality above, it was clearly stated that the client's consent *is* always required for the use of genetic data for counselling their relatives. The question arises whether such consent can be inferred from the patient's agreement to the recording of their own data. The rules of privacy governing the clinical genetics registers specify that their uses include informing, counselling and treating relatives; one might, therefore, assume that clients are aware that their data might be used to help relatives. By not exercising their right to withhold consent to the recording of their own data, clients might be said to have implicitly agreed to this use of the information. However, this argument may take insufficient account of the subject's right to privacy. The consent should be requested in advance (when the data are first recorded) for use of the information within the centre for the purpose of aiding relatives, provided that such authorization is specifically requested, and obtained in writing.

Genetic data may also be used for research. Since the use of such data must be restricted to the purpose for which they were collected, information recorded for the purpose of individual care may not be used in research without the consent of the subject. Departures from this principle are permissible only in very special circumstances. As has been

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noted, the proposed legislation on medical treatment contracts permits such a departure only *if* four conditions are met. The committee finds this a rather broad formulation and feels that a restrictive interpretation is necessary, certainly in the case of genetic data.

When a register serves more than one purpose (for example, data may be used for both individual care and research), consent must be obtained for each of them. We agree that consent may be sought in advance for the use of data for several purposes, specified by name and known to the subject, provided that such authorization is explicit and as specific as possible. It will not always be possible to specify research goals in advance, but they should always serve medical purposes.

Finally, the third use of genetic data may be considered, in analyses done for policy development. Our committee questions the view that no conditions need be attached to the use of non-traceable genetic data in this context. Aggregated anonymous data can have consequences for groups of subjects, for example, statistical data on the costs of caring for the mentally handicapped could have repercussions for families with affected members. There are also questions as to the technicalities of non-traceability of data: the Social Insurance Council's commentary (SVR87) on the proposed legislation on medical treatment contracts noted that when a specialist holds information on a small number of characteristics, it is nearly always possible to trace data to specific individuals. While the Data Protection Act does not restrict the storage and use of non-traceable data, future advances in data processing may well create a need for protection against the uncontrolled use of previously-obtained data for the purpose of making policy decisions.

We consider that special vigilance is required with respect to the use of genetic data outside the field of health care. There is increasing pressure to make such information available for non-health uses: for example, genetic data may be sought for the assessment of individual financial claims,

or for access to employment or insurance. The protection of individual privacy in the context of genetic registries should exclude such uses. The Data Protection Act provides a way to do this: it prohibits the disclosure of data to third parties when the data are protected by professional confidentiality, and the subject's consent alone cannot lift this prohibition. This solution is, however, inadequate. If a person knows that information obtained from genetic testing is being held, and if they are asked, for example by a prospective employer, they are obliged to reveal that fact.

The question of the use of genetic data outside the field of health care will return in Section 4.4.

In summary, we believe that the use of genetic data should be limited to the purpose for which they have been collected, and that the privacy rules governing the information systems in question must include safeguards to ensure compliance with this principle. The purpose of a registry must be clear to the subjects, which will facilitate the monitoring of the uses of the data stored in it.

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Time limits

The regulations governing genetic registries must also set limits for the length of time that data may be held; the purpose of such databanks means that this needs to be longer than is usual in health care. The proposed legislation on medical treatment contracts sets a general time limit of ten years. In the case of genetic records, however, a ten or even a thirty-year limit is far too short, because the data must be held through several generations if they are to be of value. As families become smaller, the importance of a generous time limit becomes ever greater. Moreover, many parents seeking information already ask that their results be retained, especially for the benefit of their children.

It would not be practical to seek a solution in different time limits for different kinds of data. Extending the limits can create risks for the protection of individual

privacy, but there is little choice. Those holding genetic records have a twofold task, both the protection of privacy, and the storage of data often through several generations, in order to counsel relatives. The latter also means that information will often have to be kept after the death of the subject, as long as it is safe to assume that that person would not have objected.

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Monitoring systems for genetic records

Once again, we find the proposed legal provisions for monitoring compliance with the privacy rules governing systems of genetic records as a minimum and we urge the appointment of monitoring committees. The sensitive nature of genetic data and the growing pressures on their use argue for the desirability of self-regulation by the groups of institutions concerned. The rules governing records held by the Centres for Clinical Genetics already provide for such monitoring.

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Self-regulation

As has been noted repeatedly, our committee favours additional measures and safeguards for the protection of privacy. These may be attainable to a certain extent through the General Administrative Order now in preparation, to come under Section 7 of the Data Protection Act. Although the Order sets regulations for including sensitive data in personal files (and medical data, including genetic data, are considered sensitive), it does not provide all of the additional safeguards called for. We believe that self-regulation, by those holding genetic records, could provide a sound framework for the proper protection of privacy, and consider that further legislation for this purpose (in addition to the Data Protection Act) as advocated in the Upper House (EK88) is not needed, at least not at this time. Should self-regulation prove inadequate in offering safeguards (and research on this point will be needed), it will always be possible to draw up legislation specifically for this area.

Patients' organizations should be actively involved in the establishment and regulation of systems of genetic records and in monitoring their operation (as was done in 1983, when the privacy regulations for the Centres for Clinical Genetics were drawn up (KGC83)). Patients' organizations also have an important contribution to make in the contact between those holding record systems and the subjects of them, to be sure that clients' rights are realized.

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4.2.4 Storage and use of cell samples

Taking and analyzing samples of cellular material is normal practice in health care. In the case of genetic testing, it is often necessary to freeze such material, and to store it for long periods (An88, EAM88, Ge89, Kn89). There are two reasons for this, related to diagnosis. Firstly, prenatal diagnosis of hereditary disease often depends on comparisons of foetal cell material with that from both parents (carriers) and from a patient with the disease in question. *It is* necessary to store the material if it is to be available when required. Secondly, a relatively large proportion of sufferers from hereditary diseases die young, and the storage of cellular material makes further testing possible, should research produce new information. Diagnostic tests on material from a deceased patient can make a major contribution to subsequent genetic counselling for family members of the deceased.

The need to store material for diagnostic purposes led health insurers to fund a central cell bank, maintained at the Rotterdam Centre for Clinical Genetics; its work is covered under Section 18 of the Hospital Provision Act. In that section of the cell bank concerned with genetic testing for clients and their relatives, it is essential that the material be stored under the names of the clients, or at least in an easily traceable form.

A different situation is that in which the institute involved uses the stored cellular material, or allows it to be used, for research purposes. This research is usually aimed

at clarifying the molecular basis of genetic diseases and adds to our understanding of biological processes inside and outside the cell, and of how these break down to cause disease. It also aids the development of new and better diagnostic and, sometimes, therapeutic techniques. Virtually all such research, everywhere, makes use of cellular material from cell banks and laboratories. The patient's name is removed before the material is used so that it is impossible to identify the 'donor' other than through the health professional originally approached. The results of this research are published to make them available to geneticists throughout the world for use in, and improvement of, genetic testing and counselling.

Similar procedures apply to cellular material derived from tumour tissue. Here, too, the patient's name is removed and the tumour cell lines are made available to cancer researchers throughout the world. In both oncology and genetics research, such cell lines are a vital element in our developing understanding of the processes of disease.

As long as cellular material can be traced back to the 'donor', the material is personal and its analysis could produce sensitive information. It is therefore necessary to take great care in the acquisition, storage and use of such material, as well as of information obtained from it. Management and monitoring committees have been set up to oversee the work of the Rotterdam cell bank, which receives support from the European Community for its international work. The regulations of the cell bank for the use of the data obtained do take into account the requirements of the Data Protection Act.

We recognize the value of such self-regulation, but the advance now being made in genetic testing and the resulting increase in the scale of its use necessitate general safeguards for the storage and use of cellular material. The law is currently as follows:

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- the right of privacy and the inviolability of the

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human body mean that samples of body tissues may be taken only with the specific and voluntary consent of the individual concerned;

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those who donate organs, blood or germ cells intend their action to benefit others; 'donors' of cellular material for genetic testing, in contrast, deposit material with the information on them intending it to be stored. In principle it remains their property, including any new material that may be derived from it. Ownership of the material may be transferred to the cell bank, provided explicit agreement is reached on this point;

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- Once material has been placed in a bank, the rules of information, confidentiality and privacy apply, irrespective of the question of property. 'Donors' have the right to confidentiality (non-disclosure of data on the material), the right to information (data obtained from genetic testing) and the right not to know.

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- With respect to the uses made of such material, there is a parallel with the use of personal data: it must be consistent with the purpose for which the material was obtained. Bodymaterials are currently used for three purposes in the context of genetic testing: diagnostic tests for the benefit of 'donors', for their relatives, and for scientific research. As in the case of personal data, use of the material for purposes other than that for which it was obtained requires the consent of the individual concerned.

We urge the preparation of a code of conduct which would take fully into account the above requirements, while avoiding unnecessary barriers to the use of the material for the benefit of persons other than the 'donor', or for

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research. Specific, written agreements will be needed, in which the 'donor' states whether or not he or she:

- wishes to receive all information, both now and in the future;
- consents to the use of the material for counselling relatives, both now and in the future/-
- consents to the use of the material for research.

The first point relates to the right of 'donors' not to know; it is important that they be made aware, at the time the samples are taken, of the possibility of unexpected findings, and of new results from tests which may be done at a later date. This last point relates to the storage of cellular material taken from persons with (possible) hereditary diseases or susceptibilities whose nature is still unknown but which may be elucidated in the future. In such cases, preserved cellular material (including that from since deceased patients) may be of vital importance to parents or other relatives, because it may provide information on possible risks or on preventive measures.

The second point speaks for itself, while the third is related to pure and applied research, concerned with both diagnosis and therapy, whether in the field of medicine in general or of hereditary conditions in particular. In the context of such research it may be necessary to trace data back to their 'source', and plans for such research must of course be subjected to review by medical ethics and scientific committees.

We feel that a general consent given by the 'donor' would be sufficient, that is, a single comprehensive authorization not directed at one particular research plan. Such an authorization must state whether it includes research which would require traceability; when this is required (for example, in research on gene mapping), the material must be used anonymously, with only the counsellor originally approached knowing the identity of the source.

'Donors' are also entitled to change their minds,

reversing their decision to be informed (or not), or withdrawing their consent to the use of the material for the counselling of relatives, or, when the material is traceable to the individual, for research. In the last case, 'donors' also have the right to insist that the material be destroyed.

When material is taken from a non-viable foetus, a stillborn child or from persons deemed unable to make their own decisions, the mother or the legal representative must make the decision. When 'donors' have died, agreements reached with them during their lifetime must be respected, unless they have indicated differently.

Cell samples can be used for industrial as well as research purposes, and may become available to industry through collaboration between researchers and industrial organizations, or through international cell banks. In such cases, the material supplied must be untraceable.

Research on body materials (cells, and/or fragments of DNA obtained from them) may produce results which have commercial value; in the United States, case law is developing on the question as to whether the 'property rights' of donors would entitle them to the revenue accruing from such findings (Mo88). In our culture, body materials may not be the object of commercial transactions; indeed, in the case of blood donations, the principle of non-commerciality is laid down by statute. In The Netherlands, blood and organs are not provided in return for money. Consistent with this reasoning, we believe that 'donors', in the exceptional event that material is traceable, should have no right to benefit financially from findings based on material taken from them.

The rights of 'donors' can be translated into certain obligations which would apply to those operating cell banks. Firstly, they must ensure that the 'donors' have given their informed consent to the taking of the body material; to do this, they must provide complete information on the nature and purpose of the procedure, on the type of results which could emerge from analysis of the material, and on the uses that

will be made of both the material and the results. The purpose of the cell bank itself must be made clear, as well as the purposes for which such material can be used. With this information, 'donors' can reach a well thought-out decision on whether or not to consent to the storage, analysis and further use of the material. They must also be informed about their rights to change their mind/ and to have the material destroyed, and how to exercise these rights. Finally, cell bank operators must ensure that the material is stored with adequate attention to security. The protection of data obtained from analyses must also be regulated by the rules of privacy which govern the registry involved (see section 4.2.3.).

As far as is known, no problems have arisen during the past twenty years with stored cellular material in The Netherlands, but expected increases in the scale of genetic testing require extra attention to these safeguards. This would also encourage people to participate in genetic testing and counselling by providing cell samples. The voluntary nature of such donations remains of primary importance.

We recommend that cell-bank operators ensure the necessary safeguards in the first instance through self-regulation; they should provide written information on the functions of the bank, the conditions under which material may be used for different purposes, the risks associated with storage of material, the security measures taken and the manner in which contact is made with each 'donor'. Uniformity of this self-regulation would be desirable. We also urge that relevant patients' organizations be consulted in the drawing up of the regulations. Legislation could be considered if self-regulation proves to be unsatisfactory.

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4.2.5 Epidemiological studies

Epidemiological studies in the field of genetics are done to get an idea of the incidence and distribution, aetiology, options for prevention and for intervention

(treatment), and for the recording of, congenital and hereditary conditions. Until now, epidemiology has played only a modest role in the overall field of genetic research; the existing data pertain to only a fraction of all congenital and hereditary conditions. Moreover, the long time frame within which epidemiological studies are done, means that they cannot keep pace with the rapid advances being made in genetics. As a growing number of new diagnostic techniques *is* introduced, the methods used in the past can no longer produce useful results.

As the mapping of human genetic material continues to progress during the coming few years, and our knowledge of its interaction with given external factors increases, there will also be an improvement in our understanding of the many factors contributing to such conditions as cancer, cardiovascular disease and certain neurological and psychological disorders, which may lead to the development of new preventive techniques. Here, too, epidemiology can make a contribution, especially once techniques for testing hereditary predispositions and studying external factors have been simplified to the point that large-scale application is possible. The most active organization in the field of genetic epidemiology in The Netherlands is currently the Department of Medical Genetics of the University of Groningen, which also houses the Eurocat registry (see section 4.2.3.) and the record files on Duchenne's muscular dystrophy, cystic fibrosis and (recently added) the spinal muscular atrophies. The extension of the Eurocat registry to a new trial region (see section 4.2.3) will also mean further development of the collaboration between regional health services, clinical geneticists and epidemiologists.

Epidemiological studies on genetics must be set up such that the rights of participants are carefully protected. First and foremost, this requires that they give their consent, for example, by signing an authorization which clearly indicates the purposes for which sample of body material and medical data may be used. This authorization must also indicate whether the participants wish to be informed of

test results; this is relevant whenever test data may be traceable to specific individuals, although in the epidemiological study itself the data may be anonymous. Whenever traceability is essential or desirable, the names of the participants should be known only to their counsellors. Studies must be reviewed by the medical ethics committee of the institution concerned, to provide further safeguards that the necessary care is taken.

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4.2.6 Civil liability of the health professional

Professional errors in genetic testing and counselling could lead, for example, to the unforeseen birth of a child with hereditary abnormality. A counsellor might then be accused of having supplied incorrect or incomplete information, which could result in the client's making the wrong decision. The question then arises to whether counsellors are liable under Dutch civil law for the consequences of their negligence (Sc86). Two types of cases are possible: 'wrongful birth' lawsuits, brought by the parents, and 'wrongful life' lawsuits, brought by the child who was born with the handicap. Both of these are based on a claim that the child would not have been born had the counsellor done his job properly. The 'wrongful life' suit could be brought against the counsellor or against the parent(s); the former will be considered first.

In Great Britain, Germany and especially in the United States, there has been a development of case law on doctors' liability in cases of children born with congenital anomalies (Sc86). No such case has yet come before the Dutch courts, but this is not because of the legal system here; neither type of suit is necessarily destined to fail. Dutch law does, however, provide a stronger basis for 'wrongful life' than for 'wrongful birth' suits.

The basis of liability may lie within the contract between the counsellor and the client (supplying incorrect or incomplete information would then be a breach of that

contract) or outside of it (supplying incorrect or incomplete information would then constitute an illegal act). If there was a contract between the counsellor and the plaintiff, the suit may be based on both principles; if there was no contract, only the latter (unlawful act) would apply. *In the case of 'wrongful birth', the illegality lies in the infringement of the patient's right to make his or her own decisions in the matter of procreation. Such an infringement can be regarded as an attack on the person, which under future laws would constitute grounds for compensation for emotional damages. It does not matter whether the patient expressly requested genetic counselling or not; the counsellor is considered to have a legal obligation to provide, on his or her own initiative, any information which may be of vital importance to the patient. In a 'wrongful life' suit, the essence of the illegality would lie in the failure to take due account of the reasonably foreseeable interests of the unborn, or yet-to-be-conceived child. Since these problems have not yet arisen in The Netherlands, it is impossible to say whether the court would be likely to find that the counsellor has an obligation to provide services for the unborn child.*

Given the possibility that counsellors might be held liable under Dutch law for professional errors in the field of genetic testing and counselling, the possible social and legal implications must be considered. Two possible effects in particular merit attention: the impact on the medical practitioners' professional liability insurance, and the possibility of 'wrongful life' suits directed not at the counsellor but at the parents.

Regarding the former, the availability of insurance would not be jeopardized by either type of lawsuit. The cost of the medical services involved is largely covered by the Exceptional Medical Expenses Act, while basic costs for subsistence and services related to daily living and employment are covered by the General Disability Insurance Act. The courts consider the benefits provided under these Acts when determining levels of compensation, which means that

it will always be limited. The same applies to compensation for emotional damages; the sums awarded in The Netherlands are generally quite small.

Finally, in the case of 'wrongful life' lawsuits against parents who failed to prevent the birth of a child with an abnormality, the possibility of such a claim succeeding cannot be excluded, but it would probably be outweighed by the parents' right to make their own decisions about procreation. A theoretical obligation to forego having children when there is a risk of severe inherited abnormality would be in conflict with the individual's freedom of decision in reproductive matters. Moreover, the admission of such claims could result in a potentially very strong pressure to undergo genetic testing and counselling, and for the woman, to follow rules about how to live, and to submit to invasion of her physical privacy.

In conclusion, we do not consider that professional liability, in the context of genetic counselling, gives rise to any special problems within the Dutch legal system. We would oppose any trend in the direction of 'wrongful life' lawsuits against parents.

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4.3 Mass screening

This section will focus on the systematic screening of large groups of people for hereditary characteristics which may threaten their or their descendants' health. This kind of screening would be done outside the framework of individual health care, in the sense that the process is not initiated by an individual seeking assistance, but is offered by an organization which enables the members of the target group to make use of it. Screening may be done for various purposes and in various contexts, both within and outside the health care system. Screening for other than health-care purposes, for example in connection with insurance or employment, is discussed in section 4.4; this section deals with screening aimed at the early diagnosis of abnormalities to facilitate

prevention or early treatment. Three target groups may be distinguished in this context: pregnant women (prenatal screening), newborns (neonatal screening) and adults (mainly young adults).

Screening involves the application of some sort of test or examination offered by an organization. When it contributes to the prevention or early treatment of disease, it can be of great value, but it does have disadvantages. The members of the target group are, really, healthy people; they have no symptoms and will usually have no direct reason to suspect the presence of an abnormality. Screening can thus arouse unnecessary anxiety and, if an abnormality is detected, provoke a sense of inferiority; it could also provide a false sense of security.

Whenever a screening programme is proposed, it will be necessary to include an assurance that its benefits will outweigh potential disadvantages; a pilot study is often a valuable instrument to identify possible problems. Every screening programme must also include a plan for an evaluation procedure. Consistent with an earlier Health Council report (GR80), our committee also believes that the following conditions must be met:

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1 The natural course of the disease in question must be well known, and the members of the target group fully informed about it.

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2 Prevention or treatment of the condition must be available. The screening of neonates or young adults is permissible only if the expected benefits of preventive or therapeutic intervention in the case that an abnormality is detected are considerable and worthwhile.

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3 The test to be used must be reliable and have adequate predictive power. The subjects of the study must be aware that screening is not always specific for diagnosis and that supplementary tests might be needed. The test must be able

clearly to distinguish between those affected with the condition, those who could be affected, and carriers (i.e., those not themselves affected but able to transmit the condition to their offspring). The benefits of screening to persons with a true positive test result must outweigh the damages suffered by those with a false positive or false negative result. These damages may include unnecessary follow-up testing and in some cases interventions in the case of false-positives, and no further action in the case of false-negatives.

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4 Informed consent of the subjects is essential. Participation in the screening must be entirely voluntary, with neither direct nor indirect pressure to be brought upon subjects. A further condition is that the subjects must be fully informed of the nature and the significance of the test, of the risks associated with it, etc. The emotional reactions of the subjects to the correct or incorrect diagnosis or the suspicion of an abnormality are often underestimated, and this point must also be properly covered in the information given in advance of participation.

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5 The privacy of the subjects must be respected while screening is being done. There is a real and serious danger that certain persons might be stigmatized, so that their personal and social positions might be damaged. Rigorous measures must be taken to eliminate this danger, for example by strictly observing secrecy.

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6 Contact must be maintained with family doctors and others who receive details on test results, and whose job it is to give support and guidance to those who have been tested.

It is vital that the advantages of screening outweigh the disadvantages; before a screening programme is started, it must be evaluated using the criteria adopted to assess this. In the case of genetic screening, particular attention should

be focused on the possible psychosocial risks. Considering the nature of the conditions and the risks involved, those who are tested will regularly experience more than the usual psychosocial problems. Certain of the screening programmes are already subject to a form of monitoring, for example through conditions attached to their funding.

Legislation now pending on mass screening will provide a basis for evaluation and adjustment.

As advances are made in the field of genetic testing, it can be expected that more screening programmes will gradually be introduced (Gr79, PC83, WH083, Ca87, EAM88, GR88, GR88b, We89). Technical feasibility does not, however, necessarily imply desirability; every proposed screening programme must be evaluated against at least the above-mentioned criteria.

In the following sections, certain reservations of this committee about proposals appearing in the scientific literature as to changes in existing screening programmes, or the introduction of new ones, will be expressed for the cases of prenatal screening, neonatal screening and the screening of adults, mainly young.

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4.3.1 Prenatal screening.

For several years now, considerable attention has been given to two types of screening:

- the screening of every foetus for neural-tube defects by determination of alpha-foetoprotein (AFP) levels in the maternal serum in the sixteenth week of pregnancy and
- tests for chromosomal disorders such as Down's syndrome.

The desirability or otherwise of introducing AFP screening in The Netherlands has been fully discussed in the Health Council report on neural-tube defects (GR88b), which recommended a trial programme covering a large region and

lasting two to three years.

In section 3.2.3., where it was noted that the main indication for prenatal chromosome testing was maternal age (36 years of age or more), we rejected the suggestion that the test be made available to younger women on request. In other countries, there is growing interest in various new techniques for identifying chromosomal anomalies in the foetus (Wa88). Some experts take the view that a maternal-age threshold is not the ideal basis for assuming increased risk of abnormalities, and urge that serum testing be offered to all pregnant women, since a subnormal AFP level can indicate an increased risk of chromosome abnormalities.

We consider that this type of screening programme is associated with a number of serious problems which require careful study before a decision is made to proceed with them. These include the facts that:

- many factors could influence maternal serum AFP levels, to raise or lower them;
- there *is* a relatively high probability of missing a chromosome abnormality in the foetus (the possibility that this can be increased by a combination of tests, such as for AFP together with chorionic gonadotrophin, oestriol, remains to be confirmed);
- there would be two standards for prenatal testing, one being the highly reliable tests such as chorionic villus sampling (CVS) and amniocentesis, where there is a known risk of chromosome abnormality, and the less reliable tests, such as the maternal serum AFP test; it would not be easy to explain to pregnant women the limitations of the latter type;
- amniocentesis would be required in a large number of pregnancies (approx. 5-6% of the total), although chromosomal abnormalities would be detected in only 1-2% of them.

Considering all of the above, we believe that there is as yet no reason to amend the currently accepted indications

for prenatal chromosome analysis (using CVS or amniocentesis). Once again, it must be emphasized that our society must respect the position of those who do not consider abortion acceptable.

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4.3.2 Neonatal screening

Screening of newborns in The Netherlands has been limited thus far to two treatable conditions: the hereditary disease phenylketonuria (PKU), an enzyme disorder, and congenital hypothyroidism (CHT). If new screening programmes are to be considered, distinction must be made between treatable conditions, untreatable conditions and predispositions (i.e., susceptibility to external factors which could then result in development of certain conditions). In the following, we describe our view on the main neonatal screening programmes running in other countries or advocated in the literature.

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Treatable conditions

In the case of PKU and CHT, the development of serious physical and mental handicaps can be prevented by diet and medication, respectively, when these are begun as soon as possible after birth. In addition, the parents can be offered genetic counselling. There are no other hereditary conditions for which convincing evidence exists that the disease symptoms can be prevented by screening and early intervention after birth. There are some cases for which there is evidence that neonatal screening and early intervention after birth can improve the prognosis of the children concerned, including sickle-cell disease and (beta)thalassaemia; galactosaemia; adrenal hyperplasia resulting from 21-hydroxylase deficiency, and biotinidase deficiency. The desirability of screening for one or more of these disorders is a matter requiring further study and consultation.

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Untreatable conditions

Differences of opinion are apparent from the

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literature regarding the desirability of neonatal screening for disorders for which no treatment is available. Suggested benefits include the fact that the patient can be offered medical and psychosocial support from a very early age, and parents and child may well be spared a distressing route through the health-care system. Moreover, early genetic counselling and possible preventive measures may help to prevent the birth in that family of more children with the same anomaly.

The disadvantages are that there is little if anything to offer the young patient and the parent, who are informed of a fatal condition long (sometimes years) before the first symptoms will appear. There is a real danger of early 'medicalization', partly out of fear, and a false positive test result can cause a great deal of unnecessary (although temporary) anxiety.

When the test result concerns an untreatable, late-onset condition, such as Huntington's chorea, there is another great disadvantage: the child will receive, unasked, very unpleasant news about his or her future. This is the main reason that we reject the idea of neonatal screening for untreatable late-onset conditions.

We have considered at length the cases for and against neonatal screening for untreatable conditions which will become manifest in early childhood. One screening programme which has recently attracted growing interest is that for Duchenne's muscular dystrophy (DMD). Should such a programme be introduced in The Netherlands? The main benefits are reviewed below.

Firstly, early diagnosis makes it possible to inform the parents in good time - i.e., before the woman is pregnant again - of the risk of recurrence, which would enable them to take preventive measures if they so desire. Moreover, potential carriers within the family, for example the mother's sisters, can be informed about the risks they may face. The

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isolation of the DMD gene, and characterization of the mutations which lead to DMD, have greatly improved our ability to detect carriers of this abnormality.

Secondly, doctors do occasionally fail to recognize the first symptoms of what is a rare condition, so that diagnosis may be delayed by as much as two years or even longer. Timely and accurate diagnosis saves parents a long and often frustrating route through the health-care system. Until the diagnosis is made, parents suffer anxiety, which can also lead to suffering in the family.

Finally, when screening is accompanied by information and psychosocial support, the parents of a child with an abnormality can better prepare themselves for the special tasks of care and upbringing of that child. They can also take steps related to their work, place of residence (distance from treatment centres, for example) and their home (adaptations to cope with the child's handicap).

DMD screening has, however, disadvantages as well as benefits. First, parents are made aware of a fatal condition that affects their child long before the first symptoms appear. While the impact of such presymptomatic diagnosis is not well described, it is likely that there is a real danger of early 'medicalization', that is, bringing a still-healthy person into the medical circuit. Second, fully reliable tests, which would permit really accurate prediction of the risks, are not yet available in all cases. It is not yet possible, for example, to distinguish between DMD and Becker's muscular dystrophy (which manifests between the ages of five and ten and usually shortens life), so that a positive test result cannot lead to a clear prognosis to inform the parents. Moreover, if DMD does not develop, it will be clear that the child is affected with Becker's dystrophy; when a person is burdened with this unasked-for information, this constitutes an infringement of his or her right to decide for him/herself whether to request genetic information. There are, however, indications that advances in research will make an

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accurate diagnosis possible in this case.

One of the benefits of screening for DMD, to avoid a frustrating circuitous route through the health-care system, can also be attained by improving the early detection of developmental abnormalities.

On the basis of the evidence currently available, we are not convinced that neonatal screening for Duchenne's muscular dystrophy is in the interest of the children with the condition, and we would therefore advise against the introduction of such a programme. This position will, however, be less valid if the diagnosis were to become more reliable and if the expectation that treatment will become available is borne out. This would cast an entirely new light on neonatal DMD screening, so that developments related to DMD and screening for it must be followed carefully. We further recommend that it be emphasized to health professionals that there is a need for special attention to 18-month-old boys displaying delayed motor development; they could then be tested early for DMD. There is a role here for the teams in The Netherlands concerned with the early detection of developmental abnormalities.

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Predispositions.

There are predispositions to disease, that is, susceptibilities which are genetically determined and can be detected in newborns, even when the risk they present to health will appear only later in life. When a newborn is found to be sensitive to a given substance, something can be done about it. In Sweden and elsewhere, newborn babies have been tested for alpha-1-antitrypsin deficiency (Ma88), an autosomal recessive condition affecting 1 in 1,500 babies. In 20-30% of these, an untreatable liver disease appears at an early age; later on, emphysema can develop. Carriers of this condition (with one normal and one abnormal gene) probably have an only slightly increased risk of respiratory problems upon exposure to smoke or dust. The Swedish screening programme and its

follow-up were done to study the natural course of the condition as well as to protect the children affected from the harmful effects of airborne substances such as tobacco smoke, in the hope that early respiratory problems could be prevented. After the programme had been in effect for a number of years, its psychosocial effects were evaluated (Ma88). It was found that some parents of children involved in the study suffered from physical and mental problems, and the early detection of the disorder had not been successful in limiting the main risk factor for the children's health, their parents' smoking habits. If such a programme were to be considered in The Netherlands, it would be necessary to give appropriate emphasis to information and support services.

It is likely that in the future, systematic detection in neonates of an increasing number of genetically-determined susceptibilities (for example to cardiovascular disease) will become possible. We do not feel that a generalized assessment of the advisability of neonatal screening programmes can be made. Screening for predispositions which will only lead to disease later in life raises a number of problems and questions, including the following:

- The benefit to the newborn child is remote and often uncertain. It is not that immediate danger to the child is avoided, only that information is acquired which may be useful in adulthood.
- The genetic information obtained must be stored for many years to be of use to the individual. It must be remembered that this information could be of great interest to others, such as insurers or employers; if it were to become available there could be adverse social consequences for that individual.
- The information is obtained without the consent of the individual (the newborn) concerned, which may contradict the principle that individuals must be able to decide for themselves what they wish to know about their genetic constitution. Should the substitution of the child's consent by the parents' perhaps be limited

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to those cases in which it is clearly in the interests of the child's welfare?

- Finally, the possible preventive benefit of such screening could also be achieved by offering the tests to certain risk groups later in life; individuals could then decide for themselves whether they want to be tested.

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4.3.3 Screening adults

Screening adults (usually young adults) could serve several purposes, including the detection of genetic anomalies which will or could lead to disease at a later date. Although the possibilities for this type of screening are presently limited, in the future it may become possible to screen for hereditary abnormalities in fat metabolism, for example, which may lead to cardiovascular disease, or for a predisposition to certain hereditary forms of cancer. Such programmes should only be permitted if participants will clearly benefit in the form of treatment or prevention (for example by avoiding high-risk activities which could facilitate development of the disease), according to the criteria described above.

Another reason for this type of screening might be to identify persons or couples at risk for producing a handicapped child, for example by detecting carriers of autosomal recessive mutations (see Appendix 1). Although the carriers themselves will remain healthy, if both members of a couple are carriers, there is a 25% chance of their having an affected child. The advantage of mass screening, over small-scale screening limited to families at risk because of the birth of an affected child, is that mass screening could prevent the birth of the first handicapped child. In other countries, programmes of this type involve screening, for example, for Tay-Sachs disease (which mainly affects Ashkenazi jews) or for the haemoglobinopathies or blood disorders common among those of African or Mediterranean descent (PC83). In this country, such screening programmes could at some stage be introduced to detect blood disorders among Dutch citizens of

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Turkish or Surinamese origin, and for cystic fibrosis, one of the most common hereditary conditions in The Netherlands.

Screening programmes of this nature would be permissible only if the benefits outweigh the potential disadvantages. The experience in other countries has not always been positive, but there are examples of worthwhile results; mass screening in Sardinia to identify carriers of certain haemoglobinopathies resulted in an impressive decrease in the number of affected children (Ca84).

If adult screening programmes are to contribute to the freedom of choice and the welfare of those involved, the general criteria must be supplemented with the following specific requirements:

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- Detailed consultation with representatives of the target group must take place, to decide on the programme's acceptability, since that group might become stigmatized. This is especially important when the target group is an ethnic minority.

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- Adequate and objective information must be provided through programmes of public education. It is important to make the distinction between the carrier status and being ill or afflicted with the disease. It is also essential that people do not feel forced to participate in the programme; there must be no hint of eugenics.

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- Carrier screening aimed at detecting an increased risk of having a handicapped child must be offered when the subjects are old enough to benefit from this information. Children should not, therefore, be screened in this case.

Finally, the need for individual genetic counselling can be expected to increase sharply through the introduction of screening programmes. Preparations must therefore be made to meet this future need.

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4.4 Genetic testing for purposes other than for health care

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4.4.1 Genetic testing and insurance

Our growing knowledge of the genetic origins of disease may have consequences for the access to services relevant for an individual's future health. For example, in private insurance schemes which are based on freely-entered contracts, an insurer could reject an application for a policy. Although access to basic health insurance and social security is generally guaranteed, this is not so for life insurance, private disability insurance or individual pension schemes. Genetic information could be expected to play an increasing role in insurance policies in these areas.

It is in the interests of the insurers to be able to estimate the future health risks of the applicants, and applicants are obliged to provide all relevant information, including genetic information. Under section 251 of the Commercial Code, a failure to disclose relevant facts, accurately and completely, can lead to the cancellation of the policy by the insurer.

Access to collective pension and disability insurance schemes is closely linked to access to employment; this issue is therefore dealt with together with those related to employment medical examinations (see section 4.4.2).

In this section, the use of genetic data in relation to access to life insurance, private disability insurance and individual pension schemes is considered (see also Mi88, Sa88, So88, Wi88); including both the potential use by insurers of the available genetic information and the possibility that insurers may require those seeking insurance to undergo genetic testing.

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4.4.1.1 Insurers' interest in the use of genetic information

Private insurers base their decisions on the issuing of policies, and the charges and conditions attached to them,

on actuarial calculations of the likelihood of loss or damages. It is important for the insurers that the premiums charged be consistent with the risks being insured; to achieve this, they distinguish homogeneous groups of people having the same probability of the same claims. This results in premium differentiation, members of different groups paying different premiums. The insurers need, therefore, information on the risks involved for those applying for insurance in order to determine whether and under what conditions they can provide coverage.

Differentiation can also be by self-selection; it is thought that those who know, thanks to genetic testing, that they are free from certain risks will be less likely to apply for insurance than will those at risk of developing some condition. Those at risk might even want to insure themselves for especially large sums. This kind of self-selection is particularly relevant to those types of insurance for which the individual decides not only whether to apply for insurance but also to what limit. Premiums are based on average risks, so insurers will try to neutralize the effects of self-selection by checking whether particular individuals constitute above-average risks. Considering all of this, the advances in genetic testing are obviously of great interest to insurers; developments in early diagnosis and early prediction of late-onset disorders would permit them to determine risks with ever-increasing accuracy.

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4.4.1.2 Objections to the use of genetic information

There are objections at the level of the individual and of the society to the unrestricted collection and use of genetic information on hereditary conditions and risks, and to the imposition of medical tests for selection purposes (see also We87, Fr88, Ge88a, S188, WRR88).

The objections for the individual are related to the privacy of those applying for insurance. Requiring applicants to disclose genetic information would constitute a major invasion of their privacy, considering the sensitive nature of

such information. Such information, moreover, often involves other persons than the applicant, such as his or her blood relatives, whose privacy would also then be to a certain degree at stake. If those applying for insurance were to be obliged to undergo genetic testing, they might be confronted with unwanted but distressing information, for example if the test reveals a condition which will develop in the future, and cannot be prevented. These objections are not exclusive to genetic testing, but are especially relevant in its case. Genetic testing greatly expands the scale on which predictive diagnosis may be possible, and extends the time over which predictions can be made. The information it provides is of lasting value and often concerns blood relatives and descendants as well.

Social objection to the use of genetic information for insurance selection is related in the first instance to the expectation that it will be used to differentiate among those applying for or covered by insurance. More and more people (perhaps including relatives and descendants of those immediately involved) may find it difficult to obtain coverage on acceptable terms. This could result in social isolation for those genetically at risk, not necessarily because they are ill, but only on the basis of their genetic predisposition. Another social objection is that individuals may be deterred from genetic testing by fear of difficulty in obtaining insurance; potential problems in this area are likely to make people more cautious about seeking genetic counselling.

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4.4.1.3 Desirable measures

There may be a tendency to developments through which the advances in genetics would finally harm those the new diagnostic techniques are intended to help. Already, applicants for insurance are asked by the insurers about medical conditions which may affect relatives; the applicants themselves are often asked whether they have attended or plan to attend a Centre for Clinical Genetics. Since people are required to disclose all relevant facts, they may be inhibited

about applying for certain types of coverage. The introduction of genetic testing might lead insurers to ask clients more specific questions about the family.

We find it unacceptable that people affected from birth with a genetic predisposition should be faced with additional social obstacles, and that their relatives should also be at a disadvantage in this way. It is felt that the suspicion that fear of insurance problems may deter some individuals from genetic testing is well-founded; in an atmosphere of growing uncertainty, genetic testing could be perceived as threatening.

At the same time, however, we recognize that insurers are entitled to protect themselves against exploitation by persons with prior knowledge of their own risks, for example of developing a serious hereditary disease in the near future.

These objections are occasionally countered by the argument that no real social problems are involved; private life or disability insurance are seen as luxuries, since basic living standards are guaranteed by the state social security system. Our committee would point out that the national insurance system guarantees only a basic standard of living, while the disability scheme for employees is also subject to a ceiling. Many other people need to insure themselves against the risk of incapacity or early death to allow themselves or their surviving relatives to maintain approximately the same standard of living, for example, life insurance is taken to cover loans for a new business or house.

Wider premium differentiation based on genetic information could also benefit some people, those with 'good' genetic prospects. Insurers might conceivably reduce premiums on the basis of 'good' genetic results, but one might ask what weight should be accorded genetic risks, compared to the other kinds of risks insurers include in their calculations.

It could also be reasoned that since every human being has genetic traits which may result in certain medical conditions and it is only a matter of time until all of the

traits are identified, eventually the difference between those with and without risks will disappear. Even if this were true, however, the problem would not be solved; the difference between slight risks and serious risks would persist, and serious risks will always be of interest to insurers.

These arguments are concerned mainly with the social consequences, but individual objections are also important, especially those related to violations of privacy. We consider that the various objections - violation of privacy, the risk of deterring people from seeking genetic counselling, the danger of a rift in society - must be met, and that a certain amount of restriction on the use of genetic information by insurers will be necessary.

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Possible measures

To deal with the above objections without forgetting insurers' legitimate interests, various types of measures are possible, including the following:

- a ban on genetic testing specifically by or on behalf of insurers;
- a ban on the use of existing genetic information;
- linking the measures to an insurance ceiling which can be regarded as customary and appropriate;
- financial coverage for uninsurable risks.

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Ban on specific testing

This option - that genetic testing not be permitted as part of medical examinations required for insurance access - is consistent with the principle that people should be free to decide whether to seek information on their genetic constitution. Genetic information can be highly distressing and the choice of knowing or not should not be influenced by the financial interests of third parties. This option could be given substance in a number of ways:

- all genetic testing could be excluded from medical examinations required for medical insurance;

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- the ban could be limited to genetic testing which may produce distressing information;
 - all medical tests which could produce distressing information could be excluded from medical examinations required for insurance.

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Ban on the use of existing genetic information

Again, there are various ways in which this option might be implemented. Firstly, there could be a general limit on the requirement to disclose relevant facts which would allow applicants for insurance to withhold genetic facts on the grounds that their nature and their relation to privacy makes them different from other medical information. For example, they often provide information on other family members, have lasting value, and often, predictive power. A counter-argument to this is that other kinds of medical information may also violate privacy or have predictive value; there are also practical difficulties in distinguishing genetic from non-genetic facts.

Secondly, the disclosure requirement could be limited to serious risks, the crucial factor no longer being the genetic nature but rather the seriousness of the risk. The more serious and the more difficult to treat the condition, the greater the violation of privacy when information about it is disclosed. This option would allow applicants to be asked about less serious risks. The difficulty of distinguishing between genetic and non-genetic facts would be replaced by that of deciding what is serious or not. This would also take little account of the interests of the insurers.

Thirdly, the distinction could be made between the certain and the uncertain, so that insurers could be allowed to consider, in deciding on acceptance, 'certain' risks known to the applicant; in the case of 'uncertain' risks, this would be less appropriate. The determining factor, then, would not be the genetic nature of the risk, but the certainty or not of the prognosis. This option was put forward in a report on gene technology drawn up by a committee of the West German

parliament. But it has a number of disadvantages, including the definitions of 'certain' and 'uncertain', the difficulties of pinpointing when a condition will develop and how serious it will be, and the fact that the number of 'certain' prognoses will increase with advances in genetic testing.

A very different option, finally, is to leave intact the disclosure requirement, but to withdraw the penalties for non-disclosure after a set period of time. Depending on the details, this option could satisfy the insurer's interests, while still allowing applicants to withhold information which could violate their privacy. An objection to this could be that applicants would, in some cases, be 'rewarded' financially for withholding relevant information.

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Linking measures to a customary level of insurance
Measures could be linked to a ceiling on insurance benefits in different ways. For example, the suggested limit on the disclosure requirement could apply up to but not above the ceiling. The rationale for this proposal is that the types of insurance in question - life and disability insurance and pension schemes - are commonly used by large numbers of people, but most policies are within a certain range of coverage. Insurers would then be allowed to apply risk selection only when applicants sought a level of coverage above that range. This approach would have the advantage of limiting self-selection, but the disadvantage would be the difficulty of setting an equitable ceiling.

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Measures to cover uninsurable risks

The feature common to the options in this section is that they do not restrict the insurers' rights to use selection procedures or the applicants' obligation to disclose relevant information. Instead, they try to solve the problems of those who cannot obtain insurance, or only on onerous terms. This could, for example, be solved by creating a pool or fund to finance insurance coverage for such people; the fund itself could be built up from a general surcharge on

insurance premiums or from government contributions. Against this is that the fund is not a long-term solution, since diagnostic advances will bring more and more genetic risks to light, which would force increasing numbers of people into the pool. The objection against invasion of privacy would not be removed, and such a scheme would be difficult to reconcile with a private insurance system.

Finally, in other countries, the solution is sometimes sought in agreeing on non-payment of a set proportion of the insured benefits when death results from a previously-designated disease. This is not feasible in The Netherlands, because there is a ban on the disclosure of causes of death.

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4.4.1.4 Privacy and genetic information in the context of insurance

Transfer of personal medical data between insurance companies, or between departments of one insurance company carries a real risk of invasion of privacy. Storing information on the relatives of the insured, without their knowledge (perhaps because the information is there with the information on the insured) can itself be considered a violation of privacy. It is also difficult to ensure that the information is used only for the purpose for which it was obtained, that is, relevant to an insurance application or claim. *It is not acceptable for insurers to consult medical data already in their possession in connection with another matter, such as an application for insurance from another family member.* It is also essential that a clear time limit be set on the retention of personal medical data, and that the data be destroyed once the time has expired. Section 4.2.3. dealt with the need to regulate registries of genetic information; this need extends to the files held by insurers.

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4.4.1.5 Recommendations

We can offer no complete and final solutions to the problems outlined above; the issues are too complex, and expert input is needed from the insurers themselves. Moreover,

these problems are not relevant only for genetic testing, but for all types of medical examinations. Nevertheless, we feel obliged, in the context of this report, at least to suggest a few provisional solutions for the problems arising in relation to genetic testing. This in no way decreases the need for further study and consultation on the use of predictive medical facts in a broader sense in relation to access to social facilities; consultation is also needed with the insurers.

In arriving at the recommendations below, we have constantly kept in mind both respect for the individual's freedom of choice about undergoing genetic testing, and the importance of unimpeded access to such testing.

The first recommendation is that genetic testing specifically in connection with an insurance application be prohibited. Everyone should be able to choose whether to receive information on their genetic constitution and a requirement to undergo testing in order to obtain insurance would be an excessive infringement of personal choice and may violate family privacy. Another principle of ethics is also at stake: no one may be forced to undergo testing which could damage their physical or mental health. Moreover, the insured person's greater interest in not being subjected to unwanted and unrequested genetic testing is compared with the insurers lesser interest in knowing. As long as the insured has not been tested, no benefit can be derived from information unavailable to the insurer.

A ban on genetic testing for insurance purposes would mean that insurers could not try to identify genetic risks of any kind, serious or slight, 'certain' or less certain, distressing or not; it would not, however, imply that genetic risks identified in the course of an insurance medical examination, not designed for that purpose, could not be taken into account in a decision about accepting an applicant. It is clear that there are also non-genetic predictive medical data about which objections could be raised if they are

deliberately collected in relation to an application for insurance.

The second recommendation, closely linked to the first, is that the use of data collected previously should be restricted. A ban on genetic testing for insurance purposes would not eliminate the objections to their using existing information, so limits should be set on the right of insurers to ask questions. Our committee would favour a combination of measures: applicants for insurance should not be required to disclose the results of genetic tests done on them or their relatives, as long as the coverage sought is below the ceiling appropriate to the applicants social and financial circumstances.

Such a regulation would at least partly meet the objection that privacy is violated by a requirement to disclose genetic information. It is also consistent with unimpeded access to genetic testing, when there is no need to reveal its results. Moreover, it allows insurers some scope for protecting themselves against self-selection: at levels of coverage above the ceiling, the obligation to disclose all relevant facts is retained, while for all cases allowing insurers to consider any genetic data which may emerge from other forms of medical examination (for example, an increased risk of a hereditary form of intestinal cancer revealed by analysis of the applicant's medical history during a general examination). The essential point here is not the genetic nature of the data, but whether or not they were obtained through voluntary genetic testing. When the requirement to disclose results of genetic testing is waived because the coverage requested is below the ceiling, the information is no longer relevant, and insurers may cease to request it.

Although practical objections can be made to this option, we feel it to be consistent with the need to maintain access to genetic counselling without fear of the consequences. Given the current practices in genetic counselling, so that clients are provided with written

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information, *it* will be clear to all concerned what is and is not covered by the disclosure requirement.

With regard to the setting of the ceiling for disclosure requirement, a case-by-case approach is needed to establish 'customary and appropriate' limits. Universal limits are inevitably arbitrary and will not reflect individual circumstances. The social and financial circumstances of each applicant must be considered in setting the 'ceiling of real need'. We recognize that the applicability and the details of this criterium will need further working out.

This committee believes that regulation will be needed to implement the restrictions on using genetic information in relation to insurance applications. The opening of the European frontiers in 1992 will bring a need for Community regulations; the developments taking place in EC insurance law may be relevant here. EC directives to harmonize insurance law are now being prepared; they cover the freedom to establish insurance activities and freedom of movement of services. This development will require further study, but it can be assumed that restrictions based on self-regulation will cease to be effective after 1992; regulations will have to be anchored in national or Community legislation.

Continuing the theme from section 4.4.1.4., we believe that there is an urgent need for regulations to protect privacy in the insurance sector. The Data Protection Act, which does not prescribe the application of such rules in the private sector, provides no safeguards for the protection of privacy related to records of genetic data on persons applying for or covered by insurance. We would therefore recommend regulation by means of the General Administrative Order envisaged in Section 7 of the Act.

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4.4.2 Genetic testing and employment.

Genetic information may be of interest not only to insurers but also to employers (OTA83, Gev87, Ko88), because the reaction of the individual to potentially harmful factors

in the work environment - ionizing radiation, certain chemicals - depends partly on physical functions determined by genes, such as a capacity for recovery or detoxification, or the immune system. Certain genetically-determined predispositions or susceptibilities may also be a disadvantage at work, when they facilitate damage to the person's health. Finally, environmental factors can affect genetic material directly.

It must be remembered here that very little *is* known at this point about such environmental factors in the work sphere, and that there are few reliable methods to measure them.

A possible application of genetics to employment practices would be to test current and prospective employees for components in their genetic constitution which could imply a significant chance of damage to their health if they do certain types of work, or are exposed to certain substances. The results of such tests would affect decisions on their acceptability for specific jobs. Genetic testing could also be used to investigate whether particular types of work cause damage to the genetic material itself. Early identification of potential or actual damage could lead to intervention, for example to changes in working conditions.

Genetic testing could thus be relevant to employment in two situations:

- as a means of selection for specific jobs, to check for any genetically-determined susceptibility to factors which could damage health. Such testing would be done only once, at the time of application for employment.
- as a form of monitoring during employment, to detect damage to the genetic material as a results of working conditions. This testing would be done repeatedly.

Before discussing the acceptability of these two ways to apply genetic testing, we will first review the links

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between occupational diseases and genetic constitution.

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4.4.2.1 Occupational health and genetic constitution

A growing number of occupational diseases is being identified in which genetic factors play a role. These usually involve abnormalities in the processing of substances by the body (metabolic disorders) or abnormal reactions to particular situations, such a shortage of oxygen. Genetic components are most easily demonstrated when only one, or at most a small number of genes are responsible. If several genes are involved in an apparent increased sensitivity to factors in the work environment, the link will be very difficult to establish because of the great diversity in the genetic material. Moreover, environmental and genetic factors are not always easy to differentiate, while certain genetic 'configurations' may have a protective effect under other circumstances (carriers of sickle-cell disease, for example, have increased resistance to malaria).

Theoretically, every 'genetic configuration' is associated with some level of physical resistance to potentially harmful influences, but to identify these in detail is difficult, considering the many ways in which the body can defend itself against external factors. The predictive capacity of genetic testing for occupational diseases, and the scope for preventing such conditions through genetic testing, are very limited at the present stage of scientific development.

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4.4.2.2 Genetic testing as a condition for employment.

Genetic tests may eventually be developed which can help to protect workers' health, but the possible benefits will be offset by disadvantages. Requiring people to undergo genetic testing as a condition for particular jobs could confront them with distressing information which they had not freely chosen to receive. The use of genetic testing as a selection tool could result in exclusion of workers sensitive to particular external factors, rather than leading to reduced

risks and improved working conditions for all. It could also increase the inequalities in access to employment as discrimination might be increasingly based on characteristics or sensitivities not directly related to disease. Exclusion from work on the grounds of genetic constitution could have serious consequences for the employment prospects of the individuals concerned, and indeed for their blood relatives. Apart from the last point, these objections are not specific to genetic testing, but apply generally to all medical examinations related to employment. They would, however, appear to be especially important in the case of genetic testing, particularly when the analysis of risk covers more territory than is relevant to the individual's medical suitability for the job in question.

The Comprehensive DNA Committee (a committee reporting to the Dutch government in the early eighties) rejected genetic testing in connection with access to employment (BDC83), on the grounds that the Working Conditions Act requires that work be adapted to the worker, rather than the other way round. A second argument used by this Committee was that the purpose of employment medical examinations is to determine the state of the individual's health at the time of employment; carrier screening would thus not be relevant. Genetic testing of employees (current or prospective) would be permissible if it were done entirely at the employee's own request and not as a means of selection by employers.

The recent report of the Interdepartmental Working Group on Employment Medical Examinations adopted the provisional standpoint that tests for particular genetic predispositions should not be a part of medical examinations conducted in connection with access to employment (IWA89).

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Employment medical examinations

Before considering whether there is a place for tests of genetic constitution in the context of an employment medical, it may be sensible to look first at the function and content of these examinations in general. The

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Interdepartmental Working Group felt that they should be concerned with the individual's medical suitability for a particular job(s); it also made the following recommendation:

"In many situations, it is inappropriate to include medical examinations in the selection process, partly because they lack validity and do not effectively distinguish between applicants, and partly because of the possible social consequences for the individuals concerned. In such situations, it may be desirable to conduct post-hiring examinations, aimed at counselling and support rather than selection, as part of the induction process. (.....) The information sought through medical examinations conducted for selection of applicants should be relevant to the job in question; there should be no unnecessary violation of applicants' privacy nor mental or physical integrity. To cover situations in which medical examinations are needed for selection purposes, criteria must be formulated to determine the permissibility of the methods used. Initial suggestions for such criteria are the following:

- i the health problem concerned must be an important one, with major implications for the (health of) the individuals concerned and those around them;
- ii the validity of the tests used must be such that possible errors of interpretation are proportional to the ultimate goal;
- iii any disadvantages of the methods used (risks, costs, social consequences, etc.) must also be proportional to the ultimate goal;
- iv individuals could be selected out only when it cannot reasonably be expected that the nature of the work be adapted;
- v when test results provide grounds for it, the medical officer conducting the examination should ensure that appropriate follow-up care is offered by the curative health services;
- vi the methods used in medical examinations must be compatible with the constitutional protection of subjects' privacy and physical and mental integrity;
- vii the methods must not result in erosion of the subjects' legal position."

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Permissibility of tests for genetic predisposition as
a means of selection

Two of the views in the Working Group's report are relevant to this point. Firstly, the view that in many situations, such as when the job in question involves no special health requirements, medical examinations have no place in selection procedures. We endorse that standpoint and would add that in such situations there is also no

justification for genetic testing. There is a need, however, for a clearer definition of the situations in which pre-hiring medical examinations can reasonably be required because of the nature of the work.

Secondly, the report links the pre-hiring medical examination, when this is justified, to the specific purpose of assessing the applicant's medical suitability for the job in question. We also fully endorse this position: medical examinations should be limited to assessing the compatibility of the physical and mental capacities of the applicant and the demands of the job. Moreover, the sole purpose of the assessment is to protect the health interests of the person concerned and those around him or her, who could be fellow workers or, for example, passengers in a bus he or she is driving. Medical examinations may not serve other interests, such as the financial interests of the employer, which may be at stake in selection procedures. Tests of genetic predisposition, therefore, should focus only on possible damage to health caused directly by doing the job in question, or on future medical conditions which could affect job performance so as to create risks for other people. There is no place in this position for attempts to predict the probability that individuals will become unable to do their work, when that is not directly influenced by the job in question.

In order to determine the permissibility of tests of genetic predisposition in selection procedures, when both of the above conditions are met, we considered first whether the tests involved met the criteria formulated by the Working Group. No exceptions can be allowed; all conditions must be met if such testing is to be permitted and this is not the case for current tests. The role of genetic constitution in occupational disease is still far from clear, which makes it difficult to establish its importance. Genetic components can be unequivocally demonstrated in only a limited number of occupational conditions, and even the tests used to detect

these are often indirect, with an accuracy of less than 100%, which is not sufficient. The first two criteria proposed by the Working Group are thus met only in exceptional circumstances or not at all.

Besides these scientific objections to tests for genetic predisposition, which may disappear with advances in testing techniques, there are objections of principle, embodied in the third, fourth and fifth of the Working Group's criteria. We feel that these criteria, concerned with pre-hiring medical examinations in general, need strengthening for application of tests for genetic predispositions. The nature of genetic testing gives extra weight to both the individual and the social objections to 'involuntary' medical examinations. Firstly, there is the threat to privacy; as has been stated, we believe that people must be able to decide for themselves whether they want information on their genes, or not; such tests cannot therefore be used in selection for employment. Secondly, the social consequences of such testing for the individual - reduced job prospects immediately or in the longer term, and stigmatization - can be far-reaching, and may extend to his or her blood relatives.

The criteria are concerned with the protection of the individual against the personal disadvantages of the test methods used. There are, however, also general social objections to the use of these tests as a selection tool, which would retain their weight even if all the criteria were met. Such tests would increase the chances of unfair discrimination, for example, if a particular genetic configuration were associated with ethnic traits. The configuration could even become the hallmark of a 'new' social category, a 'genetic proletariat'. If testing attempted to identify increased susceptibility to particular diseases, it could lead to the creation of disadvantaged groups in the society.

We conclude, therefore, that pre-hiring medical

examinations should not include tests for genetic predisposition, although the possibility of special cases in which the absence of such tests could lead to avoidable damage to health was considered. For example, if a person from a family affected by Huntington's chorea, with its early symptom of periods of inattention, applied for work as a bus driver, there would clearly be a health threat both to the person and to those for whom he or she was responsible. Moreover, there is a test available with an accuracy of nearly 100%. This test, however, requires the cooperation of relatives to determine the pattern of DNA markers within the family which would indicate the presence of the disease gene, so that there is little or no possibility that this test could be required as a condition for employment. Techniques may eventually be developed which could detect the disease gene itself in the individual at risk, in which case it could be argued that the disadvantages of the test would be balanced by its purpose, to protect the safety of others, and that the criteria would, therefore, be met.

Although we continue to reject tests of genetic constitution as a selection tool for employment, it is nevertheless recognized that in the future, very exceptional cases could arise in which the general social objections should be set aside in favour of a demonstrable benefit for health (in the above example, of the passengers), provided that all criteria are met. If this conclusion were to be reached, considering all the circumstances, the employer could then require the applicant to choose between being tested (to eliminate uncertainty) and withdrawing his or her application.

We recommend that the conditions governing pre-hiring medical examinations be brought into line with this standpoint. One good way to do this would be to augment the criteria already drawn up by the Interdepartmental Working Group on Employment Medical Examinations, strengthening them as necessary and supplementing them with the general social proviso that testing must not lead to unfair differentiation between or discrimination against groups within the society.

Compliance with these conditions is urgently needed, and if self-regulation does not produce the desired results within a reasonable time - perhaps six months after the government has stated its position on the Working Group's report - then legislation should be introduced.

Finally, in agreement with the Comprehensive DNA Committee, we note that there can be no objection to tests of genetic predisposition that are done at the request of prospective employees, who may well wish to know whether certain factors in the work environment may present particular risks to them before they decide whether to take the job. Such tests would be entirely separate from the selection procedure, and their outcome would not be subject to any obligation to disclose relevant information.

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Use of existing genetic data

The next issue to be considered also arises in the context of access to insurance; this is the extent of the applicant's obligation to disclose any existing information on genetic predispositions which may be relevant to the job in question (VGR79, Gev87). It is generally assumed that an applicant is under some obligation to inform the doctor conducting the examination of any relevant medical facts, and indeed that it is in his or her interest to do so. But considering the applicant's right to privacy, and dependent position, there can be no question of complete freedom of choice, and that obligation extends no further than can reasonably be demanded in the light only of the health requirements of the job in question. Applicants must disclose any information relevant to the demands of the job, even when the information might be sensitive; again, the essential point is the medical suitability of the applicant for the job.

Consequently, the right of the examining doctor to ask questions is similarly limited; it does not exceed what is necessary to know for the purposes of the examination. Doctors will have to balance possible benefits from obtaining the

information against the infringement of the applicant's privacy. Our committee endorses the position taken by the Working Group, that the content of questions and questionnaires should be determined but also limited by the purposes of the examination.

Further, applicants should be entitled to refuse to answer certain questions, when there are substantial grounds to do that. The Working Group advocated the establishment of such a right, which is consistent with the limits on one's legal obligation to provide information for social security.

We expect that job applicants will often find it difficult to decide whether a question is relevant or not, and to justify their decision. As far as the use of existing information in pre-hiring medical examinations is concerned, we feel that it is not sufficient that the right to ask questions be restricted to those directly related to the purpose of the examination, coupled to a right to refuse to answer. Examining doctors must comply with the condition that questions must be strictly relevant to the purpose, and if self-regulation does not produce this result within a reasonable period of time, legal regulations should be introduced.

If the above rules are observed, there is no call for special rules for genetic information. Although these data can be highly personal and sensitive, the condition of 'relevance to the purpose' when strictly observed should offer adequate safeguards for the protection of privacy. In contrast to access to insurance, where theoretically all genetic facts are relevant and may be of interest to the insurer, in the case of access to employment there are clear limits set by the purpose of the examination.

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4.4.2.3 Privacy and genetic data in relation to hiring.

Prospective employees are naturally vitally concerned that genetic information collected during hiring procedures be handled with great care. The Interdepartmental Working Group

set out regulations for this and included them in its recommendations for the legal protection of those who undergo medical examinations (IWA89). Briefly, the regulations state that these persons are entitled to be fully informed, that their consent is required for the reporting of test results or for any exchange of data, that they are entitled to obtain and inspect copies of reports, and that the data may not be used in any other way nor be retained for any longer than is necessary for the purpose of the examination conducted.

We endorse these recommendations, but feel that they require strengthening for the particular case of genetic data.

Results of genetic tests are intended to be used only once, at the time of the medical examination; after the decision about hiring has been made, there is no reason to keep them and they should normally be destroyed. When there may be grounds for retaining them (for example for the monitoring of the workers' health during employment), the data will be held for purposes different from those for which they were collected. The new purpose must then determine which data will be stored and for how long, etc. We would like to see a rigid division between the information held by the firm's medical officer and the employer's personnel files. When the medical officers maintain personal records as defined by the Data Protection Act, they are bound by that act; if they have data in another form, this would probably be covered by the proposed legislation on medical treatment contracts, and medical officers are in every instance bound by professional secrecy. Our committee considers that including genetic data in such databanks (see comments on the protection of privacy in section 4.2.3.) need to be better regulated because of the requirement for consent and the right to have records destroyed. The necessary regulations could also be incorporated into the General Administrative Order envisaged in Section 7 of the Data Protection Act. Pending statutory provisions, the above safeguards for employees' privacy must be achieved through self-regulation.

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4.4.2.4 Genetic testing and access to collective disability insurance and pension schemes

Access to collective disability insurance and pension schemes involves interests other than those for access to employment (IWA89). The risks to be insured (death and invalidity) are not usually related to the work done, and the purpose of medical examinations conducted for access to such schemes is different from, and often in conflict with, that of the employment medical. Theoretically, certain genetic information quite irrelevant to the medical suitability of the individual for a particular job, and therefore not obtained in the context of the employment medical, might be helpful in assessing life expectancy, and thus be of interest to the operator of the pension scheme. The medical examinations conducted in the process of hiring and for access to a pension scheme are nevertheless often combined; such combined medical examinations may lead to confusion for all concerned and lead to wrong decisions. Moreover, it is not necessarily obvious that entry to a collective scheme should depend on a medical examination. Joining a personal insurance or pension scheme is a matter of personal choice; the individual can decide whether to apply for insurance, and for how much, while entry into a collective scheme is generally linked to employment with a particular firm. Joining the scheme is one of the conditions of employment and the risks of all of the employees are covered collectively. Given the nature of collective coverage, the phenomenon of self-selection (involving personal decisions on application for insurance and for how much) is unlikely to play a significant role.

Following earlier and similar recommendations, the Interdepartmental Working Group suggested a number of regulations. These are, briefly, that pre-employment medical examinations should provide the basis for both hiring decisions and admission to collective pension schemes. If a medical examination is done specifically for a pension scheme, it should have no influence on hiring, so that pension-related

medicals should not contribute in any way to recruitment and selection procedures.

These separate medical examinations would normally be unnecessary, unless there is a proven self-selection effect, but the Working Group regarded the risk of self-selection as slight and doubted the utility of pension-related medical examinations, partly because they would have low predictive value, at least for individuals.

These recommendations by the Working Group are endorsed by this committee. The nature of collective pension schemes means that there are no convincing arguments for compulsory medicals as a condition for participation; there is little point in considering the admissibility of test of genetic predisposition or of the use of existing genetic information in this context.

We would like to see the Working Group's recommendations put into practice in the near future; if this is not achieved through self-regulation, legislation should be introduced. Should special circumstances arise which might justify compulsory medicals (for example, a self-selection effect), the same principles should be applied as in the case of access to insurance on an individual basis (see section 4.4.1)

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4.4.2.5 Genetic monitoring

The purpose of genetic monitoring is the early detection, through chromosome or DNA analysis, of damage to the health of the employees (Ja86). The aim is not to uncover genetic predispositions but to identify any effects the work environment might have on the genetic material of the employees.

We will limit ourselves to a few brief comments. In the course of monitoring employees' health, tests may be used to pinpoint environmental effects which may be precursors to damage. Generally, there can be no objection to continuous health monitoring, as long as it is voluntary; the post-hiring

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medical examinations proposed by the Interdepartmental Working Group could be the starting point. Monitoring should be linked to primary prevention, that is, for the improvement of working conditions to minimize risks to health; it is not a substitute for prevention. Even if genetic monitoring did not reveal adverse effects, it could not be concluded that working conditions are satisfactory. It should go without saying that employees' health can also be affected by non-physical environmental factors; if effects on health are observed, the first step must be to improve working conditions.

Although chromosome or DNA analysis could, in principle, be included in the monitoring process, we urge caution: the tests currently available are less than perfect, the consequences for the individual worker are not clear, and test results could be misused. We also recommend revision of the Health Council report on the mutagenicity of chemical substances (GR81). The Health Council is, in fact, considering issuing a new report on this question, which would focus particular attention on the potential and the limitations of the different tests.

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4.4.3 Free movement of people

We would like to point out that there is a danger that knowledge of genetic risks might lead to restrictions on freedom of travel. There are indications that some countries request genetic information for visa applications, with the visa being refused when applicants may face certain genetic risks. Our committee regards this state of affairs as unacceptable. If discrimination is indeed being practised on the grounds of genetic predisposition, steps must be taken in international relations to put an end to such restrictions.

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4.5 Looking ahead

Chapter 3 covered current developments in science; it is now the turn of their non-medical aspects.

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4.5.1 Pre-implantation testing and the protection of the pre-embryo.

Much attention is currently focused on the in vitro testing of human pre-embryos for hereditary abnormalities. This subject was discussed in section 3.4.2., in which it was noted that the technique may in the future make the checking of pre-embryos for the presence of certain anomalies possible, so that only those without would be implanted in the uterus. Pre-implantation testing may have advantages over the tests now used later in pregnancy. The procedure, which involves removing one or more cells from the pre-embryo for genetic testing, is still in the experimental stage. It is not yet known whether the removal of cells can damage the pre-embryo's further development, and answering this question may very well require research on human pre-embryos.

In this section, we will consider whether experimentation aimed at developing safe and reliable pre-implantation tests is morally and legally permissible. Most ethicists agree that although it may be the very earliest stage of human development, the pre-embryo has an intrinsic value. There are, however, wide differences of opinion in our society as to what extent it merits or has a right to protection. Some see it as no less entitled to protection than a baby or indeed an adult; while not denying that a pre-embryo differs biologically from a newborn child, they regard this difference as morally irrelevant. Others consider that the right to protection develops with the development of the unborn child.

In legal terms, human beings, as holders of subjective rights, do not enter the legal community until they are born. Indeed, a stillborn child is not legally considered to have existed. The foetus is thus not covered by the European Convention on the Protection of Human Rights and Fundamental Freedoms, and the legal significance of birth is underlined in Article 2 of the Dutch Civil Code. That the law does not recognize the foetus as a person does not mean that it has no

status at all, although this has yet to be determined legally. The status of the foetus differs from that of maternal organs, in that it is more independent; the legal literature refers to the status nascendi of the foetus, starting from the moment of implantation in the womb.

According to the legal literature, the position of the embryo before implantation - the pre-embryo - can be described as status potentialis (Le88); it does not yet have status nascendi, but does have a potential for development not possessed by the separate sex cells. If life before birth is considered to have a growing entitlement to protection, then the embryo in statu potentiale merits protection to some degree, but not necessarily to the same degree as the implanted embryo in statu nascendi. With regard to the duration of the status potentialis, there is no obvious reason to distinguish between the pre-embryo in vivo and in vitro.

The views of the members of our committee differ on the ethical issue of the pre-embryo's right to protection. A majority accepts the concept of a progressively growing right; there is an obligation to protect the pre-embryo, based on its human origin and its potential to develop into a child, but this is tempered by the fact that its process of development has only just begun. As the new life develops, so its right to protection grows. One of the members, however, consider that the foetus - and a fortiori the pre-embryo - has a greater right to protection than adults or older children, who have independent lives.

To assess the permissibility of experiments aimed at developing pre-implantation tests for use on human pre-embryos, some understanding is needed of the advances made in prenatal testing over the past twenty years. The purpose of prenatal testing is to reach a diagnosis at the earliest possible point in the foetal developmental process, to facilitate early abortion when this is desired. This approach is consistent with a growing right to protection. Prenatal

testing previously relied on amniocentesis in the sixteenth to eighteenth week of pregnancy; now, chorionic villus sampling enables chromosome, biochemical and DNA analyses to be done from the tenth week. *If* the concept of a growing foetal right to protection is accepted, then pre-implantation testing would represent a further step in the right direction, of intervention as early as possible in foetal development. Technical problems had to be solved in the development of amniocentesis and chorionic villus sampling; this is now the case for pre-implantation testing, especially with regard to the possibility that the technique itself might cause abnormalities. What is known about the safety of amniocentesis and chorionic villus sampling is based mainly first on animal experimentation and later on epidemiological studies on human beings. The same process is likely to be followed for pre-implantation tests, although some research on human pre-embryos may be needed.

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The use of 'excess' and specially-grown pre-embryos. As far as experiments for development of pre-implantation tests are permissible, there is no legal distinction between the use of excess and specially-grown pre-embryos for that purpose; the origin of the pre-embryo is irrelevant to its legal status. This does not imply that it would be legal to artificially create pre-embryos; there is no mention of this case in the statutes.

Ethically, there is a difference between experiments on excess pre-embryos and the creation of pre-embryos purely for experimental purposes. The former takes advantage of the existence of pre-embryos produced in the course of treatment for infertility but not (or no longer) useful for that purpose, while the latter, the pre-embryos are made only for experimental purposes, and were never intended for implantation in the womb.

One of the members of our committee objects in principle to both types of experimentation on pre-embryos. The

others hold divergent views as to whether the distinction (between using excess pre-embryos and deliberately creating pre-embryos for experimental purposes) is morally significant enough to make the former permissible but not the latter. Some members see the creation of pre-embryos only for use in research as irreconcilable with the pre-embryos' right to protection; they object less or not at all to the use of excess pre-embryos produced for IVF because these would have been destroyed in any case. Yet other members are prepared to accept both types of experimentation, especially when, as mentioned above, the research is aimed at answering questions needed to help people.

The members who would accept experiments on pre-embryos in this framework would subject them, as a minimum, to the following conditions (set out in the report by the Health Council on artificial procreation, GR86).

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Scientific conditions;

- The knowledge sought must not be obtainable by other means (for example, through animal experimentation).
- The pre-embryo should not be allowed to continue growth for longer than is necessary to answer the question formulated in the test protocol, and never longer than fourteen days after fertilization (excluding any period during which its development is arrested).
- Pre-embryos used for experiments must not be implanted,

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Procedural conditions:

The members setting these conditions consider that prior consent must be obtained from the persons providing the reproductive cells, from the medical ethics committee of the institution concerned, and from the Health Council's Central Committee on the Ethics of Medical Research.

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4.5.2 Gene therapy

The scientific aspects of intervention in the genome

were considered in section 3.4.3; here other aspects are considered. A distinction may be made between interventions for therapeutic purposes and for other purposes. Therapeutic purposes would be for the correction of hereditary abnormalities. For a recessively inherited disorder, this involves the introduction of a 'healthy copy of the gene in cells if one (in sex-linked disorders) or two (in autosomal recessive disorders) abnormal genes are present. In dominantly inherited abnormalities, the abnormal gene would have to be inactivated. Non-therapeutic interventions would include activation of the operation of a normal gene, or the introduction of new genes for a purpose other than the prevention of disease (that is, for eugenic purposes).

Theoretically, either type of intervention could be done on either somatic cells or germ line cells (either sperm or ova, or the undifferentiated pre-embryo), but in practice the latter is not a realistic possibility. *If* genetic intervention were to involve pre-embryos, links with the issues considered in the previous section would be clear. Firstly, diagnostic tests focused on the genes would have to be done, before deliberate changes could be made to the pre-embryonic genome; pre-implantation diagnosis of genetic abnormalities is therefore a precondition for germ-line cell therapy. Secondly, the introduction of clinical germ-line cell gene therapy would probably have to be preceded by non-therapeutic research on human pre-embryos to acquire information about the safety of the technique. The previous section considers the regulatory aspects of such experimentation.

Genetic intervention which does not fall into these categories would also be possible as part of fundamental research.

The potentially far-reaching consequences of interventions in the human genome have stimulated debate, in this country and abroad, on the social acceptability of these techniques (PC82, OTA84, F185, Fr85, GR86, Ro86, Ca87, La87, He87, EMRC88, Le88, We88, We89). The Council of Europe, for

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example, adopted a highly cautious attitude in 1982, in which only certain therapeutic interventions in the genome were considered, under certain conditions, to be permissible. In the United States, the President's Commission issued a report in 1982 which specifies the conditions to be met before permission can be given for somatic-cell gene therapy experiments to be done on human beings (PC82). This provides for review and approval by ethics committees at various levels. In The Netherlands, the Comprehensive DNA Committee found that somatic-cell gene therapy did not in principle raise any new ethical problems, but it rejected intervention in the genome of germ cells (BDC83). The Health Council's report on artificial procreation (GR86) considered germ-line cell gene therapy to be unacceptable, at least for the time being, because of the great risk of mutagenesis and the lack of certainty as to the effectiveness of this kind of treatment. In 1988, the Medical Research Councils of eleven European countries, including The Netherlands, issued recommendations regarding gene therapy (EMRC88): only somatic-cell gene therapy, and not germ-line, should be considered, but even in this field, experiments on human beings would not be justified as long as so many risks are associated with the technique.

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Somatic-cell gene therapy

This involves correcting abnormalities by adding, or inactivating, genes in body cells other than the sperm or ova (for example, in the blood-forming cells of the bone marrow, see section 3.4.3.). Because of the enduring nature of the change introduced, the procedure is analogous with organ transplantation. Somatic-cell gene therapy is a complex treatment which could considerably improve the quality of health. Its effect is limited to the individual patient, so that the decision to have it can be seen as a matter of personal choice. This is in principle no different from such current treatments as organ transplantation.

The technique is presently at an early, experimental

stage. When consideration will be given to human gene-therapy trials in The Netherlands, they will be regulated by the rules for medical experiments on human beings. They must, for example, include appropriate standards of care and observe all rules on patients' rights; they will have to be approved by a medical ethics committee. In the light of the risks outlined in section 3.4.2, however, we believe that additional regulations, concerning both scientific and procedural issues, will need to be applied until the experimental stage has been passed. The Central Committee on Medical Research Ethics, recently established by ministerial order and attached to the Health Council, will have to review all experiments. Research should also be monitored continuously to ensure compliance with the protocols; proposed legislation on medical experiments provides for this procedure through the Central Committee.

When proposed experiments are being reviewed, particular attention must be given to scientific acceptability and to safety; they must satisfy stringent conditions. Among other points, it must first be established, through animal and in vitro cell culture experiments, to a high degree of certainty that:

- the introduction of a 'healthy' gene or the inactivation of a 'diseased' gene will not result in unwanted changes, which may for example initiate cancer processes or otherwise disturb cell or tissue metabolism in the treated cells' other genes, or in their expression;
- the treated gene displays the desired pattern of expression.

Once the experimental stage has been passed, that is, when risks have been reduced to an acceptable level and a reasonable chance of success is ensured, we would not consider somatic-cell gene therapy to differ in any significant way from other medical treatments. The generally-accepted rules concerning therapy, such as the obligation for practitioners

to provide information and to obtain the patient's consent, will of course apply.

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Germ-line cell gene therapy

This type of gene therapy (see also section 3.4.3.) involves changes in the genes in sperm or ova, or in the pre-embryo. It is more radical than somatic-cell gene therapy, because the changes introduced can be passed on to subsequent generations. This therapy is not just a matter of personal choice, because it potentially affects the individual's future children and their descendants as well. The responsibility of the present generation to future generations comes into play. The purpose of gene therapy in germ-line cells, as for somatic cells, is to eliminate disease. It would, however, appear to be more 'efficient' than somatic-cell therapy; because the changes introduced are transmissible, the therapeutic effect extends to subsequent generations.

A number of issues come up in assessment of the acceptability of germ-line cell gene therapy. Firstly, there is the matter of the right to inherit a genetic pattern not altered by deliberate human action; in 1982, the Council of Europe determined that respect for human dignity entailed the recognition of such a right (CE82). It added immediately, however, that therapeutic intervention in the germ-line could not be seen as violating this right. Reports in the recent literature reject this reasoning, and condemn germ-line cell gene therapy a priori as incompatible with the human dignity of future persons (Lo85, Ca87). We do not believe that such an a priori condemnation is tenable; this therapy could indeed be regarded as a manifestation of respect for human dignity.

Theoretically, the treatment offers the possibility of preventing serious suffering in future individuals, but a major difficulty with intervention in the germ-line is that it is impossible to predict all of its consequences. Animal experiments have shown that the risks to the treated embryos are considerable; the embryos rarely develop into viable young, and those which do survive are often found to

have serious abnormalities, probably as a result of the genetic intervention. There may also be longer-term health risks, such as an increased likelihood of cancer in subsequent generations.

The risks associated with germ-line cell gene therapy are such as to exclude any possibility of its clinical application in the foreseeable future. Should further animal experimentation result in significant reduction of the risks to the following generations, however, some authors have suggested considering non-therapeutic laboratory experiments involving altered human embryos, aimed at obtaining a clearer picture of the risks to future children. The stand taken by this committee in the previous section on research on diagnostic tests on pre-implantation embryos also applies here. It is doubtful, however, whether research on human embryos would produce sufficiently reliable conclusions about the risks, particularly the long-term risks, of germ-line cell gene therapy.

Before germ-line cell gene therapy - still purely theoretical - can be applied, pre-implantation diagnosis will have to be done, and this is still being developed. Hereditary defects will have to be detected before they can be corrected. In nearly all cases, the germ cells of the couple involved will produce not only defective pre-embryos but also pre-embryos free from the expected abnormality. Since risks are associated with germ-line cell therapy, it may be preferable to implant only pre-embryos free of the anomaly, instead of attempting to correct the defect with gene therapy. On the other hand, selective implantation implies the destruction of defective pre-embryos, while correction of the anomaly would avoid that destruction. The option to be preferred will depend on whether priority is given to avoiding unnecessary health risks to descendants, or promoting the chances for development of every embryo, healthy or otherwise.

Further, it is not possible to distinguish clearly between therapeutic and non-therapeutic objectives in the context of interfering with the genetic material of the germ

cells, which makes *it* difficult to prevent misuse of the knowledge obtained for purposes not related to therapy. Other objections to interference with the germ cells include the erosion of humanity's natural diversity, the uncertain consequences for our biological evolution, and the impossibility of reversing the changes once they have been introduced. Our position on non-therapeutic genetic manipulation is made clear in the next section.

Considering all of the points related to germ-line cell gene therapy, we feel that the many uncertainties surrounding the technique's safety constitute sufficient grounds for urging a voluntary moratorium on this type of experimentation in human beings.

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4.5.3 Genetic intervention for non-therapeutic purposes

In this section, the acceptability of genetic intervention for other than therapeutic purposes is considered,

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Non-therapeutic interventions in somatic cells

It is conceivable that in the future it will be possible to modify somatic cells for non-therapeutic purposes. To assess these possibilities, the distinction between disease prevention and positive eugenics is important. In the case of the former, interference with bone marrow cells, for example, might decrease the chance of developing cancer for some people. Should it emerge that the probability that a person infected with HIV will develop AIDS is determined partly by a genetic factor, then it might be reduced by altering or eliminating that factor. Such applications - still entirely theoretical - are not in principle unacceptable; although disease is not eliminated, the individual's chances of contracting a serious disease may be considerably reduced. If experimental preventive genetic interventions in somatic cells should emerge as a real option in the future, then, as for experiments in somatic-cell gene therapy, the merits should be decided by weighing the advantages against the disadvantages

(health risks) to the individuals concerned.

We would like to stress, however, that great expectations should not be entertained regarding preventive genetic intervention in somatic cells, particularly in connection with abnormalities (or the risk of them) determined by multiple factors. The application of such techniques is beyond the current horizon of science.

It is difficult to imagine what might be achieved by eugenic intervention in somatic cells, but should it become feasible in the future, we would urge great caution in its use. Not only would such intervention serve no medical purpose, but it could expose healthy persons to major health risks with no obvious benefits to offset them.

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Non-therapeutic interventions in the germ line

Regarding the acceptability of non-therapeutic interventions in the germ line, it should first be pointed out that the objections to germ-line cell gene therapy in human beings outlined in section 3.5.2 apply with even greater force to interventions for non-therapeutic purposes. Should this technique ever prove to be feasible and safe (which is presently far from the case) then in principle, it could be ethically and legally acceptable precisely because of its therapeutic usefulness. The elimination of disease would justify intervention in human genetic material even if that had unalterable consequences for future generations. In the absence of this justification, the intervention would be regarded as unacceptable, particularly when its purpose was eugenic. The current generation may not determine arbitrarily the genetic patterns of its successors and any attempt to 'grow' individuals with characteristics that happen to be valued in the present would be an illegitimate exercise of power over future generations.

This rejection of non-therapeutic genetic interventions in the germ line should be reconsidered only in cases in which they can be demonstrated to be aimed at preventing disease (by correcting a genetically-determined

predisposition to disease), and would not create short- or long-term health risks.

Professor H.D.C. Roscam Abbing
Chair

G.M.W.R. de Wert
Secretary

E.T.M. Olsthoorn-Heim
Secretary

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APPENDIX 1

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Heredity and disease

From: the Health Council publication 'Het gen en de geneeskunde' (Genes and medicine), a report compiled by G. Feenstra, The Hague, 1988.

In 1977, the Health Council estimated that half of all deaths of children in the first year, and 20% of deaths in the first fifteen years, were related to genetic abnormalities. In The Netherlands, approximately ten thousand children are born every year with hereditary disorders or congenital anomalies of varying severity.

Hereditary disorders and congenital anomalies can be caused by various factors. Congenital anomalies - defects immediately identifiable at birth - may have a genetic basis, but this is not necessarily the case. Important exceptions are defects due to alcohol or drug abuse by the mother during pregnancy, or to infections such as rubella and toxoplasmosis contracted during pregnancy.

Hereditary disorders, although they are always present at birth may not be manifested immediately; indeed, some manifest themselves only well into adult life. Huntington's chorea, for example, is a serious disease of the nervous system which does not develop until after the age of 30 or 40.

Hereditary disorders and congenital anomalies may

result from a defect in the number or the form of chromosomes, or in one or more separate genes.

Human genetic material is present in every cell, grouped into 46 chromosomes which in turn form 23 pairs. All but one pair are autosomal (that is, not sex chromosomes), while the two chromosomes determining sex are designated as pair 23. Females have two X chromosomes, and males one X and one Y chromosome.

A well-known example of a chromosomal anomaly is Down's syndrome, which results from the presence of three instead of the normal two chromosomes (trisomy) of pair 21. The abnormality results from an error in germ-cell division before fertilization; it usually occurs in the ovum and is more common in older women, although errors in the production of sperm cells can also contribute to the occurrence of Down's syndrome.

The 46 chromosomes carry among them at least 50,000 genes, the basic units of DNA which determine, or code for, the particular features of the individual. Hereditary disorders may be caused by defects in a single gene, or in several genes at the same time.

Approximately four thousand disorders have so far been attributed to defects in a single gene (monogenic disorders); although each of these is rare, together they affect one percent of all newborns.

Single-gene disorders fall into two groups, depending on the mode of transmission, which may be dominant or recessive. In dominant transmission, the abnormal trait overrides the normal, and the condition can be passed to the child if only one of the parents has the abnormal gene. Each child will then have a 50% chance of inheriting the affected gene. A recessively-inherited condition, on the contrary, can

only develop if both (healthy) parents have the abnormal gene; each child then has a risk of 25% of inheriting the affected gene from both parents, and thus of developing the disease.

Single-gene disorders can further be distinguished according to whether the gene involved is on an autosome or a sex chromosome. Commonly-occurring disorders in the latter group are the X-linked recessive conditions such as haemophilia and Duchenne's muscular dystrophy. The disorder may be carried by a healthy woman and passed on to her sons, who have a 50% chance of inheriting the condition. Her daughters will be healthy but will have a 50% chance of carrying the gene themselves.

In addition to the various single-gene conditions, there is a much larger category of multifactorial hereditary disorders and congenital anomalies. Most of these are still poorly understood; it is assumed that several defective genes are involved, or that there is detrimental interaction between genetic constitution and environmental influences, but precisely what happens and how is still largely unknown. Examples of such conditions include congenital heart defects, spina bifida, juvenile-onset diabetes, epilepsy, rheumatism, certain mental diseases and clubfoot.

Not all disorders resulting from genetic defects are inherited from the father or mother; children can suffer from serious genetically-determined conditions even when neither parent's genetic material shows any abnormality. This results from spontaneous mutations in the germ cells of one or the other parent, and such changes cannot be predicted.

Spontaneous mutations play an important role in some hereditary disorders; it is believed, for example, that twenty percent of all single-gene conditions arise from new mutations; in the case of some X-linked disorders the proportion may be much higher, perhaps thirty percent.

At this time, little is known with certainty about the causes of new mutations, although exposure to toxic substances or ionizing or ultraviolet radiation and the effects of viruses are thought to play a role. That new mutations do arise implies severe limitations on our ability to predict and, if so desired, to prevent hereditary diseases.

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APPENDIX 2.....
Centres for Clinical Genetics

Since 1979, seven organizations concerned with clinical genetics have grown up in The Netherlands; among them they operate eight centres. This became possible with the introduction of social insurance coverage for postnatal chromosome analysis, chemical tests for hereditary metabolic disorders and amniocentesis. In addition, grants were available under the Exceptional Medical Expenses Act to cover genetic counselling in complex cases and for postnatal enzyme tests and prenatal biochemical tests for hereditary metabolic disorders.

Close cooperation among all the concerned parties over a period of ten years has produced an organizational structure for clinical genetics in the Netherlands that stands as a model for other countries.

The eight centres are closely linked to teaching hospitals and/or university laboratories, but are organizationally separate from them. The centres have a regional function and their number was determined by internationally-accepted standards which stipulate, for example, that one centre for genetic counselling is sufficient for a region with a population of two million. Chemical testing for hereditary metabolic disorders is also done in these eight centres, while postnatal chromosome analysis is done not only in the eight university laboratories but also in a number of district laboratories (Enschede, Eindhoven).

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Prenatal screening for chromosomal anomalies and neural-tube defects (by testing alpha-foetoprotein levels in amniotic fluid) is done in the university centres, while amniocentesis and chorionic-villus sampling is done in a small number of local gynaecological centres.

The indications for the various tests are stipulated rather precisely and the centres are asked to submit annual reports on the numbers of patients/carriers tested in the different indicated groups, as well as the numbers of abnormalities detected. This gives the health insurance organizations and medical advisers an idea, independently of the granting of authorizations, of the trends in the numbers of activities. The analyses reveal great similarities among the centres in terms of indications, rates of diagnosis and the nature of the issues handled in genetic counselling. There are, however, quantitative differences among the centres in some areas.

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Quality control

Quality control in clinical genetics is the subject of regular structured consultations at the following levels:

- National meetings of genetic counsellors
The monthly meetings of clinical geneticists working as genetic counsellors deal not only with diagnostic questions for individual patients and families, but also with professional matters, the criteria governing their work, and approaches to clinical problems. Every effort is made to achieve a consistent approach.

- National meetings of cytogeneticists
Meetings for cytogeneticists working on prenatal and postnatal chromosome analysis provide a forum not only for the exchange of information but also for the setting of quality standards and of indications for the different types of chromosome analysis.

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- The clinical application of DNA analysis is covered by a national consulting group of Centres for Clinical Genetics, in which geneticists and molecular biologists working on such analyses participate. Grants are paid under the Exceptional Medical Expenses Act to four of the Centres for Clinical Genetics (in future, this may be extended to the other four as well) for the development and clinical application of DNA analysis. The use of this support is supervised by a committee of the Health Insurance Funds Council. This committee deals, for example, with the indications for testing, the demarcation between clinical application and research, and estimates of needs.

 - Recording genetic data in Centres for Clinical Genetics follows national regulations drawn up and approved in 1983 by the Ministry of Welfare, Health and Cultural Affairs. Certain of the Centres for Clinical Genetics use computer systems to maintain their records. Cooperation among the Centres and the Health Care Information Centre (SIG) has led to the establishment of an organization to promote information management in the separate centres. These developments are monitored by the committee the Health Insurance Funds Council.

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APPENDIX 3

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Reports and recommendations

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Genetic counselling (Health Council report, 1977)

The work of the genetic counsellor is defined as the diagnosis of inherited abnormalities, the provision of information on the risk of recurrence and the discussion of the consequences of increased risk, and of the preventive measures available. In the report it is stressed that the purpose of genetic counselling is to enable the people directly concerned to reach the decisions most suited to their own interests and beliefs. Prenatal testing should be seen not only as a way to prevent the birth of handicapped babies but also a way to offer hope to those at risk who might otherwise not have dared to have children. When abnormalities have been detected in prenatal tests, it is of course the couple who must decide whether or not to terminate the pregnancy. Finally, it is noted that to improve genetic testing, a change of attitude is necessary in (potential) clients as well as in the experts; the former must actively seek the best information, while the latter must support them in that process.

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Screening for Congenital Metabolic Disorders (Health Council Report, 1979.)

In this report, it is recommended that screening for congenital anomalies of the thyroid be incorporated into the national screening system. The possible advantages and disadvantages of screening for hereditary diseases which

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cannot - at least, at present - be treated are also discussed. The advantages are that an early start can be made on the medical and psychosocial care of both patient and family, and that with the help of timely genetic counselling and appropriate preventive steps, the birth of more children with the same abnormality can be avoided. The disadvantages are that little hope can be offered to patient and parents, and that parents are told about the fatal condition even though it may be several years, even many, before the first symptoms appear. No definitive conclusion could be reached and a public debate on the issue is advocated.

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The Ethics of Genetic Counselling (Health Council Report, 1980)

The various stages of genetic counselling are described as a process of communication between counsellors and clients in which, vital though the input of the expert is, clients have complete freedom to reach the final decisions for themselves. This implies limits on the counsellor's function and a clear recognition of the client's own responsibility, especially when, in addition to the client's own interests which are of course paramount, the interests of other individuals, or the public in general, are at stake.

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Artificial Procreation (Health Council Report. 1986)

This report covers the technical, psychosocial and ethical aspects of the techniques of artificial procreation, especially in vitro fertilization (IVF) and artificial insemination by donor (AID). In the latter, it is recommended that donors be tested for genetic risks; sperm banks may refuse donors only on grounds of established genetic risk or the presence of a transmissible disorder. Mixing of sperm from different donors is incorrect, because it would then be nearly impossible (or possible only with difficult and expensive testing) to reconstruct the genetic background of the children produced. Data which could identify individual donors should be recorded with the protection of anonymity and should not be

available to receiving parents or their children. Genetic data and certain general traits of the donor should be coded and recorded so that they can be recalled separately from information specific to the individual; such data should be available to recipients and their children. Specific characteristics of the donor should not be recorded.

With regard to the experimental use of pre-embryos, the position in the report assumes that every form of human life, however early the stage, has an intrinsic value. Nevertheless, it is possible that other values and interests outweigh the value of the pre-embryo. When the vital interests of large numbers of people are at stake, as in the case of important research which cannot be done using animal embryos or in any other way, then consideration may be given, as an exception, to the use of human pre-embryos for research. Because such research can only be done as an exception, it must be governed by stringent conditions. The growing of pre-embryos especially for research would violate the right to protection of a unique human life and is considered to be morally unacceptable.

A number of conditions are stipulated for somatic-cell gene therapy. Gene therapy on the pre-embryo is considered to be inadmissible, at least for the present, on the grounds of the uncertainty as to its effectiveness and of the high risk of mutagenicity.

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The Prevention of Congenital Abnormalities (memorandum of the Secretary of State for Welfare, Health and Cultural Affairs, 1987) and The Prevention of Congenital Abnormalities (further note, 1989)

This memorandum details current policy on the prevention of congenital abnormalities, and delineates government plans for the future. There is no specific attention to ethical and psychosocial issues, but reference is made to the present report; a number of points from the memorandum are nonetheless relevant. Genetic counselling is mentioned as a means of minimizing morbidity and mortality

rates. Specialized prenatal testing is aimed at both prevention and, where possible, treatment. Prenatal tests can be used to detect disorders, inherited or otherwise, in the foetus; termination following detection of a serious congenital condition is regarded as secondary prevention. Prevention of congenital anomalies puts a heavy responsibility on the parents, not least in the demand for a healthy lifestyle, and the role to be played by the State in this area is not obvious. It is noted that society at large favours limitation of the State's influence with respect to responsible parenthood.

Systematic records on the occurrence of congenital anomalies in The Netherlands are a vital contribution to prevention, while effective regulations to ensure the privacy of such records are needed for both individual counselling and for general research. Great importance is attached to the development of initiatives in the area of the effectiveness and the cost-effectiveness of medical intervention.

The Secretary of State's further note (1989) amplifies certain sections of the memorandum. The government rejects entirely any policy of eugenics which would diminish the parent's own responsibility; the state has no role in decisions relating to parenthood. The State does have a role in ensuring that advances in medicine are made available, through experts and facilities, in the form of information for parents. The role of the State also includes the protection of the handicapped and their families, as far as possible, from any rejection by society.

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Developments in Human Genetic Testing (Report of the Steering Committee on Scenarios for the Future of Health Care, 1988)

Genetic testing can help to prevent disease, suffering and expense. In some ways, individual freedom is enhanced, although the procedures can also have adverse effects on the welfare, privacy and freedom of choice of citizens, and on

certain community values such as equality of opportunity and social cohesion. The interests of individuals do not always coincide with those of relatives, insurers, employers and the state. With the help of expert information and advice, all concerned should arrive at a forward-looking policy on genetic testing, which will lead to the gradual and cautious introduction of new techniques. The report includes a number of conclusions, for example that the government should create a standing committee to monitor new developments in genetic testing, promote public debate and advise health professionals. The Steering Committee believes that such functions would best be carried out by the Health Council (in fact, they are already carried out by this council). Legislation should be prepared to guarantee that data on the genetic characteristics of individuals can be used only to promote their own health or to prevent the birth of handicapped children. Such legislation should cover in particular the inclusion of genetic testing in medical examinations for various purposes and in mass screening programmes. Finally, the importance of public information campaigns on the scope, advantages and disadvantages of genetic testing is stressed in the report.

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Neural-tube Defects (Health Council Report. 1988)

This report discusses the desirability of screening all pregnant women in the Netherlands for neural-tube defects in the foetus. While the seriousness and frequency of such defects justifies preventive measures, the introduction of mass screening, to enable pregnant women who so wish to know whether their unborn child has such a defect, and then to reach an informed decision about termination, is not without drawbacks. Some neural-tube defects will not be detected, while relatively large numbers of pregnant women will be subjected to needless anxiety; the sum of these two factors might eventually undermine confidence in the screening programme, and perhaps even in prenatal testing of all kinds. A majority of the members of the Committee on Neural-tube

Defects felt that no final judgement can be made at this time, and wish to see a pilot region designated in which maternal serum AFP screening could be evaluated over a period of two to three years.

APPENDIX 4

The costs of serious hereditary disease

In this appendix, some aspects of the cost of early diagnosis are discussed, as well as of medical care and support associated with a serious hereditary disease, illustrated with the example of Duchenne's muscular dystrophy (DMD).

DMD is a hereditary condition; the gene responsible has a high mutation rate: in one patient in three the disorder is the result of a new mutation, so that it could not have been predicted nor the birth of the affected child prevented. The disorder has a frequency of approximately one in 3,500 newborn males, which means that there are about thirty new patients every year in The Netherlands. It is fatal, most patients dying in early adulthood. The costs of medical care and support amount to approximately 50,000 guilders per patient per year. Women are nearly always the carriers, and tests are usually done to identify as many carriers as possible within the families of patients. The cost of carrier screening is 3,000 guilders. Over the past three years, 618 women have been tested in Leyden, using DNA technology; 269 were found to be carriers and 229 were shown not to be carriers. The latter had no need to undergo further testing and could have children without fear of their being affected by DMD, which in the past was not possible. For the remaining women, it was impossible to determine whether they were carriers, but prenatal testing was still possible. Prenatal testing could also be offered to carriers. Each prenatal test costs about 2,200 guilders. During the same period, prenatal

DNA analysis was performed on 65 male fetuses; in thirty cases, the foetus was found to be unaffected and healthy babies were born. Tests on male fetuses became possible only with the introduction of DNA analysis. The women who underwent prenatal testing had all decided on termination if the foetus were to be affected.

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