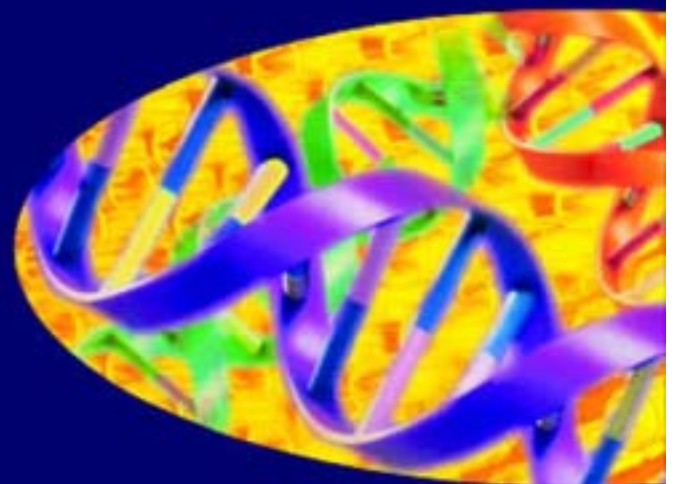




**GUIDELINES ON ETHICS
FOR MEDICAL RESEARCH:
REPRODUCTIVE BIOLOGY
AND GENETIC RESEARCH**



Book 2: Reproductive Biology and Genetic research.

Complete book available in pdf format (kb)

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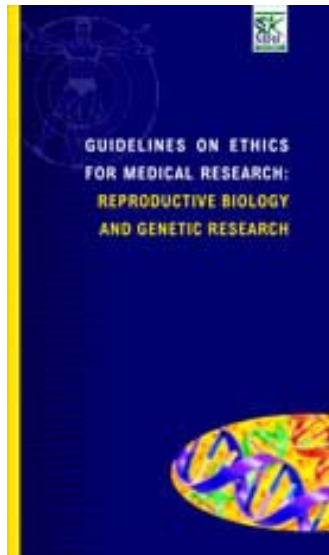
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Book 2: Preface

The Medical Research Council of South Africa has a 33-year experience and history of ethics in health sciences research. The entrenchment of the culture of human rights as core value in health research and as one of the four strategic goals of the MRC, has elevated the critical role ethics play in the conduct of research and in society-particularly in a developing country undergoing major changes. Ethics is an integral part of every research project but, more critically, ethics is vital for improving the quality of research.

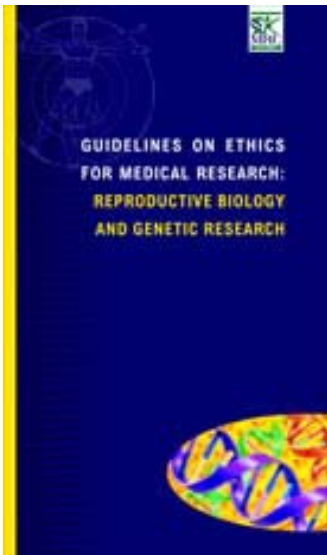
The 1st (1977) and 2nd (1987) editions of the MRC guidelines on ethics outlined general philosophical approaches to research ethics based on the Declarations of Helsinki and Nuremburg which, while brief, had to be read.

The 3rd (1993) edition differed considerably from the first two by presenting information in a codified form with more detailed, specific recommendations. It was more of a handbook than the first two editions and could be used as a ready reference. Under the Chairmanship of Professor Solomon Benatar and his co-authors, this was an excellent handbook.

The 3rd edition was closely based on guidelines of the Royal College of Physicians of London with some flavour for South Africa, but the thrust was essentially that of a developed country - which reflected world-wide trends at the time and also fitted the concepts put forward by WHO and CIOMS. Of the four principles of ethics (autonomy, beneficence, non-maleficence, justice), non-maleficence was emphasised - a somewhat traditional and paternalistic approach. The guidelines were nevertheless very useful for South African researchers and have been used as the 'gold' standard by South African research ethics committees.

A number of important factors necessitated the revision of the MRC ethics guidelines:

- i. major sociopolitical transformation in South Africa since 1993 plus the South African Constitution with its Bill of Rights;
- ii. the Truth and Reconciliation Commission; and
- iii. a surge of interest world-wide in the field of bioethics, particularly as transgressions of ethics around the world have been exposed.
- iv. In addition to these factors, two major scientific events - the revolution in biology often referred to as the Human Genome Project, and the HIV/AIDS epidemic that is sweeping sub-Saharan Africa - have elevated ethics, raising issues such as the following:
 - o Will genetic coding, embryo stem cell research, the cloning of Dolly by Scottish researchers, the current human cloning debates, and germ-line therapy redefine how illnesses are treated?
 - o Will the HIV/AIDS epidemic define the African Renaissance in terms of ethics, morality and innovations? Will the current unequal access to anti-retrovirals,



the 'virodene' saga, the availability and accessibility of anti-retroviral therapy for mother-to-child transmission of the human immunodeficiency virus and in the public health systems, and the impending availability of HIV vaccine candidate products for clinical trials mainly in developing countries, raise imponderable ethical questions for researchers in society?

- v. In addition, in the past few years research ethics guidelines have been reviewed and published elsewhere, for example in Australia and Canada, the latter being a co-operative effort between three research councils. While maintaining established general principles, each increased their local flavour. There has also been a rise in awareness that developing countries have situations different to developed countries and that individuals and communities in these countries have the right not to be exploited.

So, for the 4th edition the MRC Ethics Committee decided that the guidelines must have emphasis on South African needs, and that the dignity of the individual (autonomy) and the importance of informed consent would be strongly emphasised, particularly since informed consent is entrenched in our Constitution's Bill of Rights.

The MRC Ethics Committee wanted to cut down on duplication of sections within the 3rd edition and other international and SA guidelines, hence the removal of clinical trial guidelines from the MRC book in favour of the International Conference on Harmonisation and South African National Department of Health clinical trial guidelines. There was no reason to 'reinvent the wheel'.

The revised guidelines have tried to ensure that the concept of 'the best interest of the research participant' is clear. We have changed the term 'research subject' to 'research participant' to emphasise that research is a partnership; and changed 'doctor' to 'clinician' to make it clear that clinical research is not done only by doctors.

These guidelines emphasise that developing communities must not be exploited and that in some way participating communities must benefit from the research done in or with them.

The MRC Ethics Committee decided on a number of booklets instead of one tome to allow easy updating because research ethics is a 'fluid' field constantly changing. Contributors to each book were chosen for their knowledge and expertise in specific fields. So, while the series editors oversee the production of the books, each book has its own contributors. In this way many colleagues from a variety of disciplines across the country have been involved, which we hope will increase a sense of ownership, multiple perspectives and interpretations. Each book draft was placed on the MRC web site for comment, to widen awareness of the rewriting.

The challenges facing health science research and its development are no longer technical but largely social. The future of health science research lies in the three areas of ethics, communication and attending to societal concerns. The need for science to be understood by the public; the need for scientists to communicate better; the need for the public to make choices about what science has to offer in their daily life; the need for the public to participate in and shape the scientific process; and the need for science to integrate the wealth of information that is already existent (convergence theory) have never been greater than today. These are the ideas or questions that are exercising the minds of ethicists, policy planners, health educators, academic researchers and societies that take long-term strategic planning seriously and as part and parcel of innovation and international competitiveness.

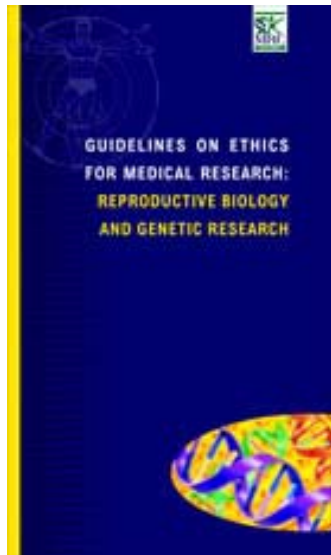
In conclusion:

- i. Ethics of research in a developing country poses exciting challenges for scholars, practitioners and communities that are driven by the principles of equity, human rights and the genuine protection of both the powerful and powerless.
- ii. Ethics in developing countries continues to demystify and destroy the male liberal racial theory that emerged in the last century.
- iii. Informed consent that is based on the language, idiom and culture of the participant is empowering, not only to the subject but also to the investigator.
- iv. Ethics in developing countries remains an important beacon of hope, an integral component and an instrument of transforming society, consolidating young democracies, defining national identities, reclaiming lost cultures and contributing to the global village.
- v. Ethics allows us to probe and understand the intricate, multifaceted nature of and subtle relationship between power and equality.

These guidelines are the first step in trying to provide information and answers to some of these challenges and dilemmas.

On behalf of the MRC, I want to thank Professor Peter Cleaton-Jones and his Committee and all those who have taken their time to participate and contribute to the development of these guidelines. Many researchers and participants will use this set of updated guidelines to the benefit of society and the improvement of health research.

Dr Malegapuru Makgoba
MRC President



Book 2: Foreword to the fourth edition

In his foreword to the third edition of these Guidelines, Professor Solly Benatar eloquently wrote of the 'resurgence of interest in the moral aspects of medical practice' including research. In the intervening years, that interest has increased at an exponential rate. Investigators, participants and sponsors have become more aware of rights and responsibilities.

This increase in ethics information has made the task of the Editorial Committee a difficult one. We decided to keep the basic framework of the third edition, but to split the original single volume into five. Our reasoning is that this will facilitate future updating and reprinting and will enable people with specific interests to find the book that suits them best. We tackled much of the task ourselves, but approached experts in specific fields to produce specialised sections. To these colleagues we are indebted, and they are acknowledged in the front of each book. Draft copies were placed on the South African HealthInfo website (<http://www.sahealthinfo.org/ethics/ethics.htm>) for comment, and we thank those people who responded.

As with anything written by different teams, there are differences in style for which we ask our readers' indulgence. Fortunately the differences have been eased by the editorial skills of Mr Brian Johnson-Barker. For consistency throughout the books, the 'research subject' has been replaced with 'research participant' to emphasise the team approach, 'researcher' is now 'investigator' and 'doctor' is now 'clinician'. This last term acknowledges that clinicians other than doctors do medical research.

The large section on clinical trials that appeared in the third edition has been removed. In its place there is reference to South African and international Good Clinical Practice Guidelines. We saw no need to reinvent the wheel and thereby waste scarce resources.

Of course these Guidelines are among many produced round the world. While all share principles, inevitably there are differences. Such differences have been starkly indicated by the passionate response to the 2000 revision of the Declaration of Helsinki (Appendix VI) which has been welcomed by some and rejected by others. Our Guidelines have a developing-country perspective, an African outlook, we believe. Our approach has been strongly influenced by the South African Constitution, which was adopted in 1996 and entrenches in the Bill of Rights the principle of informed consent of participants in medical and scientific experimentation. Given the vulnerable populations in our country, the Editorial Committee's decision has been to emphasise the principle of autonomy - particularly from the perspective of 'non-exploitation' of research participants. The theme of 'informed consent' recurs throughout. This is a complex matter and recommended reading includes the excellent compendium of views produced by the British Medical Journal (Doyal L, Tobias JT, Editors. Informed consent in medical research. London: BMJ Books, 2001: 1- 334).

There are two final points. First, there is considerably more 'legalese' in this edition. This is deliberate and has arisen from the many queries directed to members of the Ethics Committee. Second, we accept that there will be colleagues who disagree with some things we have written; some may have additional points and some may spot errors. Please send comments to the MRC (see the HealthInfo website mentioned opposite) so that whoever writes future editions may consider them.

The Editorial Committee

There are five books in the series Guidelines on Ethics for Medical Research.

Book 1

Guidelines on Ethics for Medical Research: General Principles.

Book 2

Guidelines on Ethics for Medical Research: Reproductive Biology and Genetic Research.

Book 3

Guidelines on Ethics for Medical Research: Use of Animals in Research.

Book 4

Guidelines on Ethics for Medical Research: Use of Biohazards and Radiation.

Book 5

Guidelines on Ethics for Medical Research: HIV Vaccine Trials.



1. What is the South African Medical Research Council's ethics policy?

1.1 General policy

The MRC recognises injustices in our past and subscribes to the values enshrined in the Constitution of the Republic of South Africa Act, No. 108 of 1996: human dignity, the achievement of equality and the advancement of human rights and freedoms.

The ethics policy of the MRC is clear. All research sponsored by the Council must be of the highest ethics standard. No research will be sponsored without ethics clearance from a Research Ethics Committee recognised by the Council and operating in accordance with MRC ethics guidelines.

1.2 For whom are these Guidelines intended?

The MRC Guidelines are concerned with research on human participants and animals. The Guidelines consider all forms of research on individual persons, whether they be volunteers or patients, and include the study of treatment which might benefit the individual patient (therapeutic research) and the acquisition of knowledge that may be of no immediate benefit to the healthy volunteer (non-therapeutic research). These Guidelines apply also to non-clinical research on humans. Guidelines on ethics in the use of animals in research are dealt with in Book 3 of the current MRC Guidelines series.

What follows in the chapters of this Book 2 of the series Guidelines on Ethics for Medical Research is extensively based on three previous editions and on international documents¹⁻⁹ (see also Appendices V - VII, in Book 1) but is adapted for South African conditions and law.

1.3 Ethics principles

1.3.1 The MRC promotes the four principles of biomedical ethics:

- autonomy (respect for the person - a notion of human dignity)
- beneficence (benefit to the research participant)
- non-maleficence (absence of harm to the research participant)
- justice (notably distributive justice - equal distribution of risks and benefits between communities)

There is considerable debate about whether one or more of these principles require or deserve preference when ethical problems are considered. For example, the trend in most Western countries seems to emphasise autonomy over beneficence. This counters the alleged danger of paternalism in the practice of medicine, and emphasises the importance of the consent and freedom of patients in making decisions about their own health and well-

being. Such views are questioned in the context of many developing countries, where solidarity within communities is valued together with respect for individual choices, and where there is increasing concern about conflict between personal autonomy and public safety in the face of, for example, infectious diseases such as tuberculosis and particularly today the HIV/AIDS pandemic. Concern for distributive justice in developing countries also enjoys a higher priority than in some wealthy Western nations.

The MRC is convinced of the importance of adherence to the four classical principles of biomedical ethics, and of the importance of human rights and individual dignity, but it takes no prejudicial position in debates on the ranking of these principles. The MRC also does not commit to any one approach to moral reasoning or to any one strategy for the resolution of complex ethical dilemmas. It seems clear that, in most disputes in biomedical ethics, some balance between the four principles should be pursued. In maintaining commitment to the classical principles, the complexities of each case must be understood and taken into account in any effort to make justified moral judgements. Of more importance than the consistent adherence to a specific approach or strategy for the resolution of moral dilemmas is the willingness and ability to justify whatever position is taken through sound moral reasoning.

1.4 Conclusion

Application of ethics standards requires a critical evaluation of the relative merits of each of the four principles of ethics to produce a harmony appropriate for a particular research project.



2. Reproductive biology

2.1 Introduction

Certain areas of research in reproductive biology may give rise to complex ethical problems, particularly because various moral, cultural, religious, family and personal factors are involved.^{10,11}

Research is essential in order to improve knowledge but it should not cause moral dilemmas or be harmful to the patient. The balance between these two extremes can be achieved only by in-depth discussion of the research protocol and by ensuring that all protocols are submitted to the institution's Research Ethics Committee for approval.

Because of the diversity of reproductive biology research programmes, ethics guidelines should not be too rigid. Only basic issues in the various areas of reproductive research will be addressed here.

2.2 Research on pre-embryos

A pre-embryo is defined as the product of gamete union from the time of fertilisation to the appearance of the embryonic axis. The pre-embryonic stage is considered to last for 14 days. The pre-embryo should be treated with the utmost respect because it is a genetically unique, viable human entity. If pre-embryo transfer to the uterus is envisaged, special care should be taken to ensure the welfare of the potential fetus. The production of excess embryos for the sole purpose of research should be discouraged.

2.3 *In vitro* fertilisation (IVF)

Probably no medical procedure has been examined as carefully from a moral and ethical point of view as *in vitro* fertilisation. About 85 reports from various official bodies in 20 countries have been published, 15 of them more than 50 pages in length.¹² There is consensus that there is no moral problem intrinsic in using this technique in cases where gametes from the husband and wife are used.¹³

Since 10-15% of married couples are affected by some or other form of infertility, investigation and treatment of these couples involve a substantial part of gynaecological practice.

Also since IVF, as applied today, is effective in only about 15-20% of cases, more research is necessary to improve results.

2.4 Gamete intrafallopian transfer (GIFT)

The ethics considerations in GIFT and other methods of artificial reproduction are similar to

those applicable to IVF. Research to improve the efficacy of GIFT is therefore ethically acceptable.

2.5 Artificial insemination - husband

The use of the husband's sperm for artificial insemination has been practised for many years, and this technique is ethically acceptable. However, more structured studies are needed to assess the efficacy of insemination in the clinic. Research is also needed to improve techniques for cryo-preservation of sperm in sperm banks because there are cases where surgery, radiotherapy or chemotherapy may permanently impair gonadal function.

2.6 Artificial insemination - donor (AID)

The main indication for the use of donor sperm is infertility in couples where abnormal semen findings exist in the male, but the female partner is potentially fertile.

The primary reservation concerning AID is the uncertainty that arises with the introduction of third-party gametes into the marital unit. These concerns are mainly due to potential psychological problems, the risk of transmitting serious genetic disorders and the danger of transmitting infectious diseases, especially AIDS.

The MRC recommends that research methods in AID should be limited to the essential, and that adequate consent should be obtained from all people involved in the donation or reception of gametes.

Artificial insemination procedures should be performed in full compliance with the regulations promulgated in terms of the Human Tissue Act, No. 65 of 1983, Section 37. These regulations are embodied in Government Notice R1182 of 20 June 1986.

2.7 Donor sperm

Treatment of male infertility is one of the main aims of IVF and GIFT. In cases of severe subfertility, the use of donor sperm is the only method of treatment. Although the ethical considerations of using donor sperm and thus introducing a third party into the fertilisation process must be considered as controversial, careful counselling and informed consent by all persons involved should help to resolve many of the dilemmas.

2.8 Donor eggs

Use of donor eggs remains controversial. This, again, is due to general concern about the involvement of a third party. Provided the donor receives no compensation for donating the egg, the MRC finds the use of donor eggs ethically acceptable. However, attempts to extend child-bearing beyond the menopause have many medical, familial and sociological disadvantages, and research in this field is usually ethically unacceptable.

2.9 Pre-embryo from IVF for donation

Since the failure rate of IVF is high, three or four pre-embryos are usually transferred. To obtain this number of embryos, superovulation needs to be induced. All oocytes are fertilised in vitro. The transfer of more than four embryos may occasionally lead to multiple pregnancies of a grand order, and is therefore not recommended. In this way supernumerary pre-embryos, which are not going to be used immediately, are sometimes obtained. These are immediately cryopreserved. If not required any longer by the couple (after successful IVF, for instance), the pre-embryos become available for donation. Since these pre-embryos may be used in couples who might otherwise not produce a pregnancy, research in this field is ethically acceptable.

2.10 Uterine lavage for pre-embryo transfer

Uterine lavage for pre-embryo transfer carries the risk that some of the pre-embryos may be retained in the uterus. Research using this procedure is legal in countries where abortion on demand is provided for by law. This is the case in South Africa where the Choice on Termination of Pregnancy Act, No. 92 of 1996, provides for abortion on demand during the first 12 weeks of pregnancy. The husband's consent is not needed for a lawful abortion, and no age limit is set by the Act for the woman seeking an abortion.

2.11 Consent

Written consent to use gametes or pre-embryos should be obtained from the donor(s) as well as from their spouses.

2.12 Zygote intrafallopian transfer

Primary use of this technique is in candidates for GIFT, in whom evidence of the fertilising capacity of gametes is also desired. Main indications are usually in patients with low or abnormal sperm counts, or in patients with unexplained infertility who have had unsuccessful GIFT procedures. Research in this field should therefore not be restricted.

2.13 Peritoneal ovum and sperm transfer

Transvaginal and transabdominal peritoneal ovum and sperm transfer have been described as alternatives to GIFT. The technique is still regarded as experimental. No specific ethics dilemmas are foreseen.

2.14 In vitro maintenance of embryos

Maintenance of embryos in vitro beyond the gestational age of 2 weeks is not ethically justifiable.

2.15 Contraception research

Many new methods of fertility control are being investigated, but their efficacy in the human is still uncertain. This research is allowed in South Africa, where non-therapeutic abortion on demand is legal during the first 12 weeks of pregnancy.

2.16 Research on selecting fetal sex

Research into the selection of the fetal sex may be inappropriate if it may result in a request for an abortion because the sex of the fetus is unacceptable to the parents. On the other hand, gender selection may be beneficial in sex-linked genetic diseases and may be justified under exceptional circumstances.

2.17 Pre-embryo manipulation and research

Pre-embryo manipulation and research may yield valuable medical information. However, it can be regarded as ethical only if the embryos are not specifically produced for the purpose of research. In addition, the embryos should not be transferred to the uterus unless there is reasonable certainty that the manipulation carries no potential risks for the fetus.

2.18 Embryo research

At this stage, a great deal of the work concerned with embryos is developmental. Work involving animal embryos is subject to the guidelines on the use of animals in biomedical research (see Book 3). Work concerned with human embryos is subject to the guidelines on ethics for the use of human embryos in research (see 2.1-2.16). The use of recombinant technology in selecting fetal sex is subject to the guidelines on human embryos, and is currently regarded as not ethical.

However, gender testing in connection with sex-linked genetic diseases and aimed at

therapeutic abortion, may be considered as ethical, subject to the broader guidelines on ethics in human biology and subject to the laws of South Africa (see the Choice on Termination of Pregnancy Act, No. 92 of 1996). Equally, testing of human embryo or other extra-embryonic tissue, aimed at determining genetic diseases which are not sex-linked, is subject to the same guidelines.

3. Ethics in genetic research and practice

3.1 A narrative of ethics

Scientific enquiry is an art involving the study, pursuit and application of research. The possibility of human benefit from this art may be subject to the possibility of contingent or inadvertent harm caused by a breach of values. These values, dubbed 'ethics', are a systematic reflection by a community on the moral life and its conflicts.¹⁴ Undoubtedly, these values differ between communities, and they represent no more than the moral convictions of thoughtful and conscientious people. For that very reason a South African investigation of the convictions of our moral community is imperative. These convictions are generally derived from a compound of natural philosophy and religion, and reflect intuitive principles. To some extent the same moral or ethical standpoints are reflected in the Constitution of the Republic of South Africa Act, No. 108 of 1996, for instance in the reverence for life and respect for the dignity and integrity of the person; the right to freedom of religion, belief and opinion, the respect for privacy and the overarching importance of an open and democratic society based on human dignity, equality and freedom.

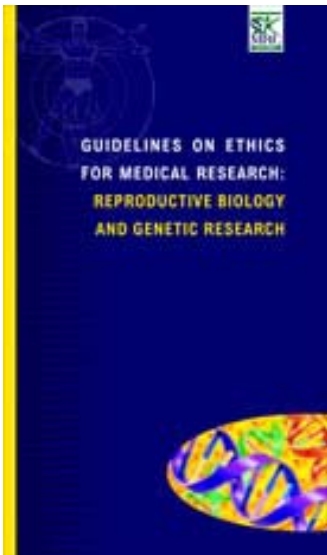
There are two fundamental elements to the analysis of constitutional rights - the application and interpretation thereof. First, our Constitution applies as between the State and individuals, and also, where it appears from the nature of the right in question, as between individuals. In the context of this debate, the rights of the investigator or clinician on the one hand and the participant on the other need to be considered. Second, in the interpretation of the provisions of the Constitution, regard must be had to the values that underlie an open and democratic society, based on respect for human dignity, as well as equality and freedom. Thus, the ambit of each right enshrined in the Constitution is determined in the context of the environment in which we live, and the application of these rights is sensitive to the mores of society, as determined by a body of informed, impartial and objective persons.

This book embraces international viewpoints together with the values enshrined in our Constitution and attempts to place the ethics of research and practice within a South African framework.

3.2 Gene therapy

This book sets out general international ethics principles regarding genetic research and gene therapy. Where applicable, specific reference is made to the South African situation.

Genetic manipulation is an awesome power within our grasp, and responsibility rides on the back of that power. Discussing the ethics of gene therapy is like the toss of a coin - the outcome depends solely on which face is presented to the world. This theme recurs in the commentary that follows, and it requires more than just fleeting attention. It is mindful of the potential for both advancement and harm that the ethics of this procedure are explored.



Essentially, the practice of gene therapy relates to two groups of cells - somatic cells and germ-line cells. A germ-line cell is a cell which, during the first few weeks after conception, is put aside in the embryonic sex organs to provide, possibly decades later, ova or sperm. A somatic cell is any body cell except a germ-line cell.¹⁵

"The genes carried by each of these two kinds of cell have distinct roles, and the distinction is very important. Genes which are carried by germ-line cells may be transmitted to offspring and successive generations. Genes which are carried by somatic cells have their role in the corporate life of those cells within the tissues and organs of the individual whom they endow. So far as is known, an alteration to the genes of somatic cells will affect only that individual, but an alteration to the genes of germ-line cells might affect offspring and successive generations."¹⁵

Concerns with regard to somatic cell gene therapy are much the same as those regarding any novel form of medical practice or treatment. Somatic cell gene therapy impacts only on the individual subject of the gene therapy, and ethical concerns are centred around the risk to the participant or patient and the concomitant obligations of the investigator.

3.2.1 Innovative practice or research?

The ethics of gene therapy are largely dependent on its status either as medical practice or as research. While practice is undertaken with the primary intention of benefiting an individual patient, research is undertaken with the prime purpose of testing a hypothesis and permitting conclusions to be drawn, in the hope of contributing to general knowledge¹⁵ (see also 2, Book 1). At present, gene therapy has not yet been assimilated into mainstream medical practice. It is still perceived to be different, both in its nature and possible consequences, from any treatment used hitherto in medical practice.¹⁵ Thus, gene therapy should be considered to be in the research stages and subject, therefore, to those ethical considerations that currently govern genetic and medical research:

"... accordingly, any proposal to conduct gene therapy should be subject to approval following authoritative ethical review, which includes critical scrutiny of its medical and scientific merit, the legal implications, and wider public concerns. It should also be subject to conditions laid down for the conduct and oversight of therapy and evaluation and reporting of the outcome."¹⁵

National guidelines for the conduct of human gene therapy are essential. These, with an expert national body to consider and approve proposals for such therapy, would ensure public confidence in the introduction of novel and sophisticated gene therapy practices.¹⁶ A regulatory system would go far in allaying public fears that gene therapy might be misused, or that it might be extended to enhancement uses beyond what is strictly medical therapy.¹⁷ This is discussed further in the topic 'Supervision of gene therapy' under 3.2.4 and 'Regulation of cloning research' under 3.4.5.

3.2.2 Somatic cell gene therapy

Somatic cell gene therapy takes multiple forms. In its simplest form, it entails supplementing or replacing dysfunctional or faulty genes with ones that are able to function correctly.¹⁸ Ideally, somatic cell gene therapy provides the correct genetic information in those cells which require it for their normal function.¹⁵ This form of therapy corrects or alleviates the genetic defect present in the individual alone, without impacting on the genetic information transmitted to any issue.¹⁵ It is argued that, in principle, somatic cell gene therapy is similar to current routine therapies such as organ transplantation, and therefore raises no new ethical issues.^{16,18} However, there is a greater danger present in gene therapy:

"The correcting gene might be inserted into the wrong cell type, or be expressed inappropriately, either in the wrong amount or at the wrong time during development. The therapy might then do more harm than good. The gene might [also] be inserted in such a way as to cause a new mutation, by disrupting some other gene or its means of control. This might initiate a new genetic disease, or perhaps an uncontrollable multiplication of cells which could lead to cancer."¹⁵

These factors bear on the effectiveness, safety and risk of somatic cell gene therapy. Safety should be the paramount factor when considering whether to conduct somatic cell gene therapy on a particular individual as a form of medical practice. One commentator remarking on the future of the practice of somatic cell gene therapy stated that:

"Judgements on the ethics of gene therapy in man will initially apply to individual cases and will require assessment of factors such as safety, efficacy, alternative treatments and prognosis - in other words, the balance of risk and benefit for the patient. In the near future, treatment by gene therapy might be justified in cases of invariably fatal or life threatening diseases for which no alternative treatment is available...If damage caused by a genetic disorder in a particular patient is irreversible, then there may be no case for intervention through gene therapy."¹⁶

Different considerations apply in somatic cell gene therapy research. The Report of the Committee on the Ethics of Gene Therapy¹⁵ has set out the following conditions as prerequisites to gene therapy research:

- a. There must be sufficient scientific and medical knowledge, together with knowledge of those proposing to undertake the research, to make sound judgements on:
 - i. the scientific merit of the research;
 - ii. its probable efficacy and safety;
 - iii. the competence of those who wish to undertake the research;
 - iv. the requirements for effective monitoring.
- b. The clinical course of the disorder must be known sufficiently well for the investigators and those entrusted with counselling to:
 - i. give accurate information and advice;
 - ii. assess the outcomes of therapy.

3.2.2.1 Public policy and the practice of somatic cell gene therapy

Where are the boundaries for the practice of somatic cell gene therapy? It is arguable that current gene therapy should be directed to alleviating disease in individuals.¹⁵ However, gene therapy could have a wider application than the correction of single gene disorders.¹⁵

"For example, it is being investigated as a possible new approach to the management of a wide spectrum of diseases, ranging from infections such as AIDS to cancer, and it is being studied as a means of strengthening the body's immune response to viral infections. Various approaches are being used which require the insertion of genes into particular cell populations in an attempt to counter some of the basic changes in cells which lead to them becoming cancerous. Gene therapy is also being explored for the management of chronic diseases such as diabetes."

There are other non-disease-related uses to which genetic manipulation could be put.^{19,a} The current limits placed on the use of gene modification, however, curtail its use for the enhancement or change of human traits not associated with disease. Somatic cell gene therapy will be a new kind of treatment, but it does not represent a major departure from

established medical practice; nor does it, in our view, pose new ethical challenges.

It will, of course, raise familiar issues, which attend any new medical procedure. However, there are public concerns about a medical intervention that may be perceived, understandably, as different from any used hitherto. In addition, because of the special qualities of an individual's genetic make-up and the complex nature of genetic disorders, the issues will assume greater prominence. They are:

- i. questions of safety, which are heightened by the possibility of inadvertent and unpredictable consequences of gene therapy to the patient, and the possible long-term consequences;
- ii. the need for long-term surveillance and follow-up;
- iii. the matter of consent, especially in view of 3.2.2 (a) above;
- iv. the probability that children will be among the first candidates for therapy;
- v. confidentiality, and disclosure of genetic information important to kindred.

It is essential to ensure that these issues are properly considered, and to demonstrate satisfactorily that this has been done.

It is therefore recommended that, initially, somatic cell gene therapy should be governed by the exacting requirements which already apply to other research involving human participants in South Africa.

While the safety and effectiveness of somatic cell gene therapy remain uncertain, this new treatment, as with any other treatment, should be limited to patients in whom the potential for benefit is greatest in relation to possible inadvertent harm. We therefore recommend that the first candidates for gene therapy should be patients:

- i. in whom the disorder is life threatening or causes serious handicap;
- ii. for whom treatment is at present unavailable or is unsatisfactory but for whom treatment may be beneficial.

Gene therapy should be directed to alleviating disease in individual patients, although wider applications may soon call for attention. In the present state of knowledge, any attempt by gene modification to change human traits not associated with disease would be unacceptable.

3.2.3 Germ-line gene therapy

"The insertion of genes into fertilised eggs or very early embryos is fundamentally different because these genes would be passed on to the offspring in subsequent generations. Germ-line therapy should not be contemplated."^{16,18}

See Section 39A of the Human Tissue Act, No. 65 of 1983, which seems to prohibit the genetic manipulation of gametes and zygotes outside the human body in South Africa if there is any intention of implanting the zygote. (It is not clear if experimentation on the zygote or the pre-embryo would be permitted so long as implantation would not follow.)

This line of thinking is, fundamentally, the point of departure for most commentators on the ethics of gene therapy.^{16,b} It is also a simplistic response to a complex ethical issue. The predominant feature of germ-line therapy which posits the greatest ethical dilemmas is also its greatest advantage:

"Gene modification at an early stage of embryonic development, before differentiation of the germ line, might be a way of correcting gene defects in both the germ line and somatic cells."¹⁵

It is fundamental to separate the various ethical issues surrounding germ-line gene therapy. There are at least three aspects to the ethical concerns raised. First, that relating to the research of germ-line gene therapy; second, that of the safety of the procedure and its impact on the patient; third, the public policy issues relating to the practice of germ-line gene therapy. The first two questions pose no new ethical concerns.^{18, c} It is the public policy questions regarding the use and misuse of germ-line therapy, both in medical practice and outside of the practice of medicine, with which these guidelines are most concerned.

3.2.3.1 Public policy and the practice of germ-line gene therapy

There are no simple solutions to the dilemmas presented by the practice of germ-line gene therapy. On one hand, germ-line gene therapy may lead to the eradication of genetic disorders in the human genome; on the other, the line between the elimination of genetic disorders and the genetic enhancement of normal human traits becomes blurred.

"At present, no human germ-line manipulation is possible, and none, so far as we know, is contemplated in any part of the world...The question for the future is, whether the possible benefits might outweigh the disadvantages sufficiently to justify removing the current prohibition on research."¹⁸

It is with germ-line therapy that the question of boundaries is most starkly confronted. Once sufficient knowledge has been attained to evaluate the risks to future generations, the question of limitation becomes central. It is in this context that ethics becomes paramount.

Eugenics is widely defined. It accepts within its confines both the enhancement of certain human traits and the reduction of the incidence of certain severe hereditary diseases.¹⁴ It is seen to be either a private issue or a matter for State intervention. This book assumes a definition of eugenics that incorporates only the enhancement of attractive traits, either through social programmes or private operations. A universal response to eugenics in this sense is one of opposition.

"This is an approach to which people around the world object, because it denies human freedom, devalues some human beings, and falsely elevates the reproductive status of others...mandatory approaches, including refusal of marriage licences, forced contraception, forced sterilisation, forced prenatal diagnosis, forced abortion and forced childbearing are all affronts to human dignity...In undertaking genetic programmes such as carrier screening or biochemical screening in pregnancy, the primary goal must be the welfare of the individuals/couples, not the welfare of the State, future generations or the gene pool."¹⁴

Eugenics, better termed 'genetic enhancement', has dogged our history. Nazi Germany is only one example of the pursuit of eugenic goals. There are many current examples, and two are cited below.

"The government of Singapore instituted a policy of providing financial incentives to 'smart' people to have more babies. The California-based Repository for Germinal Choice, known more colloquially as the Nobel Prize sperm bank, has assigned itself the mission of seeking out and storing gametes from men selected for their scientific, athletic or entrepreneurial acumen. Their sperm is made available to women of high intelligence for the express purpose of creating genetically superior children who can improve the long term happiness and stability of human society."²⁰

Criticism of genetic enhancement is neither invalid nor inappropriate. There are many ethical dangers in pursuing genetic enhancement, including increased social inequality and a lowered tolerance for human diversity.¹⁴ One perceived consequence of the development of genetic knowledge is the use of genetic information in social policy development.²¹ This theme is developed by Jerome Bickenbach who surmises that:

"In times of perceived restraint on social resources, policy makers will be driven to seek ways of predicting future costs. Genetic information is optimal for these purposes. If a health care policy analyst could have at her disposal accurate information about the prevalence of a variety of mental and physical conditions in the population, then precise cost and resource projections could be made. If a specialist in income security policy could predict with accuracy the number of people who will need income supports in the next fifty years, she would be able to integrate this policy into the general supply-side labour policy, with considerable savings."²¹

Enhancement creates inequality in the competition for social goods such as wealth, status or power in a meritocracy²² and violates the goals of medicine.^{14,e} In this context genetic enhancement is seen to be a misallocation of scarce resources that would be better placed in serving medical practices. However, it begs the question to state that gene therapy should be limited to medical practices. What are the boundaries of a medical practice? One method of differentiating between genetic enhancement and medical practice lies in the definition of disease, and yet, how does one assess the significance between difference and abnormality?

Understanding that the potential for 'the most profound form of stigmatising' exists in the labelling of genetic disorders,²¹ it is suggested that the response to the question is not a novel one:

"The question of disease as currently assessed in the realm of clinical genetics is not entirely a hypothetical one. After all, counsellors and clinicians have been treating patients for genetic diseases for decades. It is instructive to look and see how they currently define disease and health."²⁰

Initially scientists took a restrictive view of what constituted a genetic disease. This was expressed in the view that "the simplest, most straightforward definition of a genetic disease (type 1) was a single locus defect, with a 100% heritability."²³ This definition evolved over the years to encompass "polygenic traits with less than 100% heritability... (type two)"²³ so that any traits which included a genetic component, fell within the ambit of the definition. The definition evolved further to encompass "complex behavioural traits where the evidence for heritability was less clear (type three)."^{23,f} It has been even further amplified by the inclusion within the ambit of 'genetic disease' of any trait which can be altered by gene therapy.^{23,g} The expanded definition no longer assumes the heritability of the trait. This is easily explained from a scientific basis,^{23,h} but from an ethical perspective it may not be advisable to adopt such a broad definition of genetic disease. This definition does not distinguish between medical and non-medical gene therapy.

The purpose of defining disease in the ethical context is to draw a distinction between acceptable and unacceptable gene therapy practices, those practices designed to prevent, correct or alleviate disease being acceptable while all other forms of gene therapy are not acceptable. However, it is not sufficient to delineate health as the basis for distinction. Health, like disease, is not readily ascertainable without reference to an individual opinion. Certain 'disorders' such as idiopathic haemochromatosis, which results in increased iron absorption,

are an advantage to communities under starvation conditions, but are a disorder in any other circumstance.²⁴ The distinction between 'health' and 'defect' is particularly dangerous when applied to mental or intellectual capacities and behavioural traits - the ideal of a norm 'healthy', against which 'defect' is judged, cannot find a valid place in an eclectic society where diversity of opinion is protected by the most powerful law of the land. There must be other factors that can be used as indicators of what constitutes acceptable gene therapy.

Serious consequences follow the labelling of a condition as a genetic disease. For this reason, labelling genetic variations as abnormal or disease should be done with caution. One commentator states that:

"For now, clinical genetics ought to restrict itself to the identification and assessment of only those genetic states which are known to be dysfunctional as well as different. It should discourage efforts to allow 'fishing expeditions' to become part of prenatal, carrier or workplace screening. And, it should assert clearly that the central goal of human clinical genetics is the prevention or amelioration of disease, not the improvement of the genome."²⁰

It is recommended that further investigation of the distinction between medical and non-medical therapy be undertaken before gene therapy is considered. It is indisputable that prior to being introduced into medical practice, gene therapy must be ethically acceptable.¹⁵ To find a position which commands acceptance, requires wide consultation. In the interim, germ-line gene therapy should not be contemplated on human subjects. However, we have concluded that the development of safe and effective means of gene modification, for the purpose of alleviating disease in individual patients, is a proper goal for medical science.

"The way to handle legitimate concerns about the dangers and potential abuse of new knowledge generated by the genome is to forthrightly examine what are and are not appropriate goals for those who provide services and interventions in health care. There is nothing sacrosanct about the human genome. It is only our inability to openly and clearly define what constitutes disease in the domain of genetics that makes us feel that intervention with the germ line is playing with moral fire."²⁰

Thus, it is recommended that the necessary research on the distinction between medical and non-medical therapy should continue. It is clear that there is at present insufficient knowledge to evaluate the risks to future generations of gene modification of the germ line. It is therefore recommended that gene modification of the human germ line should not yet be attempted until such time that it is clearly sanctioned by South African law.

3.2.4 Supervision of gene therapy

3.2.4.1 Expert supervisory body

Continuing supervision of gene therapy is necessary. No existing body is constituted for this task. Therefore it is recommended that a new, expert supervisory body be established. An example of such a body is the British Human Fertilization and Embryo Authority.

The supervisory body should be of sufficient standing to command the confidence of existing Research Ethics Committees and of the public, the professions and Parliament. It should have a responsibility for:

- i. advising on the content of proposals, including the details of protocols, for therapeutic research in somatic cell gene modification;
- ii. advising on the design and conduct of the research;

- iii. advising on the facilities and service arrangements necessary for the proper conduct of the research;
- iv. advising on the arrangements necessary for the long-term surveillance and follow-up of treated patients;
- v. receiving proposals from clinicians who wish to conduct gene therapy in individual patients, and making an assessment of:
 - a. the clinical status of the patient;
 - b. the scientific quality of the proposal, with particular regard to the technical competence and scientific requirements for achieving therapy effectively and safely;
 - c. whether the clinical course of the particular disorder is known sufficiently well
 - for sound information, counselling and advice to be given to the patient (or those acting on behalf of the patient)
 - for the outcomes of therapy to be assessable;
 - d. the potential benefits and risks for the patient of what is proposed;
 - e. the ethical acceptability of the proposal; and
 - f. the informed consent documents (see 5.3, Book 1).

In the light of this assessment the expert supervisory body should make a recommendation on whether the proposal should be approved, and if so on what, if any, conditions. The supervisory body should also have a responsibility for:

- vi. acting in co-ordination with existing Research Ethics Committees;
- vii. acting as a repository of up-to-date information on research in gene therapy internationally;
- viii. setting up and maintaining a confidential register of patients who have been the subjects of gene therapy;
- ix. oversight and monitoring of the research; and
- x. providing advice to Health Ministers, on scientific and medical developments which bear on the safety and efficacy of human gene modification.

It is recommended that any proposal for gene therapy be approved by this body as well as by a properly constituted Research Ethics Committee.

At first, and probably for several years, gene therapy will be applicable to a small number of uncommon disorders and be confined to a few patients. As with other new, specialised medical interventions, it is recommended that it be confined to a small number of centres while experience is gained.

3.3 Genetic screening and testing

Essentially, the screening process may be divided into three phases - the preparation of the participant or patient; the analysis of the genetic material; the interpretation of the analysis coupled with ensuing support programmes.²⁵ It is useful to distinguish between these three phases in a discussion of the ethics of genetic screening and testing. During the preparatory phase, ethical considerations revolving around informed consent must be addressed. The analysis phase raises familiar issues such as adequacy of procedure and confidentiality with respect to the participant or patient. The final phase raises ethical concerns relating to the management of genetic disorders and the subsequent impact of the screening process on the individual and his or her family.²⁵

Genetic screening should be distinguished from genetic testing at the outset. The terms are often used interchangeably, although they represent two different forms of genetic practice. Genetic screening is carried out on groups of people, which could consist of a section of the

population defined by age, sex, or other risk factor, or a subgroup within the population, or within broad groups in which genetic factors may be responsible for certain disabilities.²⁶ Genetic screening may be defined as:

"... a search in a population to identify individuals who may have, or be susceptible to, a serious genetic disease, or who, though not at risk themselves, as gene carriers may be at risk of having children with that genetic disease."²⁶

Genetic testing, on the other hand, leads to a definitive diagnosis in individuals, and is defined to be:

"... the analysis of a specific gene, its product or function, or other DNA and chromosome analysis, to detect or exclude an alteration likely to be associated with a genetic disorder."²⁵

Individuals may desire testing where there is a family history of a specific disease, if they exhibit symptoms of a genetic disorder; or if they are concerned about passing on genetic disorders to their children.²⁷ In addition, genetic testing in individuals is used as a 'fingerprint' in forensics. The areas of focus for genetic testing at present are thus carrier and susceptibility testing, prenatal diagnosis, newborn testing, and forensic testing.²⁸

Screening programmes play a useful part in public health care systems in identifying potentially serious risks that can be prevented by timely treatment. Testing allows couples the possibility of making informed choices about parenthood and, possibly, in identifying genetic susceptibility to common serious diseases.²⁶ Three goals have been identified for genetic screening:²⁶

- i. to contribute to improving the health of persons who suffer from genetic disorders;
- ii. to allow carriers for a given abnormal gene to make informed choices regarding reproduction; and
- iii. to move towards alleviating the anxieties of families and communities faced with the prospect of serious genetic disease.

A fourth goal could be added to this list - the reduction of public health costs. Genetic screening is an attractive option for those institutions seeking to manage their public health exposure. It is feared that the greater our ability to predict the costs of heritable diseases, the greater the public pressures on adults not to pass on genes that are associated with particularly bad outcomes.²⁹ Pressure may also be brought to bear on individuals to be tested for genetic predispositions and to act "to save society long-term costs resulting in a new eugenics based, not on undesirable characteristics, but rather on cost-saving."²⁸

However, some consider any aspirations to a 'healthy public' to be misguided because genetic control of the human population, or any form of 'genome cleansing' could easily slide into eugenics.³⁰ Others hold the view that genetic screening at embryo level will take place in developed countries, and if this is not done in developing countries the discrepancy between the two will widen even further.

3.3.1 Scientific basis

Inheritance is determined by the genes, of which there are an estimated 32 000 in the human genome. Genes are large molecules made up of a substance, DNA, whose double helical structure allows both copying and division. The particular sequence of individual chemical sub-units in a gene serves as a molecular code to specify the manufacture of a particular protein. An alteration (mutation) at even a single position of the DNA sequence may cause serious

malfunction of the resulting protein. Modern advances in genetics are due to the ability to study DNA directly. At present we have, at best, information on only one-third of the genes.

The genes are arranged in a fixed order on the chromosomes. Chromosomes are elongated strings of DNA and protein that occur in the nucleus of every cell in the body. Unlike genes, chromosomes can be seen through a light microscope, especially when they become compacted during cell division. In the normal human there are two sets of 23 chromosomes, 46 in all, one set having been inherited from the father, the other from the mother. The members of 22 of the 23 pairs appear identical: these are the autosomes. The remaining pair, the sex chromosomes, differ between males and females; females have a pair of X chromosomes whereas a male has one X chromosome (inherited from his mother) and one Y chromosome (inherited from his father).

Medical genetics is part of the human genetics concerned with the role of genes in illness. Traditionally, the analysis of the genetic contribution to illness and human characteristics has been divided into:

- i. disorders due to changes in single genes;
- ii. disorders influenced by more than one gene (polygenic); and
- iii. chromosomal disorders.

In addition to the genetic contribution, the environment often plays an important part in influencing both the onset and severity of disease, particularly in the polygenic disorders.

3.3.1.1 Single gene diseases

Inherited single gene diseases may show three common types of inheritance pattern.

- i. Autosomal dominant: such diseases (Huntington's disease, for instance) result from one of a pair of matched autosomal genes having a disease-associated alteration, the other being normal. The chance of inheriting the altered gene from an affected parent is 1 in 2 in each pregnancy. Autosomal dominant diseases commonly affect several individuals in successive generations.
- ii. Autosomal recessive: these diseases (such as cystic fibrosis) require the inheritance from both parents of the same disease-associated abnormal autosomal gene. The parents are usually themselves unaffected, but are gene carriers. When both parents carry the same altered gene, the chance of inheriting two altered genes and thereby of having the disease is 1 in 4 in each pregnancy. Autosomal-recessive diseases usually only affect the brothers and sisters within a single generation; the incidence of the disease in individuals in previous or subsequent generations is usually very small. Hence diseases with this form of inheritance tend to occur 'out of the blue'.
- iii. X-linked: diseases due to genes on the X chromosome (such as haemophilia) show a special inheritance pattern: they are also known as sex-linked disorders. Most X-linked conditions occur only in males who inherit the abnormal gene from their mothers. These mothers are carriers of the altered gene but are usually unaffected themselves, because their other X chromosome has the normal gene (as in autosomal-recessive disease). Females may occasionally show some features of the disease, depending on the condition. An affected male never transmits the disease to his sons. When the mother carries a gene for an X-linked disease, the chance of inheriting the altered gene is 1 in 2 in each pregnancy for both boys and girls, but only the male offspring will be affected. X-linked disease may thus give rise to the disease in males in several different generations, connected through the female line.

3.3.1.2 Polygenic disorders

Many common diseases with a genetic basis result from abnormalities in more than one gene. The inheritance pattern is complicated because of the larger number of different genetic combinations and uncertainties about how the genes interact. Environmental factors frequently play a major part in such disorders, which are more often known as multifactorial diseases. Because of this, screening can yield results that are less clear-cut. At the same time, as we advance our knowledge of all the environmental and genetic factors involved, it will become possible to identify individuals who are at increased risk of a disorder and who would benefit from advice on how to minimise the risk. This could lead to screening for genetic predisposition to common diseases, such as coronary heart disease, diabetes and some cancers.

3.3.1.3 Chromosomal disorders

Chromosomal disorders fall into two broad categories.

- i. Where an entire chromosome is added or is missing. For example, in Down's syndrome there is an extra (third) copy of chromosome 21 found in the cells of affected individuals (hence the technical term for it, Trisomy 21). In Turner's syndrome, one of the X chromosomes in girls is missing. This type of disorder is not inherited but occurs during the production of a gamete (egg or sperm).
- ii. Rearrangement of chromosomal material. If this involves either net loss or gain of chromosomal material, harmful clinical effects are likely. On the other hand, if a simple exchange occurs between chromosomes (translocation) or within them (inversion), the chromosome make-up may be 'balanced', and serious clinical effects are much less frequent.

3.3.1.4 Types of genetic tests

All forms of genetic test aim to identify particular genetic characteristics but approach this in different ways.

3.3.1.4.1 Chromosomal tests (cytogenetics)

Microscopic examination of chromosomes from cells in blood, amniotic fluid or fetal tissue may be used to detect the chromosomal changes mentioned above. Until recent years it was possible to detect only large alterations on a chromosome involving many genes, but new techniques are making it possible to detect much smaller defects, allowing recognition of disorders involving only a small amount of genetic material.

3.3.1.4.2 Tests for disorders involving a single gene

Genes cannot be seen through the light microscope, so tests for single gene disorders have been largely indirect, involving what the gene produces (protein), or another substance affected by it, rather than the gene itself. The protein is still unknown for the majority of genes, so testing for single gene disorders has been very limited until recently.

3.3.1.4.3 Direct tests

Various techniques have been developed for identifying important human genes directly. The two main approaches are:

- i. the gene may be isolated if the product (protein) it normally produces is known. This approach was used for the genes involved with the main blood cell protein, haemoglobin (important for tests involving sickle cell disease and thalassaemia). The genes causing some metabolic diseases, where a specific chemical defect involving an enzyme was already known, have also been isolated in this way;
- ii. the gene may be isolated if its position on a chromosome is known (positional cloning). This approach is increasingly successful in allowing genes to be isolated

even when we know nothing about their function or what protein they normally produce. One reason for this success is that detailed genetic maps of the different chromosomes are being produced. This approach not only pinpoints the chromosome region where the gene lies, but can provide genetic markers (identifiable pieces of DNA) which lie close to the gene, and enables an accurate test for a genetic disorder to be made even before the gene itself is isolated.

Once the gene responsible for a disorder has been isolated, it is possible to study its different changes (mutations) that may result in disease. These range from complete absence of the gene to faults in a single chemical subunit of the gene. A single gene disorder may be caused by many different changes in the gene responsible. By careful study of particular populations of people it may be possible to determine which mutations for a disease are the commonest and most important, and to design a test programme accordingly.

Direct genetic testing by DNA techniques differs in several important respects from most other forms of medical testing. Any body tissue can be used since genes are present in almost all cells. Although blood is most commonly used, cells obtained by mouthwash are proving especially suitable for some screening programmes. Since genes do not usually change during life, a DNA test can be performed at any time from conception onwards. This is a practical advantage for tests in early pregnancy, as it allows the detection of a serious genetic abnormality that, otherwise, would not show itself until after birth. However, this raises difficult ethical problems, especially in relation to diseases that do not appear until later childhood or adulthood.

Major scientific advances have occurred in the sensitivity of genetic techniques, allowing minute amounts of DNA or protein products to be analysed. A particularly important advance has been the polymerase chain reaction (PCR), which allows a single copy of a small part of a gene to be amplified many thousand times. Testing of single cells may make preconception testing of a single egg feasible, and may also allow testing of fetal cells in the mother's blood during early pregnancy. The dried blood spot taken onto filter paper from all babies in the newborn period can be stored and used for a wide range of genetic tests. New techniques increase the potential impact of genetic testing, because they are often suitable for mass population screening.

An important discovery is that many stretches of normal DNA vary between different people and together provide a pattern that is unique for every individual (apart from identical twins). This powerful technique, known as genetic fingerprinting, has many applications, especially in legal cases. There are important ethical issues as to when and how it should be used.

3.3.1.4.4 Indirect (biochemical) tests

These tests do not detect the gene itself, but some aspect of its function. The most nearly direct tests are for the specific protein that the gene produces. In a genetic disorder, tests may show that the protein is not being made or is present in reduced amount; or that it may be altered so that it does not function adequately. Such tests are important; for example, for detecting abnormalities of haemoglobin (in thalassaemia or sickle cell disease).

Where the gene or its product cannot easily be tested, it may be possible to measure some other substance that is altered in the disease. Thus the screening test for the disorder phenylketonuria (PKU), commonly used in Britain and South Africa on all newborn babies, is based on measuring the amino acid, phenylalanine, which builds up in the blood of affected persons.

3.3.1.4.5 Ultrasound

A quite different but very important technique is ultrasound imaging, which gives a virtually risk-free method of identifying structural and some functional abnormalities that may result from genetic disease. This technique is widely used during pregnancy for the detection of fetal malformations, some of which are genetic in origin. Some early manifestations of serious genetic disorders that may develop in later life, such as polycystic kidney disease (enlarged kidneys with cysts) or certain types of cardiomyopathy (heart muscle disease) may also be detected.

3.3.2 Current screening programmes

In reviewing existing screening programmes, some of which are well established and others barely beyond the pilot stage, various ethical problems may arise.

Screening programmes are broadly divided into four groups, depending on the timing of the testing. These are:

- i. neonatal (in the newborn);
- ii. older children;
- iii. testing of couples or individuals before pregnancy (adults); and
- iv. antenatal (during pregnancy).

There may be no single stage of life at which genetic screening is most suitable. Screening may best be offered in a variety of ways, and the optimal approach may change as the community becomes better informed. For example, genetic screening for thalassaemia in Cyprus and Sardinia (countries where this disorder is particularly common) has progressed from the antenatal stage to the premarital stage and towards screening in schools. This type of progression may prove to be a common pattern as genetic screening becomes a more established component of primary health care.

3.3.2.1 Neonatal screening

The blood spot test for phenylketonuria (PKU) has not created any major ethical problems. Likewise the test for congenital hypothyroidism, which is carried out on the same sample, does not appear to have raised any major ethical problems. This may be partly because both diseases are severe and can be adequately treated if detected.

Nevertheless, there is evidence that many women do not understand the purpose of the test. A study in Britain of new mothers' knowledge of the blood test for PKU and hypothyroidism, showed that two-thirds said that the test had been fully explained. Most, in fact, did not know what the test was for, and many incorrectly believed that it also detected other disorders. Such results clearly challenge any notion that women are giving informed consent for their babies to be tested, although they believe themselves to be informed. There is no reason to believe that South Africa would be any different.

Some laboratories carrying out neonatal screening for PKU and hypothyroidism, in Britain and in other countries, have chosen to add tests for other serious conditions. It is not always clear to what extent parents are fully informed about these tests. A neonatal screening programme in Pittsburgh, USA, has chosen to employ 'informed dissent', where parents are required to express a wish to opt out if they so desire.

The present method of screening for PKU, which is recessively inherited, is indirect and does not identify the genes involved. If direct gene testing were introduced, so that carriers as well as affected individuals were identified, a different order of ethical issues would arise. The finding of a carrier child has no disease implications for the child, but may become important to that child in later life, when reproductive decisions are being made. How and when the

child should be told would require careful consideration.

Neonatal screening for sickle cell disease is cheap and reliable, and it is recommended for populations with a significant incidence of this disease. Early diagnosis of affected infants reduces childhood mortality and morbidity, and allows parents to be counselled about subsequent pregnancies. In some inner-city areas in Britain, all newborns, regardless of ethnic origin, are now screened for sickle cell disease. Screening, however, does detect carriers as well as affected individuals, and thus raises ethical issues for the families as discussed above.

Neonatal screening for cystic fibrosis (CF) by indirect testing (for trypsin in the blood) is carried out only in certain areas and is still under evaluation. There is some, but not conclusive, evidence that neonatal identification of infants with cystic fibrosis may improve their prognosis, because preventive management can be started before their lungs are damaged. Parents of affected children can also be offered prenatal diagnosis in subsequent pregnancies. DNA techniques, which identify carriers as well as affected children, have been used for confirmation of the diagnosis in the newborn period.

Pilot neonatal screening programmes for early identification of Duchenne muscular dystrophy have been set up in Britain (in Wales) and several other countries. All of these programmes have been based on an indirect method; the detection of the level of the enzyme, creatine kinase, in the blood. These programmes vary somewhat in detail, and in the manner of obtaining consent: the Pittsburgh study, for example, employs informed dissent. The X-linked nature of this disease raises particular ethical issues in terms of implications for the extended family.

Because neonatal screening for Duchenne muscular dystrophy is essentially still in the pilot stage, evaluation of all the ethical issues is not possible. Most workers involved consider that extensive, well-monitored pilot phases should precede a decision on more general implementations.

All newborn babies have a physical examination which may detect congenital disorders, some of which may have a genetic component. Examinations are often carried out in the presence of the mother, and the parents are informed about any abnormalities and their implications.

3.3.2.2 Later childhood screening

As part of routine child health surveillance, all children have a physical examination for a variety of diseases that may, in part, have a genetic basis. For example, hearing defects may be detected. Programmes of screening for specific genetic disorders are in the pilot stage. These need to adhere to the principles of informed consent (see 5.3 in Book 1).

3.3.2.3 Adult screening

Screening of adults may be carried out to detect existing disease or predisposition to a disease, or it may identify carriers with a reproductive genetic risk. Most presymptomatic testing for late onset genetic diseases (such as Huntington's disease) is currently offered to family members at risk. Increasingly, general screening for such late-onset genetic diseases is becoming technically feasible, although not necessarily desirable.

Screening programmes for various cancers that may have a genetic basis are currently the main form of genetic screening in the adult population. Testing the gene itself is now possible for familial adenomatous polyposis, an inherited form of colorectal cancer. It may soon be possible to screen a subgroup of women at high risk of familial breast cancer, although at

present such screening is aimed at early detection of the cancer itself. These testing programmes in families already known to be at risk, may be the forerunners of future screening programmes.

The general screening of individuals who may be carriers of inherited disease genes is currently used only as a service to those in an ethnic group known to have a high incidence of an inherited disease; for example, the haemoglobin disorders in people of African, Mediterranean and South East Asian origin and Tay-Sachs disease in Ashkenazi Jews.

Pilot projects have been undertaken in several centres in Britain to detect carriers of cystic fibrosis in adults aged between 16 and 45 years through screening in general practice.

3.3.2.4 Pre-pregnancy and premarital screening

Testing before pregnancy is not systematically practised to any extent in Britain or South Africa. Screening for carriers of the haemoglobin disorders may be offered through family planning clinics and general practice. Insufficient information is available to evaluate these programmes.

In Cyprus, antenatal screening for thalassaemia has been almost totally superseded by premarital screening. The religious authorities had ethical objections to screening during pregnancy, on the grounds that it excluded most options other than termination of affected pregnancies. The church in Cyprus therefore insists on testing as a formal prerequisite to church weddings. The certificate required states merely that the partners have been tested and appropriately advised. In this way the confidentiality of the test result is preserved and the couple can exercise an informed choice about reproduction.

General population carrier-screening programmes for thalassaemia have been established throughout the Mediterranean area. A comparative study of these programmes has shown they are most rapidly and equitably implemented when a small community at high risk is served by motivated staff working from a single centre, with the help of a lay support association (for example, Sardinia and Cyprus). Such programmes have developed more slowly in larger countries, as they must be delivered through the general health care system, and staff must be trained to integrate screening and counselling into routine services. It has proved particularly difficult to organise carrier screening for haemoglobin disorders where they are not a problem for the whole community, but primarily affect ethnic minorities, as in Britain. This problem is the subject of the Report of a Working Party of the Standing Medical Advisory Committee on Sickle Cell, Thalassaemia and other Haemoglobinopathies.³¹ This report provides guidelines to health service purchasers and providers on the provision of information, screening and counselling services.

3.3.2.5 Screening during pregnancy

Screening during pregnancy may be carried out on the mother, on the fetus, or on both. If, through screening, a woman is found to be a carrier of a gene for a recessive disorder, her partner may be offered genetic testing to find out whether the couple is at risk of having an affected child. If both parents carry the gene for a recessive disorder, if the mother carries the gene for an X-linked disorder, or if either parent has the gene for a dominant disorder, tests may be done on the developing fetus. There are several methods of obtaining samples for genetic tests on the fetus, the most common being amniocentesis and chorionic villus sampling (CVS). Genetic diagnosis can be achieved before 12 weeks' gestation with CVS, compared with about 16-20 weeks by amniocentesis. However, the risk of miscarriage is slightly higher for CVS (about 1-2% in excess of expectation at this stage of pregnancy) than for amniocentesis (0.5-1%). The emotional trauma caused by the need to consider a termination and to decide whether or not to have one, must not be ignored. This is a major

ethical issue that applies to many screening procedures where the disease is serious and where there is no effective treatment. Informing parents of the reproductive choices, places a considerable burden on them, and counselling and support will be needed - whatever the decision.

In Britain, antenatal screening tests are carried out on all women for a predisposition to rhesus haemolytic disease of the newborn and rubella (German measles). Rubella screening was the first screening programme undertaken with the objective of offering detection and abortion of potentially affected fetuses. Severe congenital disorders may result from rubella infection during pregnancy. Both rhesus and rubella screening appear to be well accepted. Whereas the finding of a rhesus negative blood group results in preventive treatment, a positive rubella test gives rise to the need for very painful decisions, including the termination of the pregnancy.

Ultrasound scanning of the fetus is generally practised, and routine ultrasound may reveal congenital abnormalities, some of which may have a genetic basis. Expert fetal anomaly scanning, a specialised form of ultrasound scanning, is offered to women known to be at increased risk of having a malformed fetus because of genetic or other reasons. In addition, it is increasingly offered to all women on a routine basis, as about 70-80% of all severe malformations can be detected by the technique. Although the majority of women are aware of ultrasound, the amount of explanation given regarding the possibility of detecting abnormalities varies greatly, as does expertise in interpreting the results.

The offspring of women with insulin-dependent diabetes mellitus have an increased risk of stillbirth, neonatal ill health and major congenital malformations, especially if their diabetes is poorly controlled. In many women with diabetes the diagnosis will already be known, but all women are screened early in pregnancy by blood and urine tests to detect undiagnosed cases. Expert fetal anomaly scanning by ultrasound is offered to all pregnant diabetics.

In many areas, screening is carried out to detect neural tube defects (spina bifida and anencephaly). Maternal serum alpha-fetoprotein (AFP) determination is now offered routinely to all pregnant women between 16 and 18 weeks of gestation, but in about half of all pregnancies with a raised maternal serum AFP, no cause can be found, either pre- or postnatally. A raised maternal serum AFP normally leads to expert ultrasound examination for a fetal malformation, with or without amniocentesis for confirmatory biochemical tests.

Pilot studies of screening during pregnancy for carriers of the common disorder, cystic fibrosis, are currently being undertaken in a number of centres in Britain, where 85- 90% of carriers can be detected by a simple DNA screening test based on a mouthwash sample.

The various studies of cystic fibrosis screening have devoted considerable effort to the psychological and ethical issues surrounding genetic screening programmes, especially since not all carriers can be detected.

Antenatal screening is offered to women in specific risk groups. All women over an age that varies by area between 35 and 37 are offered testing by chromosome studies for the presence of Down's syndrome in the baby. Down's syndrome occurs in approximately 1 in 600 of all births; but is much less common in children born to younger women (1 in 1 500 at age 20). Its birth incidence increases with maternal age, being about 1 in 350 at age 35, and as high as 1 in 100 at age 40. Recently, maternal serum screening tests have been developed that can be offered to all pregnant women, regardless of age, to detect those who may be at increased risk of having a child with Down's syndrome, in order to offer the choice of amniocentesis and chromosome testing. Unfortunately, only just over 60% of affected

babies will be detected in this way and 5% of the screened pregnancies will give results necessitating an amniocentesis, to reassure the participating women that they are not carrying a fetus with Down's syndrome.

3.3.2.6 Practice implications

Health professionals must recognise women's fears that the unborn baby might have a serious abnormality and their need for information about the implications where such a diagnosis is confirmed. Further, protocols concerning the implementation of screening programmes should include adequate psychosocial support for participants.

3.3.3 Counselling, providing information and obtaining consent

Genetic counselling is the provision of accurate, full and unbiased information that individuals and families require to make decisions in an empathetic relationship that offers guidance and assists people to work towards their own decisions.³² The information should include a full description of the risks, diagnosis, symptoms and treatment of the disorder in question. Information about financial costs, emotional costs, education, and both positive and negative effects on the marriage and family unit should be included, as well as available social and financial supports for persons with genetic conditions.¹⁴

It is fundamental that actual knowledge or understanding on the part of the patient, or person consenting on behalf of the patient, is achieved. It is not sufficient for the practitioner to have reasonably explained the information. Informed consent is valid only when it represents true understanding.¹⁴ This rigorous test of consent is linked to the patients' right to be so informed that they understand the proposed test or procedure, the possible alternatives and any associated risks, to enable them to make a balanced judgement on whether to continue with the test or procedure or to withdraw.¹⁴ Evidence suggests that the combination of written information supplemented with face-to-face interaction is the most desirable method of ensuring that patients receive sufficient information to empower them to make this choice.²⁶ It must be clear at all stages of the screening that the participant or patient is free to withdraw from the process at any time (see 5.3 in Book 1).

It is recommended that the following ethical principles should be applied to genetic counselling:

- i. respect for persons, families and their decisions according to the principles underlying informed consent;
- ii. preservation of family integrity;
- iii. full disclosure to individuals and families, of accurate, unbiased information relevant to health;
- iv. protection of the privacy of individuals and families from unjustified intrusions by employers, insurers and schools;
- v. informing families and individuals about possible misuses of genetic information by institutional third parties;
- vi. informing individuals that it is their ethical duty to tell blood relatives of the genetic risks to which they may be exposed;
- vii. informing individuals about the wisdom of disclosing their carrier status to a spouse or partner if children are intended, and the possibility of harmful effects on the marriage from non-disclosure;
- viii. informing people of their moral duty to disclose a genetic status that may affect public safety;
- ix. unbiased presentation of information, insofar as this is possible;
- x. adopting a non-directive approach, except when treatment is available, although the person being counselled may still decline treatment;

- xi. involving children and adolescents whenever possible, in decisions affecting them; and
- xii. observing the duty to re-contact if appropriate and desired.³²

Informed consent is an accepted norm in the clinician-patient relationship, implying the patients' knowledge of the major characteristics of their medical disorder, an understanding of the test or procedure they are to undergo, the limitations of the test or procedure, and the possible consequence of their participation in the test or procedure followed by their agreement, or not, to undergo the test or procedure.¹⁴ This term includes a right on the part of the participants or patients to be informed of risks not actually related to the medical impact of the test or procedure, including:

"Possible socio-economic consequences of an unfavourable test result, such as loss of health or life insurance, refusal of employment, discrimination by schools, adoption agencies etc. should where applicable, be included under the description of risks."¹⁴

It is recommended, further, that information to be given to any patient undergoing genetic screening should include:

- i. the seriousness of the condition to which the genetic disorder may give rise and how variable its effects are;
- ii. the therapeutic options available;
- iii. how the disorder is transmitted, the significance of carrier status and the probability of development of the serious genetic disease;
- iv. the reliability of the screening procedure and the results of the test;
- v. information detailing how the results of the screening test will be passed on to the patient, and what will be done with the samples;
- vi. the implications of a positive result for their future and existing children and for other family members;
- vii. a warning that the screening test may reveal unexpected and awkward information; for example, about paternity.²⁶

3.3.4 Genetic screening - the law and public policy

The negative impacts of genetic screening may be separated into two categories of harm. The first is the effect on the personal choices and mental well being of the individual, and the second is the effect on the interaction of that individual with society at large. The first category of harm may include increased personal anxiety about health, decisions related to the termination of pregnancy, and deciding whether to pass on genetic information to spouses, partners or family members.²⁶ The second category involves more powerful ethical considerations with regard to eugenics, employment prospects and access to life insurance and other benefits. It is with this second-category harm that we are primarily concerned in these guidelines.

3.3.4.1 Results of genetic screening and confidentiality

Genetic information can be effectively used to reduce the health-related cost of labour. This simple fact is the most powerful reason for employers and insurers to be interested in genetic screening and testing. On the other hand, the dissemination of genetic information to employers and insurers may be linked to the dangers of "isolation, loss of insurance, educational and job opportunities for persons diagnosed with incurable and costly disorders."

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Dangers associated with genetic screening differ from those associated with genetic testing. Genetic screening is carried out at the instance of the State or large institutions, while genetic

testing is done at the instance of the individual being tested. Guidelines related to genetic screening should also govern the scope and aim of screening programmes and ethical aspects relating to the use, storage and registration of data and follow-up procedure,²⁸ while guidelines for genetic testing should be more focused on aspects pertaining to the individual and the protection of his or her rights.

3.3.4.1.1 The scope and aim of screening programmes

"The literature on genetic screening and discrimination suggests several areas of sensitivity:

1. the workplace, where employers may choose to test job applicants, or those already employed, for susceptibility to toxic substances or for genetic variations that could lead to future disabilities, thereby raising health or compensation costs. In terms of Section 7 of the Employment Equity Act, No. 55 of 1998, medical testing of employees or job applicants by employers is prohibited in South Africa unless legislation permits or requires testing, or it is justified in the light of medical facts, employment conditions, social policy, the fair distribution of employee benefits or the inherent requirements of a job. Medical testing includes any test, question, inquiry or other means designed to ascertain, or which has the effect of enabling the employer to ascertain, whether an employee has any medical condition. Medical testing could therefore include some types of genetic testing;
2. the insurers (either life or health insurance companies) who might use genetic information or tests as criteria for denying coverage or require reproductive testing to be done for cost containment purposes. In terms of the South African Medical Schemes Act No. 131 of 1998, a registered medical aid scheme may not unfairly discriminate directly or indirectly against its members on the basis of their "state of health"; and,
3. law enforcement officials, who may test and/or use information without informed consent."²⁸

It is trite to state that employers and insurers should have limited rights to initiate screening programmes. This alone will not prevent genetic discrimination from occurring for so long as employers and insurers have access to genetic information.]

3.3.4.1.2 Test results, privacy and data protection

Every individual undergoing either genetic screening or genetic testing has the right to be fully informed of the results concerning a suspected disorder.²⁶ A difficulty arises where an individual is to be informed of results that are "unexpected, unwanted, and have not been covered by consent. For example, a sex chromosome abnormality may be revealed when carrying out prenatal testing for Down's syndrome, or a different inherited disease may show up on a test designed for another purpose. Unexpected information can present ethical dilemmas for which there are no easy answers, or indeed correct answers."²⁶

Article 8(I) of the European Convention on Human Rights provides that 'Everyone has the right to respect for his private and family life, his home and his correspondence'. The right to private life, or to privacy, clearly includes the right to be protected from the unwanted publication or disclosure of intimate personal information. The South African Constitution clearly protects each individual's right to privacy. Section 14 of the Constitution and the common-law right to privacy include privacy of information; that is, the right to determine for oneself how and to what extent information about oneself is communicated to others.

These general principles are particularly important in medicine. Respect for privacy is vital to the clinician/patient relationship. The relationship must be built on trust and confidence if patients are to reveal information essential to the proper diagnosis and treatment of their

condition. Yet trust and confidence would soon be shattered if clinicians were to fail to respect the confidentiality of intimate personal information.

The case for confidentiality in medicine applies with equal force to genetic screening. Individuals agreeing to be screened need to be confident that no results will be made available to anyone other than themselves and their medical advisers, without their explicit consent. Otherwise, people may be reluctant to participate, perhaps with damaging implications for themselves, their families and, potentially, other third parties. If clinicians were to break the confidence relating to genetic information, there would be adverse implications for other areas relating to the care and treatment of the patient. The patient would fear that other medical information was being disclosed to a third party.

The rights to privacy generally, and to the confidentiality of personal medical information in particular, are of the greatest importance, but it does not necessarily follow that both should be wholly unqualified. Article 8(2) of the European Convention on Human Rights provides, for example, that the individual's right to personal privacy may be overridden by requirements prescribed by laws introduced to protect health, morals, or the rights and freedoms of others. Section 36 of the South African Constitution also provides for the limitation of rights by laws of general application, to the extent that the limitation is reasonable and justifiable in an open and democratic society, taking into account various factors. These provisions may be particularly important in genetic screening.

The decision of an individual to participate in a genetic screening or testing programme may have implications for other family members, which could affect their future. The question is whether there is an obligation on the part of health professionals to consider the interests of the family members, even if the participating individual does not wish to warn relatives who might be at risk. The HUGO Ethics Committee in a statement on DNA Sampling: Control and Access, states that the "shared biological risks [of family members] create special interests and moral obligations with respect to access, storage and destruction that may occasionally outweigh individual wishes."³³

The issue is a contentious one, because the claims of family members may vary in strength. An individual may have an interest in knowing whether a partner or prospective partner is likely to suffer from, for instance, familial colon or breast cancer, or Huntington's disease. But such an interest, while understandable, falls far short of any right to demand knowledge. The emphasis is somewhat different if having children with a particular partner is contemplated. For example, a pregnant woman may legitimately want to know the result of the screening test on the father of her child, if she herself has had a positive test, indicating that she carries a gene for cystic fibrosis or Tay-Sachs disease. A different problem may arise with blood relatives, where non-disclosure of information might lead to an unnecessary termination, or where a relative, not informed of a high genetic risk, might become the parent of a child with a serious genetic disorder. A more difficult case is made out for siblings and other blood relatives who face the same risks in respect of a genetic disorder or disease, and may well have an interest in the outcome of the screening results.

3.3.4.1.3 The ethical dilemmas

We discuss first the responsibility of the individual in resolving the dilemmas, and next, the role and responsibility of the clinician or other professional adviser. The main ethical dilemma arises from a conflict between the right of the individual to personal privacy, and the reasonable desire of family members to be fully informed. The information, after all, might play a part in important decisions about their lives. A balance needs to be struck between the two. A further complicating factor, though, is that some family members may prefer not to be presented with the information. This would become a much more serious problem if widespread screening were introduced for X-linked or autosomal dominant diseases.

The individual's responsibility

The question of responsibility has at least two dimensions here. The first is the responsibility of the individual to pass on relevant information to other family members, and the second is the responsibility of the other family members to receive the information. We adopt the view that a person acting responsibly would normally wish to communicate important genetic information to other family members. These members may have an interest in the information, and a responsible person would probably wish to receive it, particularly where it might have a bearing on decisions that he or she may take in the future. We are also of the view that the primary responsibility for communicating genetic information to a family member or other third party lies with the individual and not with the clinician, who may, however, do this at the request of the person concerned.

Where family members do not wish to know, the situation may be more difficult. If family members were unaware that a relative had been screened, they would not know whether or not they wanted to be informed about the result. In these circumstances the individual who had been tested might have to inform them - or not inform them - personally.

Although serious problems may arise as a result of non-disclosure, and certain family members may have a legitimate interest in the information, this should not always supersede the individual's right to privacy. It is difficult to contemplate how any such legal obligation would apply, and how any legal right of family members (assuming that they could be identified) could be enforced. South African law does not impose a general duty to inform, but the community values (*boni mores*) may demand disclosure, to inform potentially identifiable persons within easy reach, who might suffer serious harm. In any event, in certain circumstances there may be perfectly good reasons why an individual would not wish to inform family members about the result of a genetic test. For example, a woman who has discovered she is a carrier of Duchenne muscular dystrophy may not wish to tell her sister who is 7 months pregnant.

The best way to ensure that genetic findings are appropriately shared with family members (and occasionally with other third parties) is through information and counselling procedures. Disclosure to other family members ought not to be made a condition of participation in a screening programme. Inevitably some individuals will refuse to allow disclosure and this may present the clinician or other health professional with an ethical dilemma.

The clinician's dilemma

Just as we have rejected the suggestion that there should be a legally enforceable duty placed on people who have been screened, to inform family members or other third parties of the results, so too we reject the idea that clinicians should be placed under a legal duty to reveal information against the wishes of the individual concerned. No such general duty is acknowledged by law in this country, although the position may be different elsewhere. The furthest the law appears to go is to recognise that in exceptional and ill-defined cases the clinician may have discretion to disclose genetic information to third parties (see 3.3.4.1.2).

Privacy and confidentiality should be respected and maintained, but we also accept that there may be exceptional circumstances in which these might properly be overridden by the clinician; for example, where information is withheld out of malice. We do not suggest that the wishes of the individual should be overridden only in this type of case. However, it illustrates how exceptional are the situations in which it may be appropriate and reasonable to subordinate the individual's privacy to the interests of others.

It is impossible to foresee all the circumstances in which a doctor might properly disclose

confidential information to family members. Although a set of guidelines and a knowledge of the law may be helpful, the decision on disclosure is also made according to the facts of each case. See in this respect the ethical guidelines of the South African Medical Association on HIV/AIDS (1998) and those of the Health Professions Council of South Africa (1994), which make provision for disclosure of a patient's HIV status.

This imposes a heavy burden of responsibility on the health professional. Two factors stand out as especially relevant. The first is the consequence of the refusal to share information. There would be a stronger case for overriding individuals' objections where consequences of disclosure are potentially damaging, rather than merely inconvenient to other family members. The second factor is the reason for the individual's refusal to permit disclosure. If it can be determined that the reasons are malicious, the decision may be straightforward. However, if the reason was a fear that the information might yield compromising evidence about paternity, the ethical issues would be quite different. If information about non-paternity was not disclosed, a man who incorrectly believed himself to be the father of a child with a particular genetic status might make the wrong decisions about having other children. On the other hand, for the health professional to reveal such information might lead to harm to the woman concerned, not only because of the breach of confidentiality itself, but also because of its impact on the woman's relationship with the man involved. For this dilemma there is no easy answer.

It is recommended, therefore, that the following points be adopted as guidelines to disclosure, to families, of the results of a genetic screening programme:

- i. "the accepted standards of the confidentiality of medical information should be followed as far as possible;
2. where the application of such standards might result in grave damage to the interests of other family members, the health professional should seek to persuade the individual to allow disclosure of the genetic information. The potential seriousness of non-disclosure should be explained to the individual;
3. in exceptional circumstances, health professionals might be justified in disclosing genetic information to other family members, despite an individual's desire for confidentiality."²⁶

3.3.4.1.4 Genetic registers

In the context of genetic screening, where large numbers of tests are undertaken, this may be recorded in the form of a genetic register or similar database. Special consideration should be given to the implications for security of these grouped results.

A register may be defined as a systematic collection of relevant information on a group of individuals. Genetic registers record information on individuals with specific genetic disorders, and may include relatives at risk of developing or transmitting the condition. The information may be recorded by hand, or may be held on computer. Genetic registers may be set up for a variety of reasons, including research on the disorder, the effective provision of services to those on the register, and the systematic offer of genetic counselling to family members. The amount and type of information recorded varies greatly, as does the presence of identifying details.

There are several general ethical issues concerning genetic registers. Here we outline issues relating to genetic screening. They should be seen against the background of the following points:

- i. a genetic register may be the starting point for genetic screening; for example, the

- systematic testing of relatives of individuals with fragile X syndrome or Duchenne muscular dystrophy;
- ii. genetic screening may also be based on a register not specifically genetic in its basis; for example, registers of specific cancers or of those with severe learning difficulties;
 - iii. a genetic register may be the product of a genetic screening programme; for example, a register of carriers of cystic fibrosis or sickle cell disease in a population screened for the purpose.

It is essential to obtain individuals' consent before placing their names on a register. It is also important that individuals know that they are on the register, and what use will be made of the information.

Consent of individuals to long-term storage of information resulting from genetic screening has been emphasised earlier. However, if this is to form the foundation of a genetic register, separate and specific consent should be sought for subsequent tests or other measures, also for further use which may generate financial benefits for the investigator.

Confidentiality of all medical information is essential, and this is particularly the case with genetic registers, which may contain highly sensitive and potentially identifiable data on large numbers of individuals with, or at risk of, serious genetic disorders.

Computer-based genetic registers are subject to the Promotion of Access to Information Act, No. 2 of 2000, but there is need for additional safeguards for all genetic registers, including secure storage of information, limitation of access to those specifically responsible for a register, and the removal of identifying information when data are used for research purposes. Further, a Data Protection Act is envisaged for South Africa.

This is an important area of concern. The Department of Health, in consultation with health authorities and appropriate professional bodies, should devise effective arrangements for the preservation of confidentiality, particularly in relation to genetic registers, and should provide the necessary guidance.

3.3.4.2 Employment

Competition drives the players in the economy to reduce costs and increase efficiency. In the context of employment, genetic screening provides the employer with an opportunity to reduce the health-related costs of employment. An employer may want to screen candidates, to exclude those susceptible to either occupational or non- occupational disease.

"Healthy workers cost less: they are less often absent through illness, there are lower costs for hiring temporary replacements or for training permanent replacements, and there are fewer precautions which would need to be taken to deal with health and safety risks."²⁶

The dangers of permitting employers to embark on their own screening programmes are self evident. The result would be restrictions on the employment of individuals who are at risk of genetic disease, and the creation of class orders based on genetic disposition. In other words, genetic discrimination would ensue. Wealth most often follows employment, education follows wealth, and employment follows education: a neat circle ensuring comfort for those within its exclusive confines. The cost implications for the State are critical. Whereas the business community currently bears some of the costs of genetic disease in the population, by excluding this cost through genetic screening, business would effectively shift the their share of the cost to the State, with repercussions for social welfare and health policy in particular.

However, employees and the public at large have an interest in reducing the incidence of occupational disease. It is accepted that employers may require employees to undergo screening for illnesses or conditions that present a serious danger to third parties.²⁶ Thus genetic screening may have a limited role to play in employment. One way of achieving this is for the State to introduce screening programmes whereby individuals are made aware of their genetic disposition and are empowered to make informed decisions with regard to their employment and their health.

Section 7 of the Employment Equity Act, No. 55 of 1998, prohibits the medical testing of employees and applicants for employment, unless legislation permits or requires testing, or it is justifiable in the light of various factors, such as employment conditions or the inherent requirements of the job.

3.3.4.3 Insurance

Insurance and risk management are two separate forms of practice. Risk management seeks to reduce the costs associated with risks that will certainly eventuate, whereas insurance is more like a gamble: it is unknown whether the event will occur or not. The relevance of this to genetic screening is that at present the medical aid industry operates as a form of insurance. Insurers constantly try to determine the risk associated with potential clients, to better allocate the premiums and so attract the least risky clients.

The revolution in genetics allows insurers to reduce uncertainty about future events. This fundamentally changes the context of insurance. The more predictable the risk, the more accurately an insurer can apportion premiums. The repercussions for individuals with genetic predispositions to certain diseases are that they may not be granted health insurance at all, or may be charged higher premiums. It has to be borne in mind that The Medical Schemes Act, No. 131 of 1998, provides that a registered medical aid scheme may not unfairly discriminate directly or indirectly against its members on the basis of their 'state of health'.

However, insurers have argued that using genetic information to predict risks is nothing more radical than an extension of their current practice. At present, insurers require people seeking insurance to provide information regarding their family medical history and lifestyle, to be able to predict the risks and thereby to determine an appropriate premium. Further, insurers require insurance applicants to disclose all known information that would impact on the risk - this would include disclosure of both an HIV positive status and the results of genetic tests. It is thus argued that the additional information obtained from genetic tests is an extension of accepted practices.

At face value, the argument is persuasive. However, the results of genetic tests do not always predict outcomes, but are rather a test for a certain mutation.

"Additional statistical information linking a given test result to the occurrence of some disorder is also needed if a sound prediction of disease or of lowered life expectancy is to be made on the basis of a genetic test result. Without information that links genetic test results to incidence of disease or death, they lack actuarial import."³⁴

There is information linking the existence of certain single gene disorders to the onset of a genetic disease or lowered life expectancy. However, it is not clear whether the relevant test predicts the onset of the disease or establishes the presence of the disease.³⁴ Insurers require predictive test results, but even those predictive tests that are available cannot accurately determine the onset of the genetic disease.

Recommendations on the use of genetic screening and genetic tests by insurance companies arise from the following considerations:

- i. the difficulty of assessing sometimes slender evidence on the genetic susceptibility of individuals to develop polygenic and multi-factorial diseases (for example, some cancers and some forms of heart disease);
- ii. an awareness that ordinary commercial practice will lead companies to be overcautious in their assessment of the risks derived from medical data; and
- iii. the possibility of abuses.

3.3.4.4 Children

There are well-founded reasons for testing asymptomatic children and adolescents for genetic diseases or carrier status. However, genetic testing of children raises ethical concerns over issues such as informed consent and disclosure to the child. The test is conducted only where it is in the best interests of the child; thus the primary justification for the test should be timely medical benefit to the child.³⁵ If the provider of the test is of the view that the potential harm of the test would outweigh the potential benefit, or if medical intervention would be of no benefit until adulthood, the test should be deferred until adulthood.³⁵

There is a presumption of parental authority in our law, which acknowledges the child's lack of the capacity to make appropriate life-impacting decisions, and that parents are usually best placed to decide about the well-being of their child, and have the greatest interest in promoting their children's well-being.³⁵ The assent of the child should be sought. Related to this right is the right to make an informed decision without interference from health-care providers, although this right can be limited where there are objective reasons to believe that a decision or action has significant potential for an adverse impact on the health or well-being of the child.³⁵

The following recommendations of The American Society of Human Genetics and the American College of Medical Genetics Report³⁵ in respect of family involvement in decision-making are endorsed:

- i. education and counselling for the parents and the child, according to the child's maturity, should precede genetic testing;
2. the test provider should obtain the permission of the parents and the assent of the child or the consent of the adolescent. In terms of the Child Care Act, No. 74 of 1983, a child above the age of 14 years may consent independently to medical treatment, which would include genetic testing from which the child could benefit directly (see 5.3, Book 1);
3. the test provider is obliged to advocate the child's best interests at all times;
4. a request by a competent adolescent for the results of a genetic test should be given priority over the parents' requests to withhold information.

3.4 Introduction to cloning

3.4.1 Science and morality - whose viewpoint?

Setting down guidelines for the research and practice of cloning is uncontroversial only in an environment where the analysis presented fundamentally reflects the norms of the community. The difficulty in a pluralistic community is to determine which set of values to uphold. To a large extent in the scientific community, the excitement of discovery, new techniques and the unfolding potential for scientific advancement may often be more persuasive than moral concerns. On the other hand, a society that is not permissive of

innovation must stagnate. It is with a deep-seated respect for both the potency of scientific advancement and the value of human life that we engage with the ethics of cloning.

3.4.2 Techniques of cloning

The term 'clone' is used in its strictest sense to mean a precise genetic copy of a life-form. There are established cloning technologies in horticulture and the simpler invertebrate species, and the cloning of human and animal genes has been practised for decades.³⁶ Cloning at the molecular level involves the copying of DNA fragments containing genes that are amplified in a host cell. This results in large quantities of identical DNA, useful for scientific experiments. Cellular cloning, on the other hand, is the copying of somatic cells through growing in culture.

This form of cloning is sometimes used to test and produce new medical products.³⁶ The third form of cloning is directed at the reproduction of genetically identical animals, and can be divided into two distinct processes, blastomere separation and nuclear transplant cloning. In blastomere separation the developing embryo is split soon after fertilisation, when it is composed of from two to eight cells. Each cell, called a blastomere, is totipotent and is genetically identical to the other blastomeres. Nuclear transplantation cloning involves a more sophisticated technique. The nucleus of a somatic cell is placed into an egg, the nucleus of which has been removed. This technique permits asexual replication; the ability to predetermine the genetic make-up of a human being and the ability to create many genetically identical offspring.³⁶ See Section 39A of the Human Tissue Act, No. 65 of 1983, which seems to prohibit the genetic manipulation of gametes and zygotes outside the human body in South Africa and therefore applies to this type of cloning if there is any intention of implanting the zygote. (It is not clear if experimentation on the zygote or pre-embryo would be permitted so long as implantation would not follow.)

3.4.3 Cloning and genetic research

3.4.3.1 Informed consent of donors

Informed consent must be given prior to the donation of oocytes, spermatozoa, normal but 'surplus' fresh or frozen embryos, non-viable or abnormal embryos, abnormally fertilised eggs, and eggs and sperm used to generate embryos for the purposes of scientific research.

3.4.3.2 Research using human tissues and embryos

A human embryo is special because of its potential for human life. The recognition of this potential has traditionally limited experimentation on human embryos, regardless of the legal determinations of when life begins.

The most controversial research using human tissue at present, is that on stem cells derived from human embryos and fetuses. Stem cells are undifferentiated cells found in the embryo and which have the ability to develop into any specific adult cell required in the body,³⁷ although there are many different types of stem cells. As a general rule, all have the ability to divide and self-renew and to commit to a more specialised function. For research purposes it is important to distinguish between two forms of stem cells. Totipotent stem cells have the ability to form an entirely independent human being if placed in utero, and they are found in an embryo which is at the 16-cell stage. Pluripotent stem cells have the lesser ability to give rise to any type of specialised cell and they are found within the inner cell mass of a blastocyst.³⁸

There is no controversy over research involving the use of totipotent cells - it is not permitted. However, the ability of pluripotent stem cells to develop into any specified tissue cell makes them extraordinarily interesting to study. Theory suggests that pluripotent stem cells could be

cultured to provide an unlimited source of specified cells under the right condition, and the research of Gearhartl and Thomson on stem cells has confirmed this.³⁹ Potential medical applications include the treatment of cell-based diseases and the development of human organs for transplant purposes. The creation of human tissue cultures may even eliminate the need for animal and human trials of medical products. Despite the obvious usefulness of the research we must ask at what point we are willing to let theory remain just that.

There are several objections that must be addressed. The first is that current research involves the use of stem cells derived from human embryos. The current sources are:

1. human fetal tissue following an elective abortion;
2. human embryos created by in vitro fertilisation and no longer required;
3. human embryos created by IVF with gametes donated for the sole purpose of providing research materials; and
4. embryos generated asexually by somatic cell nuclear transfer or similar cloning techniques.⁴⁰

The fact that the source is a human embryo is itself problematic, not because of sentimentality associated with research involving human tissue (using human tissue derived from donated cadavers is not controversial) but because the extraction of stem cells from the human embryo eliminates that embryo's potential for life. It is not possible to completely rationalise this response. However, the objection must be treated with respect as the genuine response of a portion of the population, which believes that the right to life and dignity is applicable to human embryos. It does not help to enter into a legal debate as to when the embryo acquires the status and concomitant rights of a human being. The issue is not one of legality, but of mores.

There are several arguments in favour of the use of stem cells in research, which seek to justify the use of human embryos in research. The first contends that the use of human tissue derived from embryos from in vitro fertilisation processes and legal abortions cannot be any more objectionable than either of these procedures, particularly when the embryo's potential for life has already been terminated. The use of the fetal tissue does not result in the intentional destruction of a live fetus, and the fetus is not created solely for research purposes. It is also argued that, unlike an embryo, a stem cell is not capable of forming a new, independent life. The arguments also point to the potentially extraordinary life-saving applications that, but for research, will remain outside the realm of medical practice.

There is no easy resolution of the issues involved. Ethics do not and can never mean anything so restrictive as those mores of society determined by the law. Fortunately, the research of Mackay and his colleagues may allow the scientific world to side step this issue altogether. The advances made by Mackay indicate that it is possible to isolate adult stem cells derived from the adult brain and spinal cord. Although these stem cells can only differentiate into any of the three major cell types in the brain and spinal cord, there is hope that the isolation of other adult stem cells will obviate the need for research on human embryos. It is impossible to come to a clever compromise, and clarity about the status of such research is essential.

It is recommended that, for the present, the use and derivation of human stem cells should be limited to two sources, cadaveric fetal tissue and embryos remaining after infertility treatments. Some good should come from these embryos rather than that they are totally wasted.

It is also recommended that the following principles, drawn from the recommendations of the

United States National Bioethics Advisory Committee,³⁶ regulate the donation of human embryos for stem cell research:

- i. Prospective donors should be given timely, relevant and appropriate information to make informed and voluntary decisions regarding the donation of the embryos.
2. Embryos and cadaveric fetal tissue should under no circumstances be bought or sold.

3.4.4 Cloning and genetic practice

3.4.4.1 Reproductive cloning and cloning as a biogenetic tool for therapeutic purposes

3.4.4.1.1 Potential applications of cloning

3.4.4.1.1.1 Therapeutic cloning

The generation and harvesting of human tissue to satisfy the therapeutic needs of humans requires careful consideration. In principle, the application of nuclear transfer cloning could provide a host of embryos with a potential source of organs or tissues of a predetermined genetic background, namely those of the donor of the nucleus. This notion, however, elicits horror from most scientists, and undermines the human dignity afforded by Section 10 of the Constitution. It devalues the potential life element of all human embryos and prioritises the needs of a living individual over the potential life of the embryo. An embryo is being created and allowed to develop to a stage where it would be a source of 'spare parts' for the donor of the nucleus. This practice cannot be equated with abortion, where the potential life of the embryo is terminated at a woman's choice, because the reason for the creation of that embryo, and the reasons for the termination of its potential life are fundamentally different.

A more acceptable approach could be the development of specific tissue rather than an entire individual. The growth of entire organs would revolutionise organ transplantation. However, this technique should be more thoroughly investigated in animal systems before experimentation with human tissue is permitted.

Another application is the transplantation of cells or tissues from totipotent embryonic stem cells. This would not require the generation and birth of a cloned individual for cell-based applications. "It might be possible to take a cell from an early blastomere and treat it in such a manner as to direct its differentiation along a specific path. By this procedure it might be possible to generate in the laboratory sufficient numbers of specialised cells, for example bone marrow stem cells, liver cells or pancreatic pan beta cells (which produce insulin) for transplantation. If even a single tissue type could be generated from early embryonic cells by these methods and used clinically, it would constitute a major advance in transplantation medicine by providing cells that are genetically identical to the recipient."³⁶ The possible use of nuclear transfer cloning to create human embryos, as stem cell 'cultures' for the purpose of growing specified cells for transplantation, is controversial in the extreme. Two immediate concerns are raised: first, that human life is generated as a means to an end and terminated just as easily; and second, the use of the cells of early embryos for the nuclear transfer cloning.

Understanding that there are many approaches to the creation of specific stem cells, it is recommended that this research be conducted in a manner that eliminates the need for the use of human embryos. A more acceptable approach might be the development of specific tissue rather than an entire individual. The growth of entire organs would revolutionise organ transplantation, but this technique should be more thoroughly investigated in animal systems before experimentation with human tissue is permitted.

3.4.4.1.2 Reproductive cloning

Cloning is also a technique that, potentially, can be used in assisted reproduction, for the purposes of enhancing the reproductive potential of a human being. This form of cloning gives effect to the right of every individual to make choices regarding their own reproduction, a right entrenched in Section 2(z)(a) of the Constitution. Reproductive freedom includes not only the right to choose not to reproduce, or to terminate a pregnancy, but also the right to choose how to reproduce. Assisted reproductive technology is widely used and accepted, although in most situations of assisted reproduction, the cells are manipulated only to realise the union of the gametes. The strongest case for permitting the use of nuclear transfer cloning is where this potential application is a necessary means for procreation by that individual.

It is recommended that in the use of nuclear transfer the reproductive needs of an individual should not over-ride the best interests of the child produced.

3.4.4.1.2 Safety

There are important risks associated with current cloning technology, to which a cloned embryo would be exposed. These risks are potentially harmful and even life threatening to the embryo, and there can be no justification for experimenting with human embryos in these circumstances. If cloning techniques become so refined that there is no risk to a human embryo, it will become necessary to undertake a comprehensive investigation of the psychological impact of cloning on the child, the family and society. It may be possible to identify harms, such as a diminished sense of individuality and personal autonomy (although naturally produced identical twins would deny that there are harms suffered or experienced by them on this score), and the potential for discrimination, which a cloned child may suffer. Every effort must be made to alleviate these concerns before cloning is permissible as an assisted reproductive technique. Further, the circumstances in which cloning may be permissible must be enumerated. It would be unethical to permit clones for commercial or other purposes unrelated to medical necessity.

A further cause for concern is the creation of multiple embryos, which may not become viable, for the creation of one viable cloned embryo. In many respects this issue has been addressed by the techniques and practices used in in vitro fertilisation, and will not be recapitulated here.

It is arguable that the freedom of scientific enquiry must allow and encourage research and scientific advances. However, although the freedom of scientific research and academic freedom are enshrined in Section 16(1)(d) of the Constitution, that right itself must be balanced against the other rights in the Constitution. Thus, constraints on the freedom of scientific enquiry may be imposed to protect the safety of the community and individuals, and the rights and interests of the subjects of scientific enquiry.

At present there are compelling reasons to limit the inquiry into human nuclear transfer cloning. We believe that there is no scientific justification for experimenting with a human embryo that has the potential to become a human being. There are considerable risks involved in successful somatic cell nuclear transfer cloning, which we believe make it unacceptable for use in experimentation with human embryos. For instance, the technique that produced Dolly was successful in only 1 of 277 attempts, and it is not even clear whether Dolly's life expectancy will be reduced.

The risk attached to the use of the technique on humans carries the possibility of hormonal manipulation in the egg donor, multiple miscarriages in the birth mother, and possible severe developmental abnormalities in any resulting child. The potential harms outweigh the potential benefits, and until studies in animal systems reverse this circumstance, it is recommended

that the use of human nuclear transfer cloning to create a new life should be prohibited.

3.4.4.2 Fears and critique of nuclear transfer cloning

The greatest fears regarding cloning are in respect of its impact on the psyche of the cloned child, the manner in which the child will be nurtured in society, and the moral, religious and cultural values of that society. The strength of public reaction to cloning reflects a deep concern that important social values will be harmed if cloning is widely used.

Further, it has been argued that there exists a moral right to a unique identity, including a genetic identity, which cannot be permitted to be undermined, for to do so would lead to a diminishment in physical individuality and psychological autonomy - a right extended to all human beings under the protection of human dignity in the Constitution. Some ethicists disagree, arguing that cloned individuals are not more closely related genetically to the donors of the nuclei which gave rise to them than are natural identical twins.

However, it must be noted in this regard that the physical and psychological traits of individuals are not determined by genes alone. Each individual is a result of a complex interaction between his or her genetic make-up and the environment in which she or he develops.

One of the many fears surrounding nuclear transfer cloning is that it may become a form of eugenics, whereby certain human traits valued in society are effectively reproduced by those who have the financial means, thereby creating class structures based on wealth and genetic make-up. The genetic manipulation required to develop only those traits identified as positive human traits, in a cloned embryo, must be treated with the same caution outlined in the discussion of eugenics under the topic of gene therapy.

Critics have raised questions about the appropriate use of scarce resources. This is particularly important in South Africa, where public policy has determined that the extension of primary health care to all South Africans must be the nation's first priority in the field of medical care. A decision on whether research into, and the practice of cloning, are a responsible use of limited State resources must be made.

3.4.5 Regulation of cloning research

3.4.5.1 Expert supervisory body

It is recommended that continuing supervision of research into and related to cloning is necessary. At present there is no single body constituted for these tasks. Therefore, it is recommended that a new expert supervisory body be established.

In line with the recommendations for a supervisory body for gene therapy, it is recommended that this supervisory body should be of sufficient standing to command the confidence of existing Research Ethics Committees, of the public, the professions and of Parliament. It should have a responsibility for:

- i. advising on the content of proposals, including the details of protocols, for therapeutic research;
2. advising on the design and conduct of the research;
3. advising on the facilities and service arrangements necessary for the proper conduct of the research.

In the light of this assessment the expert supervisory body should make a recommendation

on whether the proposal should be approved, and on what conditions. The supervisory body should also have a responsibility for:

- iv. acting in co-ordination with existing Research Ethics Committees;
5. acting as a repository of up-to-date information on research in human cloning internationally;
6. oversight and monitoring of the research;
7. providing advice to Health Ministers on scientific and medical developments that bear on the safety and efficacy of cloning.

It is recommended that any proposal for research related to cloning be approved by this body as well as by a properly constituted Research Ethics Committee.

3.5 Patenting human genes and proteins

The patenting or 'biopiracy' of human genes and proteins is foremost a commercial issue. Patents are in essence a limited-period monopoly. The implications in the field of genetic research and practice are profound. In commercial terms a patent means revenue for the owner from licensing arrangements, product development, manufacture and sale. Profit becomes the incentive for research and development. The question is whether the price paid for the contribution to knowledge is not too high. Apart from concerns over the transactional costs of patenting human biological material, there is another response to such patenting, which posits that a human body cannot be the subject of property rights. Some base the objection on human rights' theories related to human integrity and dignity, while others base it on religious or spiritual values and beliefs. The heart of the objection is a concern that human beings should not be objectified.

Historically, patents over living organisms or phenomena of nature were disallowed, as these were not seen to comply with the requirements of novelty and innovation.^{41, o} This changed after the ruling by the US Supreme Court in the case of *Diamond v Chakrabarty* (447 U.S. 303, 1980) where a patent was granted for a genetically engineered living organism that was designed to digest and break down crude oil. Since that time, multiple patents have been registered over plant, animal and human genetic material, subject to the requirement that the subject matter be novel and innovative.

A cell-line derived from the cells of individuals is one form of 'altered human genetic material' that may be the subject matter of a patent. However, the registration of such patents is highly controversial as the applicant's proprietary rights to the cell-lines are contested by the donors of the genetic material used to create the cell-line.^p In this regard, the Supreme Court of California has held that "as biotechnology has an enormous potential benefit for humanity, giving the human source of genetic material property rights would drastically curtail the free distribution of biological samples for scientific research, thereby doing a great disservice to society."⁴¹ Ironically, the Court went on to permit the granting of proprietary rights in human genetic material on the basis that patenting is the best motivation for innovative research. The irony lies in the fact that there was no cost/benefit analysis in the determination of the Court. It is not a certainty that the commercial enticements offered for scientific research have, in fact, benefited the community. It cannot simply be taken for granted that the granting of monopolies is the best method of ensuring the greatest benefit to consumers. This has particular application in South Africa, where the majority of our community is economically under-privileged. The price of granting patents is, for the majority of the population, reduced access to potentially essential medical products, albeit for only a limited period.

The most objectionable aspect of patent, as evidenced in the US patent system and in the European Union,^q is that it encourages research work which does not require time, effort and

innovation which should be rewarded. The reference is to the permissible patenting of expressed sequence tags that involve automated sequencing technology. The research really begins with finding full-length cDNA and genomic sequences, and "the task of identifying biological functions of a gene is by far the most important step in terms both of its difficulty and its social benefit. It therefore merits the most incentive and protection."⁴² It is anomalous that straightforward processes be rewarded so substantially when the real work only begins after a patent has been granted. In effect, the patent is used to protect a future investment, which may or may not result in product development, and is not a reward for undertaking publicly useful research.

The profit-motive theory for permitting patents is therefore inapplicable, because the reward is not for the development of beneficial products, but is an incentive to spend time and money on potentially profitable research. This is not to say that tools used for the development of useful products are not patentable. However, it is queried whether an expressed sequence tag is such a tool. The sequence seems to fall more neatly into the category of 'raw material'.

Patenting becomes problematic when the patent owner imposes licence fees or restrictions on the research of other organisations, particularly where the patent owner has built on the work of others to develop the subject matter of the patent claim. Previously viable research becomes too expensive under a licence system, or is prohibited altogether. This has important implications for private patents of work that is largely indebted to publicly funded research. The public bears a double burden; first, in funding the research, and second, in paying monopolistic prices for products developed from that research. The resultant monopolistic prices impact also on the ability of public health agencies to offer free or low-cost services to the public, thus removing the economically under-privileged even further from access to beneficial medical products.

The argument in favour of patents does have some validity. What incentive exists for research where competitors can 'piggy-back' on the innovations of a product developer? Taking away incentives may cause research to become a largely publicly funded activity, guided (or stifled) by the mores (and agenda) of the incumbent government and subject to political approvals. Privatisation of research allows greater independence from political intervention. In defence of private companies it is said that the desire to make profits is not devoid of reasoning. Logic dictates that products must be priced at an affordable price for profits to be realised. The debate, however, is not merely one of price, but of public utility. Affordability does not mean utility. A product that has a cost price of R1 may still be affordable at R10, ten times the cost price. There is no dispute that development must be rewarded; the controversy rests on the question of how much development deserves reward and how much reward is sufficient.

In summary, the present incentive is for researchers to patent sequences or partial sequences of human genes. Further, the focus of substantive research has become profit driven. The patenting system grants to one entity the control of all future research and medical development with respect to the subject matter of the patent, in some instances for undertaking nothing more than a mechanical procedure.⁴³ This cannot be to the public benefit, while it promotes secrecy and hinders the exchange of scientific information, resulting in duplication of efforts, inefficiency in research and greater costs to the public for access to the resultant medical products.

It is evident that the patent system does not offer a donor much protection. However, an individual donor or donor community is not completely vulnerable. While the process of registering a patent does not involve an investigation of the proprietary rights to the subject matter of the claim, there are laws and practices with regard to informed consent, regulating the use of human tissue for research. Donors of the material must give consent to the use of

their tissues for the purposes of research and development, and further, consent must be given to the patenting of isolated genetic material gleaned from the donor samples. Any possible financial or other benefit by anyone should be disclosed to the donor.

Unfortunately, levels of informed consent are at present dubious or largely absent. Informed consent acknowledges that a subject's privacy is breached by the activity to be undertaken, and it seeks to absolve the breaching party of responsibility by requiring the subject to permit the carrying out of the activity. Lack of consent affects the legality of the activity. Thus, in a paradigm of informed consent, subjects are able to protect their rights and interests by clearly defining the ambit of the consent. This does not necessarily invalidate the patent application, but lays the applicant open to claims for damages. Further, a donor has rights of privacy over his medical records. No analysis of donor samples may be commercialised without the donor's informed consent in respect of the records (see 6.7 and 7.2.4 in Book 1). There should not be exploitation of individuals nor communities (see 11 in Book 1).

3.6 The Human Genome Diversity Project'

The Human Genome Diversity Project (HGDP) is a collaborative research project that is being developed on a global basis under the auspices of the Human Genome Organisation (HUGO). The overall goal of the project is to arrive at a much more precise definition of the origins of different world populations by integrating genetic knowledge, derived by applying the new techniques for studying genes, with knowledge of history, anthropology and language.

The cells of every human being contain the same 100,000 or so genes. Collectively known as 'the human genome', these genes contain all the information that makes us appear and function as humans rather than as members of some other species. However, many human genes exist in more than one form (or 'allele') and not all of us carry exactly the same forms of every variable ('polymorphic') gene. Each of us, apart from identical twins, is thus a unique individual, recognisably human but different from all other humans. The genetic variation from one person to another reflects the evolution of our species, because it is the result, over many generations, of the survival or loss of different forms of genes or the natural introduction of new forms. Studying this variation among people from around the world provides a great deal of information about the development of our species which, integrated with findings from archaeology, linguistics, history and other disciplines, may lead to a much richer and more complete picture of our past than has previously been possible.

The specific aims of the HGDP are:

- i. to investigate the variation occurring in the human genome by studying samples collected from populations that are representative of all of the world's peoples; and
2. ultimately, to create a resource for the benefit of all humanity and for the scientific community world-wide.

The resource is intended to exist as a collection of biological samples representing the genetic variation in human populations world-wide. It is also an open, long-term, genetic and statistical database on variation in the human species that will accumulate as the biological samples are studied by scientists from around the world.

The founders of the project intended the main value of the HGDP to lie in its enormous potential for illuminating our understanding of human history and identity. The resource created by the HGDP also provides valuable information on the role played by genetic factors in predisposition or resistance to disease. Considerable effort has been devoted to reviewing the ethical issues involved in the proposed project. The areas of concern range from the

preservation of individual rights within indigenous communities, where the presumption of 'informed consent' and adherence to 'Western ethics' are likely to be at variance with common practice, to a concern with the preservation of intellectual property rights. The two major areas of ethical concern relate to collection and storage issues, and intellectual property rights to products derived from the collected samples.

3.6.1 Collection issues

It is clearly set out in the HGDP guidelines^r that respect for individuals and their cultural integrity must be the foundation on which all collection efforts are based. This necessitates the informed consent of all those participating in the HGDP. Regardless of the varying legal requirements that may need to be met, true informed consent requires that people agreeing to participate understand:

- i. that the actual collection of the sample involves some (specified) risks although these are very small;
2. that the sample collection will cause a little discomfort; and
3. that DNA from the sample will be stored in a repository and may be used by many investigators for a long period (for many subjects this also requires that they understand that cell-lines will be established; see 5.3 Book 1).

Further, the issue of testing for disease is not only a very important aspect of collection, but is also many faceted. For example, there are obligations to resolve with regard to testing for infectious disease, which raises issues of protecting laboratory workers and investigators, as well as issues of protecting the individuals from whom samples are collected.

The disclosure of the infectious disease diagnosis to the community or participants must be closely considered. There are also obligations to resolve with regard to testing for non-infectious disease. In all cases, there are many questions to be addressed. For example, is it ethical to test for any disease without providing pre- testing counselling or evaluation of the test? (For example, in South Africa people may be tested for HIV only with proper pre- and post-test counselling.) Who is to be informed of results? If disease is tested for, what is the obligation to provide treatment?

Finally, the anonymity of all participants must be preserved, to provide protection against possible abuse or adverse effects arising from the consequences of the study. However, the HGDP is based on the fundamental principle that the resulting data may be accessed by any scientist. The primary concern regarding access to the database is the prospect of military access. Population-targeted biotech weapons are not an impossibility. In fact, the World Medical Association has expressed concern about the potential development of genetically targeted weapons, a topic of debate in the US Department of Defence, as possibilities in future combat scenarios.⁴⁴

3.6.2 Intellectual property rights

The guidelines state that patenting products derived from the samples contributed to the HGDP should include provision for the financial return on sales to benefit the sampled population or individual. However, there are many precedents where this principle has not been applied. In many areas of the world, such abuses have made people aware of this problem. While the HGDP asserts that it has no financial or commercial interest in the collection and analysis of the samples, it must be noted that the HGDP operates under the auspices of the Human Genome Organisation, and that major funding for the HGDP has been obtained from the US National Institutes of Health, while the National Science Foundation supports individual researchers. Further, the US Government is very interested in the commercial prospects of biotech products. On this basis, it would be desirable to put the

management of the database into the hands of a respected and independent international organisation.

The guidelines do not touch on the issue of patenting cell-lines derived from the genes or cell-lines of participants. Such patents by the US Government of the cell-lines of indigenous communities have elicited an outcry among indigenous peoples. Seventeen native groups have criticised the HGDP, calling for a halt to the project and asserting their entitlement to the recognition of full ownership, control and protection of their property. The potential for profit from indigenous genes is demonstrated by just one example - the isolation of genes which code against cardiovascular disease, found in an isolated community in Italy.⁴⁵

The following ethics guidelines produced for researchers of the HGDP, were proposed as a measure of protection against potential abuses of the samples and donor communities.

- i. The HGDP and its participating researchers must always respect the humanity of the sampled individuals and the cultural integrity of the sampled populations. This respect demands that collections proceed only with the informed consent of both the population and individual members. It also demands that the project observes the primary responsibility to avoid harming sampled individuals or their communities. Wherever possible, studies should be carried out by local investigators known to and trusted by the population to be sampled.
2. Informed consent is both an ethical imperative and a legal requirement. The HGDP must satisfy both conditions. To do so, the question of obtaining informed consent from participating individuals cannot be considered a mere formality but must be obtained in a culturally appropriate manner. This may differ from country to country. In addition, when scientists are funded to collect samples abroad, they must be sensitive to differences of protocol in obtaining informed consent. Funding agencies should respect these differences and not seek to impose their own cultural procedures. The requirement in all cases is for people to be informed both of the collection procedure and of the overall goals, and possible financial benefits, of the HGDP in ways they understand and that are appropriate to their culture. All participation should be voluntary. The objective should be to have the individual participants and the entire community become partners in the scientific effort. The idea of informed consent should also include an appropriate form of feedback of the results of the study to the sampled population.
3. Researchers should actively seek ways in which participation in the HGDP might bring benefits to the sampled individuals and their communities. Examples of such benefits include health screening, medical treatment or educational resources.
4. One way to avoid harming the sampled individuals or their communities is to protect the identity of those sampled and, in some cases, of the entire community - the latter to prevent possible group stigmatisation.
5. Although very unlikely, it is nevertheless possible that the results of the HGDP may lead to the production of commercially beneficial pharmaceuticals or other products. Should a patent be granted on any specific product, the investigators and sponsors must ensure that the sampled populations benefit from the financial return.
6. Human history - and the human present - is full of racism, xenophobia, hypernationalism and other tragedies stemming from beliefs about human populations. In the past, some of those tragedies have been perpetrated by, or aided by, the misuse of scientific information. All those involved in the HGDP must accept a responsibility to strive, in every way possible, to avoid misuse of the project data.
7. Many people in the world have, at best, a limited understanding of human genetics. Some fear the consequences of human genetic research, in part because of their limited knowledge. To scientists involved in the HGDP, their fears may not seem justified or even, in some cases, fully rational, but the concerns are very real to the

people involved and they must be addressed. It is essential that a world-wide 'public awareness' programme be included in the project to educate people about its aims, methods and results.

8. Inevitably, the ethical issues faced by the HGDP will evolve over time. They must therefore be kept under continual review. The widest possible consideration of the issues should be encouraged.
9. The transfer of technology to developing regions of the world, which is an integral part of the proposed project, should contribute positively to the development of self-sufficiency in these regions. The help given should not be superficial or of only short-term usefulness.
10. There should be a feedback of information to populations that participate in the HGDP, most especially about any aspect of the project in which a particular interest was expressed.

In summary, although the stated intent of the HGDP is laudable, the evidence indicates that, in carrying out its intent, the HGDP has thus far failed in its primary goal of bringing together the peoples of the world in an effort to eliminate prejudice, racism and xenophobia. The above guidelines should be adhered to, in order to improve collaborative research.

3.7 Summary of recommendations

3.7.1 Gene therapy

3.7.1.1 Somatic cell gene therapy

It is recommended that somatic cell gene therapy should be governed initially by the exacting requirements that already apply in South Africa to other research involving human subjects.

While the safety and effectiveness of somatic cell gene therapy are still uncertain, this new treatment, as with any other treatment, should be limited to patients in whom the potential for benefit is greatest in relation to possible inadvertent harm. It is recommended that the first candidates for gene therapy should be patients in whom the disorder is:

- i. life threatening or causes serious handicap;
2. one for which treatment is at present unavailable or unsatisfactory.

3.7.1.2 Germ-line gene therapy

Gene therapy should be directed to alleviating disease in individual patients, although wider applications may soon call for attention. In the present state of knowledge, any attempt by gene modification to change human traits not associated with disease would not be acceptable.

It is recommended that the necessary research should continue. There is, at present, insufficient knowledge to evaluate the risks, to future generations, of gene modification of the germ line. It is therefore recommended that gene modification of the human germ line should not yet be attempted.

3.7.1.3 Supervision of gene therapy

Continuing supervision of gene therapy is necessary. No existing body has been constituted for these tasks. Therefore, it is recommended that a new expert supervisory body be established.

This supervisory body should be of sufficient standing to command the confidence of existing

Research Ethics Committees, and of the public, the professions and of Parliament. It should have a responsibility for:

- i. advising on the content of proposals, including the details of protocols, for therapeutic research in somatic cell gene modification;
2. advising on the design and conduct of the research;
3. advising on the facilities and service arrangements necessary for the proper conduct of the research;
4. advising on the arrangements necessary for the long-term surveillance and follow-up of treated patients;
5. receiving proposals from clinicians who wish to conduct gene therapy in individual patients, and making an assessment of:
 - a. the clinical status of the patient;
 2. the scientific quality of the proposal, with particular regard to the technical competence and scientific requirements for achieving therapy effectively and safely;
 3. whether the clinical course of the particular disorder is known sufficiently well for sound information, counselling and advice to be given to the patient (or those acting on behalf of the patient) so that informed consent may be obtained (see 5.3 Book 1) - for the outcomes of therapy to be assessable;
 4. the potential benefits and risks for the patient of what is proposed;
 5. the ethical acceptability of the proposal.

In the light of this assessment, the expert supervisory body should recommend whether or not the proposal should be approved. Where applicable, conditions should be stated. The supervisory body should also have responsibility for:

- vi. acting in collaboration with existing Research Ethics Committees;
7. acting as a repository of up-to-date information on research in gene therapy internationally;
8. setting up and maintaining a confidential register of patients who have been the subjects of gene therapy;
9. oversight and monitoring of the research;
10. providing advice to Health Ministers, on scientific and medical developments that bear on the safety and efficacy of human gene modification.

We recommend that any proposal for gene therapy should be approved by this body as well as by a properly constituted Research Ethics Committee.

Initially, and probably for several years, gene therapy will be applicable to a small number of uncommon disorders and will be confined to a few patients. As with other new, specialised medical interventions, we recommend that it be confined to a small number of centres while experience is gained.

3.7.2 Genetic screening

3.7.2.1 Counselling, providing information and obtaining consent

We recommend that the following ethical principles be applied to genetic counselling:

- i. respect for persons and families, and respect for their decisions;
2. preservation of family integrity;
3. full disclosure and provision of accurate, unbiased information relevant to health, to individuals and families;

4. protection of the privacy of individuals and families from unjustified intrusions by employers, insurers and schools;
5. informing families and individuals about possible misuses of genetic information by institutional third parties;
6. informing individuals that it is their moral duty to tell blood relatives of the genetic risks to which they may be exposed;
7. informing individuals of the wisdom of disclosing their carrier status to a spouse or partner if they intend to have children, and the possibility of harmful effects of non-disclosure on the marriage;
8. informing individuals of their moral duty to disclose a genetic status that might affect public safety, for example an airline pilot with epilepsy;
9. unbiased presentation of information, insofar as this is possible;
10. a non-directive approach, except when treatment is available;
11. involving children and adolescents, whenever possible, in decisions that affect them;
12. duty to re-contact as appropriate and desired.³²

Informed consent is a term in the medical field, implying knowledge on the part of the patient, or research participant, of the major characteristics of their medical disorder if they are suffering from one, an understanding of the test or procedure which they are to undergo, the limitations of the test or procedure, and the possible consequence of their participation in the test or procedure.¹³ This term includes the research participant's or patient's right to be informed of risks not actually related to the medical impact of the test or procedure, including:

"... possible socio-economic consequences of an unfavourable test result, such as loss of health or life insurance, refusal of employment, discrimination by schools, adoption agencies etc. should where applicable, be included under the description of risks."¹⁴

It is recommended that the information to be specified to any patient undergoing genetic screening should include:

- i. the seriousness of the condition to which the genetic disorder may give rise, and how its effects may vary;
2. therapeutic options available;
3. how the disorder is transmitted, the significance of carrier status and the probability of developing the serious genetic disease;
4. the reliability of the screening procedure and the results of the test;
5. how the results of the screening test will be passed on to the patient, and what will be done with the samples;
6. the implications of screening positive for their future and existing children and for other family members;
7. a warning to women that the screening test may reveal unexpected and awkward information; for example, about paternity.²⁶

Informed consent in medical research is dealt with in detail in Section 5 of Book 1 in this series. The need to obtain informed consent to participate in research is entrenched in the South African Constitution Section 12(2)(c).

3.7.2.2 The Constitution, public policy and the practice of genetic screening

3.7.2.2.1 Results of genetic screening and confidentiality

It is trite to state that employers and insurers should have only limited rights to initiate screening programmes. This alone will not prevent genetic discrimination from occurring for so long as employers and insurers have access to genetic information.⁵ (See also 3.3.4.1.1

for references to South African law.)

The best way to ensure that genetic information is appropriately shared with family members (and occasionally with other third parties) is through information and counselling procedures. Although the desirability of sharing information with family members may be emphasised, disclosure ought not to be made a condition of participation in a screening programme. Inevitably some individuals will refuse to allow disclosure, and this may present the health professional with an ethical dilemma.

It is recommended that the following guidelines be adopted with regard to disclosure to families, of the results of a genetic screening programme:

- i. the accepted standards of the confidentiality of medical information should be followed as far as possible;
2. where the application of such standards might result in grave damage to the interests of other family members, the health professionals should seek to persuade the individual, if persuasion is necessary, to allow the disclosure of the genetic information. That task would be eased if it were accepted...that the consequences to the family of genetic information may in some cases make it unfair to confine the information gained solely to the individual who has been screened;
3. in exceptional circumstances, health professionals might be justified in disclosing genetic information to other family members despite an individual's desire for confidentiality".²⁶

This is an important area of concern. In our view the Department of Health, with health authorities and the appropriate professional bodies, should consider effective arrangements for the preservation of confidentiality, particularly in relation to genetic registers, and should issue the necessary guidance.

3.7.2.3 Employment

The recommendations of the Nuffield Council on Bioethics are endorsed, which propose that genetic screening programmes in the employment context be permitted only where the programme is approved by the appropriate regulatory body, where steps have been taken to ensure that individuals are not unfairly treated, where procedures are in place to assist the individual to find other employment, and where:

- i. "there is strong evidence of a clear connection between the working environment and the development of the condition for which the screening is conducted;
2. the condition is one which seriously endangers the health of the employee, or is one in which an affected employee is likely to present a serious danger to third parties;
3. the condition is one that cannot be eliminated or made less hazardous by reasonable measures taken by the employer to modify or respond to the environmental risks."²⁶

3.7.2.4 Insurance

It is recommended that insurance companies should adhere to their current policy of not requiring genetic tests as a prerequisite to granting insurance.

In the light of the arguments set out above, it is recommended that there should be early discussions between the State and the insurance industry about the future use of genetic data. Pending the outcome, the companies should accept a moratorium on disclosure of genetic data. There should, however, be two exceptions:

- i. in the case of individuals with a known family history of genetic disease that can be established by the conventional questions about proposers' families, individuals may be asked to disclose the results of relevant genetic tests;
2. the moratorium should apply only to policies of moderate value. The limit would be a matter to be settled between the State and the industry in the context of arranging the moratorium.

3.7.2.5 Children

The following recommendations of The American Society of Human Genetics and the American College of Medical Genetics Report³⁵ in respect of family involvement in decision-making are endorsed:

- i. education and counselling for the parents and the child, according to maturity, should precede genetic testing;
2. the provider should obtain the permission of the parents and either the assent of the child or the consent of the adolescent;
3. the provider is obliged to advocate on behalf of the child when he or she considers a genetic test to be - or not to be - in the best interests of the child;
4. a request by a competent adolescent for the results of a genetic test should be given priority over the parents' requests to withhold information.

3.7.3 Cloning

3.7.3.1 Therapeutic cloning

It is recommended that, at present, the use and derivation of human stem cells should be limited to two sources: cadaveric fetal tissue and 'surplus' embryos remaining after infertility treatments.

It is also recommended that the following principles drawn from the recommendations of the US National Bioethics Advisory Committee³⁶ should regulate the donation of human embryos for stem cell research.

- i. Prospective donors should be given timely, relevant and appropriate information to make informed and voluntary decisions regarding the donation of the embryos.
2. Embryos and cadaveric fetal tissue should under no circumstances be bought or sold.

With regard to the growth of entire organs, it is recommended that this technique should be more thoroughly investigated in animal systems before experimentation with human tissue is permitted.

3.7.3.2 Reproductive cloning

It is recommended that in the use of nuclear transfer the reproductive needs of an individual should not over-ride the best interests of the child produced.

The risk attached to the use of the technique on humans carries the possibility of hormonal manipulation in the egg donor, multiple miscarriages in the birth mother, and severe developmental abnormalities in any resulting child. The potential harms outweigh the potential benefits, and until studies in animal systems reverse this circumstance, we recommend that the use of human nuclear transfer cloning to create a new life should be prohibited.

Critics have raised questions about the appropriate use of scarce resources. This is particularly important in South Africa where public policy has determined that the extension of

primary health care to all South Africans must be the nation's first priority in the field of medical care. Is research into, and the practice of cloning, responsible use of limited State resources? The answer must be negative.

3.7.4 Expert supervisory body

It is acknowledged that continuing supervision of research related to cloning is necessary. At present there is no single existing body constituted for this task. Therefore, it is recommended that a new expert supervisory body be established.

In line with this recommendation for a supervisory body for gene therapy, it is recommended that this supervisory body should be of sufficient standing to command the confidence of existing Research Ethics Committees, and of the public, the professions and of Parliament. It should have a responsibility for:

- i. advising on the content of proposals, including the details of protocols, for therapeutic research;
2. advising on the design and conduct of research;
3. advising on the facilities and service arrangements necessary for the proper conduct of the research.

In the light of this assessment the expert supervisory body should recommend whether or not the proposal should be approved, and on what conditions. The supervisory body should also have a responsibility for:

- iv. acting in co-ordination with existing Research Ethics Committees;
5. acting as a repository of up-to-date information on research in cloning, including human cloning, internationally;
6. oversight and monitoring of the research;
7. providing advice to Health Ministers, on scientific and medical developments that bear on the safety and efficacy of cloning.

It is recommended that any proposal for research related to cloning should be approved by this body as well as by a properly constituted Research Ethics Committee.

3.7.5 Patenting human genetic material

The focus of any substantive research has become profit driven, and the incentive at present is for researchers to patent sequences or partial sequences of human genes. The patenting system grants to one entity the control of all future research and medical development with respect to the subject matter of the patent, in some instances for undertaking nothing more than a mechanical procedure.⁴³ This cannot be to the public benefit, while it promotes secrecy and hinders the exchange of scientific information, resulting in duplication of efforts, inefficiency in research and greater costs to the public for access to the resultant medical products.

3.7.6 The Human Genome Diversity Project

In summary, although the stated intent of the HGDP is laudable, the evidence indicates that, in carrying out its intent, the HGDP has failed in its primary goal of bringing together the peoples of the world in an effort to eliminate prejudice, racism and xenophobia. The guidelines of the HGDP should nevertheless be strictly adhered to, in order to improve collaborative research.

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