This publication was rescinded by National Health and Medical Research Council on 29/2/2000 and is available on the Internet ONLY for historical purposes.

**Important Notice**

This notice is not to be erased and must be included on any printed version of this publication.

- This publication was rescinded by the National Health and Medical Research Council on 29/2/2000. The National Health and Medical Research Council has made this publication available on its Internet Archives site as a service to the public for historical and research purposes ONLY.

- Rescinded publications are publications that no longer represent the Council’s position on the matters contained therein. This means that the Council no longer endorses, supports or approves these rescinded publications.

- The National Health and Medical Research Council gives no assurance as to the accuracy or relevance of any of the information contained in this rescinded publication. The National Health and Medical Research Council assumes no legal liability or responsibility for errors or omissions contained within this rescinded publication for any loss or damage incurred as a result of reliance on this publication.

- Every user of this rescinded publication acknowledges that the information contained in it may not be accurate, complete or of relevance to the user’s purposes. The user undertakes the responsibility for assessing the accuracy, completeness and relevance of the contents of this rescinded publication, including seeking independent verification of information sought to be relied upon for the user’s purposes.

- Every user of this rescinded publication is responsible for ensuring that each printed version contains this disclaimer notice, including the date of rescission and the date of downloading the archived Internet version.
Human gene therapy and related procedures

An information paper to assist in the consideration of ethical aspects of human gene therapy

National Health and Medical Research Council

N H M R C
This document is sold through the Australian Government Publishing Service at a price which covers the cost of printing and distribution only.

National Health and Medical Research Council documents are prepared by panels of experts drawn from appropriate Australian academic, professional, community and government organisations. NHMRC is grateful to these people for the excellent work they do on its behalf. This work is usually performed on an honorary basis and in addition to their usual work commitments.

Publications and Design (Public Affairs and International Branch)
Commonwealth Department of Human Services and Health

Produced by the Australian Government Publishing Service
Foreword

The field of gene therapy has undergone rapid development in recent years. Research into human gene therapy has resulted in new knowledge and innovative techniques for the diagnosis and possible treatment of genetic diseases, as well as certain cancers and infectious diseases such as AIDS.

This paper replaces the 1987 paper ‘Ethical aspects of research on human gene therapy’. Like that paper, it provides information additional to the NHMRC guidelines on human gene therapy research (Supplementary note 7 of the Statement on Human Experimentation) and encompasses the many new possibilities for genetic treatment of disease.

The aim of this information paper is to provide background information on genetic manipulation and how these techniques might be applied to research involving humans. The emphasis is on the ethical aspects of human gene therapy, and some of the concerns and fears which are often expressed about this field of research. The level of technical detail has been kept to a minimum to ensure the publication is accessible to a wide range of readers, including all members of institutional ethics committees.

I hope that the paper will be informative and helpful to members of institutional ethics committees, as well as to others interested in the field of genetic manipulation.

Robyn Layton QC
Chairperson
Australian Health Ethics Committee
Membership of the Australian Health Ethics Committee Gene Therapy Working Group

Sister Regis Dunne (Chairperson)
Director, Provincial Bioethics Centre for the Queensland Catholic Dioceses

Professor David Danks
Director, The Murdoch Institute, Melbourne

Mrs Helen Griffiths
Representative, Cystic Fibrosis Foundation

Dr Vimala Sarma
Secretary, Genetic Manipulation Advisory Committee

Professor Ron Trent
Department of Molecular Genetics, Royal Prince Alfred Hospital
Contents

Preface ix

What are genes? 1
  What do genes do? 1
  The chemical composition of genes and the way they work 1

Genetic diseases 3

Gene therapy of genetic diseases 5
  Techniques of inserting genes into cells 5
  Is there a place for germ line gene therapy? 5
  Risks and benefits 6
    Hazards of gene therapy 6
    The need for gene therapy, risks of treatment and burden of disease 7
    Experience to date 7

Alternative approaches to genetic diseases 9
  Other experimental forms of treatment 9
  Prevention of genetic disease by counselling and prenatal or presymptomatic diagnosis 9

Genes and cancer 11
  Insertion of DNA or RNA in cancer research and treatment 11

Viral diseases and the use of DNA or RNA insertion 13

General considerations 15
  Genetic enhancement 15
  NHMRC guidelines 15
Preface

It is important to emphasise that this discussion is confined to treatment or investigation of patients with serious diseases. The possibility of manipulating genes to alter human characteristics is not considered here (see ‘Genetic enhancement’ on page 15), nor is insertion of genetic material into reproductive (germ) cells or fertilised ova, except to indicate that these techniques are not envisaged as being useful for the treatment of disease (see page 5).

Inherited diseases constitute a serious health problem. Although the diseases are individually uncommon or rare, collectively the thousands of known hereditary diseases afflict at least 1 per cent of all humans. Only a small proportion of these diseases can be treated effectively and even in these the treatments need to be continued throughout life. This places heavy burdens, not only on the affected individuals, but also on their families and society.

Achievements of the last 20 years include isolation of many individual genes involved in genetic disease and precise analysis of their functions and of the faults which cause the diseases. This new knowledge has provided powerful methods of control of genetic diseases by identifying those couples who are likely to have children with these conditions and giving them the opportunity to make well-informed reproductive decisions. Prenatal diagnosis has provided many of these couples with an option which they find acceptable.

Not all genetic diseases are preventable and the development of better methods of treatment remains important. Many genetic diseases are caused by the lack of a particular gene function and are potentially correctable by insertion of a normally functioning gene into those cells in which the function is important. Some progress has been made towards making this possible in a few diseases.

It has become clear that alterations in genes play a crucial role in cancer. In each cancer a particular cell has escaped from the controls which normally limit the replication of cells in the body. The rapidly replicating cells displace and invade normal tissues. The uncontrolled cell replication is the result of changes in a number of genes. One or more of these changes may be inherited, but the remainder develop during the life of an individual. Manipulation of these deranged genes by insertion of the normal genes or by related techniques is of great potential importance in the treatment of cancer. Gene insertion is also proving important in research on cancer and cancer treatment.

These approaches to cancer, cancer treatment and cancer research have a great deal in common with somatic cell gene therapy and need to be considered along with it.

Novel approaches to treatment of serious infective diseases such as AIDS are being proposed using special forms of RNA, a class of chemical closely related to DNA, the genetic material of humans.

Guidelines need to encompass all these possibilities and not just the treatment of genetic disease as originally envisaged in 1987.
Human gene therapy and related procedures
What are genes?

Genes are the smallest functional units of the genetic systems which control the development and function of all organisms. Constancy of a set of genes determines the constancy of the main features within each species and differences in gene content are responsible for the differences between species. Within each species individuality depends upon minor differences in the function of a large number of genes. In contrast, genetic diseases are generally the result of a major change in the function of a single gene pair.

The entire genetic make-up of an organism is known as its genome. One can think of the genome as two copies of a huge construction manual containing all the information required to construct and manage the organism. The manual is divided into volumes (chromosomes), each containing many chapters (genes). In humans there are 23 pairs of chromosomes and a total of about 100,000 genes. One would expect both copies of a duplicated instruction manual to contain the same chapters arranged in the same sequence in the same volumes of each copy. All humans have the same genes arranged in the same order within the same chromosomes.

The duplication of the system is important because it allows sexual reproduction which is the production of a new individual by two parents each making an equal genetic contribution. The egg and sperm cells contain just one of each pair of chromosomes and, therefore, one of each pair of genes. The paired system is restored when a sperm fertilises an egg. The paired system also gives some protection against the harmful effect of errors that may occur in genes. The function of many gene pairs can still be carried out adequately if only one of the pair is functionally intact.

What do genes do?

Genes are mainly concerned with two types of function — determining the structure of the thousands of different proteins that are present in the human body and controlling where, when and in what quantity, each protein is made. Proteins are the molecules that do things in the body. Some form the structures of our tissues, eg collagen provides the fibrous tissue of ligaments and a framework of bones. Many are enzymes (biological catalysts) that control the thousands of chemical reactions that occur in the body. Others perform functions such as causing the blood to clot after an injury (eg clotting factor VIII which is lacking in haemophilia) or providing the contractile force in muscles. Some proteins stimulate or suppress multiplication of cells (see ‘Genes and cancer’).

Although all body cells (somatic cells) contain the whole genome, only a small subset of the possible proteins are made in any cell. Each cell makes only those proteins which it needs, Nerve cells, muscle cells and red blood cells each need different proteins. Quite a large proportion of the genes are devoted to determining when other genes will be active (expressed) in a cell. The aspects of our function which are controlled by individual pairs of genes are generally far too subtle to see by looking at a person. Conversely, the differences between people which we can observe by looking at them and talking to them are generally influenced by a large number of pairs of genes. A relatively small number of pairs of genes may be involved in minor characteristics like hair colour or eye colour, but hundreds, or even thousands, of genes play a part in determining complex characteristics like intelligence and behaviour. Nevertheless, a serious malfunction of one gene pair may disrupt normal function causing, for example, mental retardation.

The chemical composition of genes and the way they work

Genes are made of a chemical called DNA, one of a family of chemicals called nucleic acids. It is a huge molecule composed of two very long strands which are linked together by components called nucleotide bases. There are just four of these bases and they are known by the first letters of their chemical names — A (adenine), T (thymine), G (guanine) and C (cytosine). Specific chemical bonds between these molecules hold the two strands together and provide a very efficient way of ensuring faithful replication of the molecule.
whenever a cell divides. Copying of DNA is essential for cell division in order to provide each daughter cell with the same set of genes as the parent cell.

It is the sequence of the bases along one strand of the DNA molecule which constitutes the coded message which determines the function of each gene. Just as an instruction manual would have chapters which convey their message by the arrangement of letters into sequences which form words, so our DNA molecules also have instructions encoded in words composed of letters. Our written language uses 26 letters and arranges them into words of variable length. The genetic code uses only four letters (i.e., the bases A, T, G or C) and always forms three letter (base) words. This may seem a very limited coding system, but it is still capable of encoding far more than the 100,000 different messages that are required, by arranging the words in different orders.

When a gene becomes active (is expressed) the code message in the DNA in the nucleus of the cell has to be relayed to other parts of the cell where proteins are made. Another nucleic acid called messenger RNA (mRNA) is used. It is very similar to one strand of a DNA molecule and is made with exactly the same base sequence that is present in the gene. The system that makes proteins can read the message encoded in the mRNA, translating the order of three base code-words into a specific order of protein building blocks (amino acids). It is the order of amino acids in a protein that determines its function.
Genetic diseases

We know many thousands of diseases which are caused by defects in genes. In most genetic diseases there is a fault in one or both genes of a particular pair. These are the diseases upon which the present developments of gene therapy are focused. In other diseases the interactions between several pairs of genes are important or there may be a more severe genetic imbalance involving a large number of genes because a whole extra chromosome is present (eg in Down syndrome). These conditions are far too complex for the present methods of gene therapy to tackle and will not be further discussed in this paper. Even within the class of genetic diseases caused by faults in single gene pairs we have to make a distinction between some categories for which the present methods of gene therapy offer hope of success and others for which there is no current suitable approach.

The distinction between different types of inherited conditions is important when considering gene therapy. Dominantly inherited diseases are passed on from generation to generation in a family. This is because a fault in just one of a pair of genes is sufficient to cause the disease. The normal gene still present cannot fully compensate for the faulty gene or counteract its harmful effects. Huntington disease is an example. Since the present methods of gene therapy can only add an additional normally functioning gene to cells we cannot really expect to see any benefit in this class of disease. Some method which can either correct the fault within the gene or replace it by a normal gene will be needed. Such developments are not yet predictable.

Most people are much less familiar with recessive inheritance even though most serious childhood genetic diseases are inherited in this way. Disease occurs only when neither of a gene pair is functioning normally. People with one gene functioning normally and the other gene faulty are quite healthy and are known as gene carriers. Matings between gene carriers may result in one or more children with the disease. Other relatives are rarely affected. Cystic fibrosis is an example. The proposed addition of a normally functioning gene to the cells of affected individuals should restore the normal state of health seen in gene carriers.

There is a special class of recessive inheritance which is encountered with genes that are on the X chromosome. Women have two X chromosomes and hence can be healthy despite the presence of a faulty gene on one X chromosome. However, any man who inherits the same faulty gene will have the disease because men do not have a second X chromosome to provide a normally functioning gene. Haemophilia is an example of such a sex-linked genetic condition.

There are other general factors about the way genetic diseases may cause harmful effects which need to be considered when thinking about the applications of gene therapy.

There are some diseases in which the gene defect interferes with a chemical process in one organ and this causes a change in a chemical circulating in the bloodstream which may have serious effects on other organs. Phenylketonuria (PKU) is an example. The gene defect prevents the breakdown of a particular chemical in the liver, which accumulates in the blood and damages the brain. Addition of a normally functioning gene to a reasonable proportion of liver cells (eg 20 per cent of cells) should provide a capacity to break down enough of this chemical to prevent the brain damage. A diet which controls the intake of the harmful chemical is also very effective and has been used successfully for 30 years, a factor of importance in considering trials of gene therapy (see page 8).

A quite different situation exists in many other genetic diseases in which the gene fault directly damages each cell in the body, or in a particular organ. There are a number of genetic diseases, eg Tay-Sachs disease, which cause brain damage in this way. Correction by gene therapy would require introduction of a normally functioning gene into every brain cell. This cannot be achieved at present.

There are many genetic diseases of blood cells. These cells are formed in the bone marrow and then circulate to carry out their functions. In the bone marrow there are stem cells which multiply continuously to replace relatively short-lived mature cells in the circulation. If these stem cells could be harvested, and have a normally functioning gene added in the laboratory, they could be returned to the body to carry on their function. Thalassaemia and adenosine deaminase deficiency (ADA) are examples of diseases amenable to this approach.
These bone marrow diseases are the most easily accessible to gene therapy, but similar methods may be possible with liver cells as a sample of liver can be removed surgically and cells can be cultured in the laboratory. The corrected gene can be added to the stem cells which can be reintroduced into the liver where they will grow and produce further liver cells.
Gene therapy of genetic diseases

Techniques of inserting genes into cells

The ideal technique would insert the normal gene at its normal position in the chromosome, replacing the faulty gene. This is not yet achievable. Some of the methods that are available do insert the normal gene into a chromosome, but have no control over the location of insertion. The gene can be inserted into cells in culture in the laboratory by any of a number of physical or chemical techniques (eg micro injection, attached to micro ‘bullets’, precipitation on cells with calcium phosphate, in a lipid coat [liposome]), or can be carried into the chromosomes by certain classes of viruses, especially retroviruses. The retroviral technique will be described as it has been the most successful to date.

There are other methods of inserting DNA into the nucleus of a cell without incorporation into the chromosome. The use of adenoviruses as vectors (transport agents) are the best developed of these approaches and will be discussed here. Genes inserted in these vectors have a limited life (weeks or months). Attempts are being made to develop human artificial chromosomes which would remain discrete from the cellular chromosomes, and be long lasting.

The group of retroviruses includes HIV and some which cause tumours. When these viruses infect a person they insert their genetic material into the chromosomes of multiplying cells. A human gene inserted into the virus will be incorporated into the chromosome along with the viral genes. To make the process safe, the viral genes which cause harmful effects are removed and replaced by the desired human gene. The DNA insertion into chromosomes occurs randomly, a matter which is a potential source of hazard or of technical failure. At present the use of retroviruses has been limited to gene insertions into cells in the laboratory followed by reimplantation into patients. No trials have yet been conducted in which retroviruses are used to incorporate DNA directly in cells in the body. It is theoretically possible to use them in this way. The requirement for cell replication will prevent insertion of genes into some cells (eg brain cells).

Adenoviruses cause illnesses when they infect the cells lining the respiratory tract or intestine. The genes which cause these harmful effects can be replaced by a human gene which would be corrective for a particular disease. Inhalation as an aerosol should succeed in delivering the human gene to the cells of the respiratory tract for treatment of cystic fibrosis. This method has been tested successfully in mice. DNA inserted in this way would not usually be incorporated into chromosomes, but can persist within the cells for the life of each cell that has been infected. Since the cells lining the respiratory tract are replaced frequently, repeated treatment by aerosol inhalation would be required, but this may be less onerous and more effective than the current treatment of cystic fibrosis. Trials are in progress in this disease.

Even while this paper was being prepared another very interesting and surprising method of inserting DNA was described. DNA incorporated in liposomes (a fatty coat) have been injected into mice intravenously and have been taken up into many different classes of cells in the body where they have functioned satisfactorily for two or three months. Modifications of this approach may provide the simplest method yet of introducing genes and may even allow targeting of chosen classes of body cells. Many other methods are likely to be described in the coming years and in the long term the importance of gene therapy will be determined by scientists’ ability to discover more effective methods of delivering genes to the cells which need them.

Is there a place for germ line gene therapy?

All of the above discussion has focused on trying to find methods of delivering the gene to the appropriate somatic (non-reproductive) cells in the body. It must be very obvious that this is proving very difficult and one might ask why scientists are trying so hard to achieve such methods when it would surely be much easier to
insert the corrective gene into a fertilised egg cell and allow the normal processes of embryonic development to
distribute the gene to every cell.

It is indeed true that this approach would be relatively simple technically. There is already extensive experience
with injecting genes into fertilised ova of mice, rats, sheep, pigs, cattle and other species. There is every reason
to believe that injection into the nucleus of a human ovum fertilised by in vitro fertilisation would be quite
straightforward.

The problem is that there is no logical place for germ line gene therapy in the treatment of genetic disease. This
is because couples face one in two or one in four risks of genetic disease, not a 100 per cent risk. Therefore,
some ova fertilised in vitro will produce normal babies while others will produce affected babies. These classes
of fertilised ova must be distinguished before gene therapy could be used (to inject DNA into a normal
fertilised ovum would be unacceptable). If this becomes possible, selection of a normal fertilised egg for
implantation would be preferable by far to correction of a defective one. Another problem with germ line gene
therapy is that any gene damage occurring as a result of the procedure would also affect the germ cells and
could be transmitted to the offspring.

Despite its difficulties somatic cell gene therapy is the only form of gene therapy which can be contemplated.

Risks and benefits

The concerns expressed about gene therapy relate to its novelty and a general feeling of insecurity about the
rapid progress of genetic knowledge. Many people are also concerned about the potential power of the
technology, and the consequent possibility for misuse of that power. When examined carefully, the real issues
about gene therapy are like those of any other new and powerful treatment — the need to weigh carefully the
hazards and the benefits.

Hazards of gene therapy

All new forms of therapy involve a risk that the treatment may be only partially successful. In some rare
circumstances, it is conceivable that the gene therapy may create a situation for the patient and family which is
even worse than the untreated disease (see page 7). With all methods of gene insertion it is important to ensure
that the gene is not unintentionally inserted into the germ cells of the patient. This risk is negligible for current
methods of treatment which involve harvesting of the somatic cells, insertion of a gene into the cells in the
laboratory and reinserion of cells, or with therapies like adenovirus insertion into lung mucosal cells by
inhalation. Future methods of inserting genes into body cells, by intravenous injection of the gene in some form
of vector (transport agent), will require exhaustive evaluation in experimental animals to evaluate the risks.

With those techniques which insert DNA into chromosomes the main hazard relates to the inability to control
the site of insertion. The DNA generally inserts in one block at just one place in one of the chromosomes in
each cell, but the site of insertion will almost certainly be different in each cell that is treated. Retroviral gene
insertion is currently favoured because it is more efficient than the other techniques and because there is
generally only one copy of the gene inserted into each cell.

In some cells the DNA may insert in the middle of a gene. Loss of function of a single gene in a single cell
would not usually matter, especially as the cell would always have another copy of the same gene. However,
there are some genes which play important roles in controlling cell multiplication (tumour suppressor genes),
disruption of which might start a cell on the track towards becoming a cancer cell (see ‘Genes and cancer’,
page 11).

Insertion adjacent to an oncogene (a cancer promoting gene) might result in inappropriate activation of cell
multiplication. Induction of cancer has not yet been reported in experimental animals undergoing somatic cell
gene therapy, but all scientists agree this is a main potential hazard of this new form of treatment and that it will
be very important for all human subjects to be followed up for many years after treatment.

Insertion of genes in vectors which allow the gene to persist for some time in the cell nucleus without being
incorporated into the chromosomes does not seem likely to carry any particular hazard. The principal problem
is the likely transience of the effect of the treatment.

Human gene therapy and related procedures
With all viral vectors there is some slight lingering concern that the ‘disarming’ of the virus by removing viral genes which are essential for causing disease might possibly be reversed by interaction between the disarmed virus and a natural virus which might be present in the patient’s body.

**The need for gene therapy, risks of treatment and burden of disease**

There are many hundreds of genetic diseases which cause very severe disability and/or distressing symptoms and/or death. No effective conventional therapy exists for most of these conditions and the need for a new and effective treatment is apparent. Even in genetic diseases for which there is a current conventional treatment, the treatment itself may be very burdensome and many affected individuals may yearn for a ‘one shot’ cure such as might be achieved with a really effective gene therapy.

Clearly it will be necessary for the safety of gene therapy to be established in diseases for which there is no conventional therapy, before it is offered to patients with diseases for which there is some form of treatment available. The technical feasibility of treatment must also be taken into account in choosing diseases for early experiments in gene therapy.

Assuming that there is a small risk of causing cancer, how do we weigh the acceptability of this risk against the benefits of gene therapy? It is important to introduce the concept of the burden of a genetic disease. Before dietary treatment was available for phenylketonuria, the burden of severe mental retardation over a lifetime of 40 to 50 years was very high. By comparison the burden of providing a complicated dietary treatment is quite light. Despite technical feasibility, it would be inappropriate to propose that phenylketonuria be a priority for gene therapy because its burden, with current treatment, is low. The disease chosen for the first trials of somatic cell gene therapy in humans was adenosine deaminase (ADA) deficiency, an enzyme defect which causes a severe deficiency of immune function so that affected children have frequent life-threatening infections and eventually develop malignant tumours if they survive the infections. It was also a favourable disease technically because harvesting of bone marrow and treatment of long-living cells can be used. The corrected white blood cells are likely to have an advantage over the defective cells in the bone marrow. ADA deficiency therefore satisfies both the criterion of technical feasibility and that of severe burden despite the best current therapy. At some time in the future, if gene therapy becomes very efficient and its effect very long lasting, and if hazards have been shown to be negligible, then gene therapy of phenylketonuria may become appropriate.

**Experience to date**

There is now experience with gene therapy of ADA deficiency in several patients in the United States treated by retroviral insertion of the correcting gene into long living immune cells present in harvested bone marrow. Each patient has required a number of rounds of treatment and the beneficial effect has been stronger and longer lasting after each treatment. Two patients are now reported as having a sustained effect more than six months after their last treatment. The immunity is proving sufficient to allow these children out of their artificial germ free environment without developing infections, but the doctors have not felt confident enough to cease the administration of drugs which are used to give partial restoration of immunity. There is also evidence that the children may not be forming immunity against all foreign substances, as occurs in healthy individuals, but only against some of these substances. No side effects have been encountered to date.

The experimental treatment of a serious disturbance of cholesterol metabolism which leads to a very early onset of coronary artery disease has also commenced by inserting the correcting gene into liver cells cultivated from a surgically removed piece of liver, followed by reinsertion of the corrected cells into the circulation to the liver. First trials of inhalation of adenoviruses containing the cystic fibrosis gene have also commenced. No detailed reports of either of these experimental treatments are yet available.
Alternative approaches to genetic diseases

Other experimental forms of treatment

In parallel with research into gene therapy, hundreds of research groups around the world are trying to improve the conventional methods of treatment of genetic diseases such as dietary manipulation or treatment with drugs or hormones. Others are trying to develop more novel approaches such as replacement of enzymes or proteins that are lacking in the body, by those made in the laboratory by DNA technology. Use of growth hormone and insulin made by DNA technology is already standard and a wide range of other hormones are becoming available for treatment for the first time. Regular injections of an enzyme which is lacking in a genetic disease may become an alternative to gene therapy.

Research is also being conducted into methods of destroying the messenger RNA from faulty genes which actively produce symptoms in some dominantly inherited conditions. The logic behind the use of ‘anti-sense RNA’ or ‘gene shears’ for this purpose is similar to that outlined below in discussion of ‘Genes and cancer’ and ‘Viral diseases’.

These approaches are mentioned to provide a general background to the wide range of approaches that researchers are taking to find novel treatments of genetic diseases which may improve the future lifestyle of affected individuals.

Prevention of genetic disease by counselling and prenatal or presymptomatic diagnosis

To keep the therapeutic approach to genetic disease in perspective, it is important to realise that in all diseases the family members concerned should have easy access to professional counselling about the risks that they will face in future reproduction, so that they can make an informed decision about having a family. This counselling should always include information about the availability of prenatal or presymptomatic diagnosis. Prenatal diagnosis at an early stage in pregnancy (10 or 14 weeks) is available for more than 400 different genetic diseases and additional diseases are being added to this list every few weeks. Many couples wish to use prenatal diagnosis and termination of an affected pregnancy to avoid occurrence of severe genetic diseases of early onset. Presymptomatic diagnosis in young adults about to start a family can be very helpful in dominantly inherited diseases of late onset which might otherwise be passed on to children before any symptoms have made the affected parent aware of his or her condition. Naturally these matters need very delicate discussion by skilled counsellors who have learnt to impart information and to assist in decision making in a non-directive manner.

The technical difficulty of developing gene therapy for each of the many serious genetic diseases and the cost of this development will mean that the established preventive methods are likely to remain an important part of the approach to genetic disease for many years to come.
Human gene therapy and related procedures
Genes and cancer

A number of genes are involved in controlling the rate of multiplication of cells. Surges of cell multiplication are essential in certain phases of embryonic development and the multiplication must then be slowed or stopped by other genes. Some genes stimulate cell multiplication and others stop it. Some of the genes are also involved in cell turnover and replacement in adult life. Development of cancer involves inappropriate overactivity of one or more genes which stimulate cell multiplication (oncogenes) and disruption of the function of one or more pairs of genes which suppress cell multiplication (anti-oncogenes or tumour suppressor genes). Some people may inherit a fault in one of a pair of tumour suppressor genes. Then only a single fault in the other member of the gene pair in a single somatic cell during the course of life may be sufficient to start a cancer. Viruses or physical factors such as irradiation may cause such faults in individual cells.

In addition to these genes that are directly related to cancer, many different growth factors are made in the human body which either stimulate or suppress the multiplication of cells, especially the cells of bone marrow and other tissues in which there is need for a constant turnover of cells.

Manipulations of growth factor genes and/or oncogenes or tumour suppressor genes are being proposed as experimental treatments for cancer.

Cancer provides a good example of the acceptable balance between risk and benefit of an experimental treatment. Radiation treatment and the many different chemotherapy drugs that have been used to treat cancers are all themselves capable of causing cancer. Yet our society has accepted trials of new cancer therapy agents if they seem to offer even a small increase in the possibility of cure of the existing cancer.

Insertion of DNA or RNA in cancer research and treatment

Insertion of a normal tumour suppressor gene into cells that have become cancerous because of loss of both copies of that gene, should switch off their malignant behaviour. The rapid replication of cancer cells makes them take up retroviruses well. The first attempts at gene insertion into cells within the body may be in advanced stage cancer.

Research in cancer involves a careful study of the rate of multiplication of cells in the cancer itself and of the way in which body cells mount a defence against the cancer. DNA insertion has been used in research on these interactions. The very first experimental introduction of a gene into a human subject involved inserting a piece of DNA into a type of white blood cell which was believed to invade and destroy tumours, in order to trace these cells as they moved from the bloodstream into the tumours in patients with terminal cancer. Further applications of DNA insertion for cell tracking are likely to be proposed in the future.

Another novel use of DNA insertion has been evaluated in experimental animals and is now being trialed in humans. It involves injection of retroviruses carrying a particular gene from a herpes simplex virus into brain tumours so that the gene will be introduced into each cell of the tumour as it multiplies. The introduced gene makes the cells susceptible to killing by an anti-viral drug called gancyclovir. In the experimental animals the subsequent administration of the drug eradicated all tumour cells. Other related applications of gene therapy will be developed in the future.

Some RNA molecules are capable of attacking other RNA molecules, inactivating them or cutting them into pieces. These RNA molecules have been given the colourful names ‘anti-sense RNA’ and ‘gene shears’ (also named ribozymes). Hopes are held that it may be possible to use these molecules to block the function of harmful genes or to cut the RNA which forms the genetic material of the HIV and other similar viruses. It may be possible to introduce pieces of DNA into the cells to make these RNA molecules within the cell. Many technical problems need to be resolved before trials can be proposed.

It is likely that many other uses of DNA or RNA insertion in the treatment of cancers or serious viral infections will be developed in coming years.
Human gene therapy and related procedures
Viral diseases and the use of DNA or RNA insertion

Viruses are micro-organisms which can live only within the cells of another organism. They have their own genetic material, but also make use of some of the genetic material of the host organism. Some viruses have DNA as their genetic material and others use RNA. Some RNA viruses called retroviruses make a DNA copy of their RNA and insert this into the chromosomes of the host cell where the gene reading systems of the host are tricked into making the proteins that the virus needs. The genetic engineer uses these properties when retroviruses are employed to insert DNA for the treatment of genetic disease.

Progress in developing drugs like antibiotics which can be used to kill viruses has been very slow and the way in which the viruses interact with the host’s genes creates fundamental difficulties in finding drugs which will destroy the virus without damaging human cells. Vaccines have been the cornerstone of prevention of virus infections — they recognise the proteins of the virus and assist host immune cells to destroy the virus. Some viruses like HIV and hepatitis are major health problems and are still far from conquered by the vaccine approach.

Some micro-organisms have developed their own strategy for surviving in a hostile environment by producing RNA molecules (ribozymes) which act like enzymes and can attack and break down the RNA of other organisms. Scientists have worked out how these ribozymes work and have found that it may be possible to make artificial ribozymes which will cut at a particular point in a specified RNA, or perhaps even DNA, molecule. This technology has been particularly developed in Australia’s CSIRO. Hopes are held that this approach may be able to produce a method of killing viruses such as HIV and hepatitis.

If this research progresses as the scientists hope, it may be put into practice by actually administering the ribozymes to the patient by injections, by harvesting the patient’s white blood cells and incorporating the ribozyme into these before reinfusing the cells, or by developing DNA molecules which could be inserted into the chromosomes of a stem cell from the bone marrow and provide an ongoing source of ribozyme for many months or years.

It is too early to anticipate the types of experiments that might be proposed, but provision for their consideration has been incorporated in the guidelines.
Human gene therapy and related procedures
General considerations

Genetic enhancement

Many fear that germ line gene therapy may be used to enhance normal characteristics like intelligence, personality, physical features or abilities. Such interventions are not imminent because we are nowhere near having the knowledge necessary to know which genes to manipulate. We do know that variability in these features is influenced by many different genes. Many hundreds of genes are likely to be involved in influencing intelligence and personality. The variations between individuals in each of these genes are likely to be very subtle, not the crude, all or none, type of differences that we encounter in genetic diseases. There is reason to doubt whether we will ever understand this type of genetic control fully, but certainly it will take a long time to achieve that level of understanding and there will be plenty of opportunity for debate about the desirability of trying to modify the genetic constitution when there is more knowledge available. For the present, prohibition of germ line gene therapy is an appropriate way of reassuring the community while scientists continue to expand our basic knowledge.

NHMRC guidelines

NHMRC guidelines on research involving somatic cell gene therapy and other forms of experimental introduction of DNA and RNA into human subjects are contained in supplementary note 7 of the NHMRC Statement on Human Experimentation.
The National Health and Medical Research Council

The National Health and Medical Research Council (NHMRC) is a statutory authority within the portfolio of the Commonwealth Minister for Human Services and Health, established by the National Health and Medical Research Council Act 1992. The NHMRC advises the Australian community and Commonwealth, State and Territory Governments on standards of individual and public health, and supports research to improve those standards.

The NHMRC advises the Commonwealth Government on the funding of medical and public health research and training in Australia and supports many of the medical advances made by Australians.

The Council comprises nominees of Commonwealth, State and Territory health authorities, professional and scientific colleges and associations, unions, universities, business, consumer groups, welfare organisations, conservation groups and the Aboriginal and Torres Strait Islander Commission.

The Council meets twice a year to consider and make decisions on reports prepared by committees and working parties following wide consultation on the issue under consideration.

A regular publishing program ensures that Council's recommendations are widely available to governments, the community, scientific, industrial and educational groups.

The Council publishes extensively in the following areas:

- Child health
- Clinical practice
- Communicable diseases
- Dentistry
- Drugs and poisons
- Drug and substance abuse
- Environmental health
- Health ethics
- Infection control
- Mental health
- Nutrition
- Public health
- Women’s health.

A List of Current Publications is available from:

   The Publications Officer
   NHMRC
   GPO Box 9848
   Canberra ACT 2601

   Phone: (06) 289 7646 (24 hour answering machine)
   Fax:     (06) 289 6954