GENE THERAPY is important - it may revolutionise medicine during the next ten years and has great potential for the biotechnology industry. Many people think that there are associated ethical issues.

Europe needs to address the evolving questions, to join the national and international debate, and to formulate a *European* response and perspective.

A scientific expert group supported by the European Commission assessed some of the issues associated with this rapidly expanding field.
The first edition of this leaflet was written by Professor R. Williamson and Dr. B. Kampmann after consultation of the following experts at a workshop held at the Wellcome Foundation in London in December 1993, sponsored by the European Commission, DG XII. This second edition (1996) is an attempt to update the information in the light of recent developments in this highly innovative research area.

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The Scientific Background

*GENES* are made of DNA - the code of life. They are made of a sequence of chemicals with the initials A, C, G and T, just like the alphabet makes words and sentences which can be turned into instructions. Everyone inherits genes from their parents and passes them on in turn to their children. Every person's genes are different, and the changes in sequence determine the inherited differences between each of us. Some changes, usually in a single gene, may cause serious diseases (such as CYSTIC FIBROSIS, MUSCULAR DYSTROPHY OR THALASSAEMIA). More often, gene variants interact with the environment to predispose some people to CANCER, or HEART DISEASE, or other common ailments. Today doctors can look at a person's DNA using very sensitive new techniques which use as little as one hair root or drop of blood.

Our cells are divided into two groups, the somatic cells which make up the working parts of the body, and the germ cells (or sex cells: sperm in men and eggs in women) which pass on genetic material to our children. Every normal somatic cell contains the same coded DNA instructions, even if only some of them are used. Different ones will be active in different parts of the body. If a body cell is modified by

*SOMATIC GENE THERAPY*

it will only change cells in the body of the person being treated, and not be passed on to children. Somatic gene therapy can be targeted to, for example, the liver, blood or lungs, to correct a medical problem which already exists and which can be treated by the gene or its protein product, such as an inherited disease or cancer.

Sperm and egg cells are different. They are the cells which go to form the individuals of the next generation and pass the genes from both parents to the offspring. They are the GERM CELLS.

*GERM CELL GENE THERAPY*

would involve the deliberate insertion of a gene into the germ cells, deletion of a gene from them, or alteration of a gene already there. Most people agree that germ line therapy raises serious ethical issues, since changes would be inherited.
THE BIG QUESTIONS

Q. What exactly would be done in human somatic gene therapy?

Genetic therapy uses purified preparations of a gene or a fraction of a gene to treat a disease. This can be done either by correcting the functioning of a cell in which a single gene does not work properly from birth or sometimes by killing a cell which is out of control. Therefore diseases such as cystic fibrosis, diabetes, Parkinson's, Alzheimer's, heart disease and cancer are all targets for somatic gene therapy. Indeed current trials are assessing the safety and success of this kind of treatment in some of these diseases.

There are several approaches to the introduction of genetic material into a somatic cell. These include direct injection of the gene into the cell, using a VIRUS to carry a gene into a human cell, or merging it into the cell with a fat particle called a LIPOSOME, or an antibody-like protein that can recognise the cell surface. These techniques are in their infancy, but are already being used in trials to attempt to treat several rare inherited diseases such as cystic fibrosis, and some cancers.

In some ways, SOMATIC GENE THERAPY involves the delivery of a naturally occurring molecule to the patient and his/her cells. There is an implication therefore that it is likely to be more effective for particular diseases than conventional drugs. Because only somatic cells are receiving the human gene, the treatment will probably have to be repeated, perhaps for the person's lifetime.

Q. Is it new?

Yes, it is new, because it rests on the scientific techniques developed in the 1980's and 1990's to allow investigation of the structure of DNA, first discovered by Crick and Watson in 1953. There have also been significant advances made in analysis of human genes (The Global Human Genome Programme). The use of these and other techniques have allowed the genes and gene disorders to be identified and tracked through families with great accuracy. The genes, some of which have been identified for the first time using the new techniques, combine with each other and the environment to make us what we are.
Q. Does it matter?

Yes - because there is great interest in using techniques to introduce normal genes into cells in the treatment of literally dozens of diseases, from quite rare ones which for example can cause failure to digest nutrients properly (such as phenylketonuria) to more common disorders like cancer, AIDS, heart attacks or Alzheimer’s disease.

Q. Does that mean that scientists will be interfering with a person's inheritance?

No, because the new treatments that are proposed are aimed at the somatic cells, and will only treat affected cells in the body of the individual patient, such as muscle cells for muscular dystrophy, whereas germ line gene therapy in humans would be aimed at egg and sperm cells which control inheritance. This type of therapy is or will be prohibited by most European countries.

Q. Won't there be some doctors who will go ahead with germ line gene therapy, just to see if it can be done - or for money or power? How will patients be protected?

Any new discovery can be misused. That is precisely why we need a set of rules and guidelines which ensure practices are used only according to ethical standards agreed upon after political, scientific and medical discussion. We also need much more public understanding and informed discussion, since in the long term this is the only insurance against misuse.

Q. Are there a lot of new ethical questions related to somatic gene therapy?

Most philosophers, doctors, scientists, lawyers and ordinary people (and especially the patients and their families) think that somatic gene therapy to treat a serious disease is much needed, and only raises the same sort of ethical issues as in other branches of medicine for example organ transplantation. However, somatic gene therapy - like any new treatment - requires a proper assessment of safety and effectiveness, and informed patient consent.

Q. Does somatic gene therapy have anything at all to do with reproduction?

Not really - but if effective treatment such as somatic gene therapy were to exist for any serious inherited disease, parents who know they are at high risk of having children with an
inherited disease may be more willing to have an affected child, because earlier and more effective treatment should be available.

Q. What about patenting human genes for therapy? Wouldn't this be the equivalent of patenting life itself?

No, although this is a very controversial issue. Genes from any source, including humans, are chemicals and can be patented. Patenting involves protection, for a limited time, of the property rights of an inventor in return for making information about the invention available to all. The "invention" is defined legally - to be patentable, it must be novel, inventive and useful.

Patents are not granted if the exploitation would be contrary to "ordre public" or morality.

Some patient and public interest groups argue against patenting of human genes on the principle that genes are in every person, belong to all, and their use should not be restricted in any way. However, by establishing an exclusive position, a patent provides an incentive to invest in research and development. Without patent protection, companies would not invest the large amounts of money needed to develop the use of genes and gene products for therapy.

Q. What could the European Parliament do about patenting?

The draft directive of 1988 on the legal protection of biotechnological inventions was rejected by the European Parliament in March 1995. In December of the same year, the European Commission adopted a new draft taking into account several objections raised by the European Parliament, such as the exclusion from patentability of methods of germ line gene therapy on humans. The proposed directive aims at clarifying the existing national laws in a uniform manner and ensuring legal certainty throughout the European Union. It would avoid a proliferation of divergent legislation and case-law that would threaten to fragment the single market. The European Parliament by and large recognises the need for legislation, and has started its debate. The adoption of a directive in its present form would improve Europe's attractiveness for research activities.

Q. Are there already regulations to enforce safe practice for somatic gene therapy?

Yes. There are already harmonised European rules on the use of genes, particularly with respect to possible release into the environment ("The Release of Genetically Modified Organisms"). The principles applied to the use of products derived from biotechnology form the basis for gene therapy. More European wide and specific rules may be needed for gene therapy to ensure that good practice is maintained throughout Europe.
The marketing authorisations for biotechnology products are granted by the European Commission only after a thorough evaluation of safety, quality and efficacy according to strict rules and guidelines under the auspices of the European Medicines Evaluation Agency.

In many EU countries clinical trials require approval of the competent national authorities before they can be conducted and most require Ethics Committee approval at the hospitals and centres where the trial is carried out. In some countries, gene therapy trials must be reviewed by another body, a Gene Therapy Advisory Committee before they can begin.

Q. Is it good enough to have national Gene Therapy Advisory Committees, or do we need a European one?

Whether we need a European advisory committee will reflect the balance between the need for an effective European mechanism for ensuring uniform ethical and safety standards, against the delays that this might bring. Delays allow time for thought, but also mean continuing ill health to sufferers awaiting the successes of gene therapy. In order to provide a helpful line between individual countries and a European Regulatory Agency, a non-statutory group may be helpful. These people, from a range of backgrounds including scientific, medical, legal and social professions, would consider and advise on the acceptability of clinical trial proposals from social and ethical perspectives. In doing so, they would take into account the scientific merit, the potential for benefits and risks of such proposals.

Q. What about rare diseases - will they be given adequate research attention when there is little potential financial reward for investing companies?

In the United States, there is an "orphan drug" Act which helps companies financially by giving them exclusive rights to good treatments they develop for rare diseases. In November 1995, the Health Council of the EU requested the European Commission to submit a proposal on orphan drugs to foster research in this area.

Q. Will there be equal opportunities for all to have access to somatic gene therapy?

While the research which underlies gene therapy is fairly expensive as compared to some basic biological research, there are no clear indicators available yet for assessing whether research and development costs will be higher, comparable or lower for products issued from gene therapy research as compared to conventional drug development. However, it is up to society to decide how much of the resources made available for health care should be allocated to this specific type of treatment.
Q. **Is there enough investment in somatic gene therapy to keep up with the Americans?**

As in many other fields, Europe seems to lag behind other countries, particularly the United States, although a few universities, hospitals, biotech and pharmaceutical companies are exceptions. However, it would help a great deal if both the European Framework Programmes and Technology Investments in the EU gave greater priority to this very important and innovative biomedical field.

Q. **Can Europe compete in this field at all? Do we have the scientists and doctors with the right training, and the companies who can provide and use the technology?**

Basic biomedical science is still very strong in Europe. There are many groups which have an interest in human molecular genetics and in somatic -gene therapy. However, such groups are often very small and isolated, and need to be encouraged to develop and share both physical and human resources by complementary collaboration, particularly by pooling of patient data. More funding is needed for training, and this would be a natural area of priority for the European Union training programmes.

Q. **So once more, does it matter?**

Yes, because all of us - scientists, politicians, doctors, civil servants - will want to see the benefits of the new genetics help prevent and treat serious disease. Europe cannot be left out of gene therapy developments, for the health of the patients, and to keep its research community and its science-based industries healthy as well. Europe can set an example on the conduct of an informed discussion on the ethical aspects of the new genetics, which will ensure proper controls both of safety and access to all.